MASTER OF SCIENCE BY RESEARCH

Female childhood cancer survivors and the impact of flank, abdominal or pelvic radiotherapy on live birth
A systematic review and meta-analysis

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A thesis submitted in partial fulfilment of the University's requirements for the Degree of Master of Research

Contents

i) Abstract

Background: Due to increased rates of survival for children with cancer*, many now maintain their fertility into adulthood. Long-term chronic conditions of female childhood cancer survivors (CCS), coupled with physiological pressures of pregnancy and birth warrants further investigation by health care providers.

Objectives: To investigate the impact upon live birth outcome for female CCS who received radiotherapy to the flank, abdomen or pelvic areas. A Patient and public involvement and engagement (PPIE) survey was used to align the review outcomes to patient need and results were presented.

Data sources: A search of MEDLINE, PUBMED, CINAHL, Google Scholar, TRIP, SCOPUS and ProQuest databases was undertaken until 30th September 2017.

Study criteria and participants:

- Female CCS treated with radiotherapy to the flank, abdomen or pelvis
- English language publications
- Population data from a recognised data registry and from UK, USA, Canada, Australia or EU
- Quantitative methodology

Appraisal and synthesis: Data were extracted, and meta-analysis performed with *EPPI Reviewer4* software. The Newcastle Ottawa scale was used for risk of bias assessment.

Results: A statistically significant effect upon the odds of a premature birth (odds ratio 3.27, 95% CI 2.71-3.96) and stillbirth (odds ratio 1.62, 95% CI1.10-2.40) was noted. There was no statistically significant effect on live birth outcome or additional adverse pregnancy outcomes. The PPIE survey demonstrated that 'maternal complications in pregnancy and birth' was the primary concern of CCS with a call for more communication of likelihood of long-term complications related to cancer treatments.

Limitations: Limitations were noted with software, heterogeneity of outcomes, lack of evidence and a reliance on self-reported data.

Conclusions: Female CCS treated with radiotherapy to the flank, abdomen or pelvis need high risk antenatal care referral and surveillance due to increased odds of premature birth and stillbirth.

Registration: PROSPERO ID- CRD42017054533

** Throughout this thesis, unless explicitly specified, the word children and childhood will be used to mean children, teenagers and young adults 0-24 years.*

ii) Glossary and abbreviations

Abdomen	The part of the body between the thorax (chest) and the pelvis.
ALL (Acute Lymphoblastic Leukaemia)	A type of blood cancer that arises from young white blood cells called lymphocytes in the bone marrow
Anthracyclines	A class of drugs used in chemotherapy
ART	Artificial reproductive technologies
ATHENS	An online account which facilitates searching on information databases
Atrophy	Wastage of a body tissue or organ
Autologous	Cells obtained from the same individual
BCCSS	The British Childhood Cancer Survivorship Study
Cardio-toxic	Toxic or damaging to the heart
Cardiovascular disease	A class of diseases that involve the heart or blood vessels
CCS	Childhood cancer survivors
CCSS	The Childhood Cancer Survivorship study
CI	Confidence interval
CTIMP	Clinical Trial of an Investigational Medicinal Product
DIPG	Diffuse intrinsic pontine gliomas, a highly aggressive brain tumour
DNA	Deoxyribonucleic acid (genetic make-up)
Embryonal tumour	A mass of rapidly growing cells that begin in embryonic (fetal) tissue
EU	European Union
Fibrosis	The thickening or scarring of tissue
Flank	The side of the body between the ribs and the hip

Germ cell tumour	A type of cancer that originates in the ovaries or testes and derives from germ cells
Gy	Grey (measurement of dose in radiotherapy)
HEE	Health Education England
Hodgkin's Lymphoma	a type of lymphoma resulting from the white blood cells, usually presents in the lymph nodes
ICCC	International classification of childhood cancers
IMRT	Intensity Modulated Arc Therapy. A precision delivery radiotherapy treatment
INVOLVE	A national advisory group for patient and public involvement in research funded by the NIHR
IRAS	Integrated Research Application system
IVF	In vitro fertilization
Lymphoma	A type of cancer that begins in the infection fighting cells of the immune system called lymphocytes
Malignancy	Cancer
Malposition of the fetus	A position of the fetus in labour that is not optimal for birth
Menarche	The first occurrence of menstruation
MeSH	Medical subject headings used in databases
Metastases	Secondary cancerous growths at a distance from the primary tumour site
Myometrium	The middle layer of the uterine wall
Neuroblastoma	A type of cancer which forms in the nerve tissues
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research

NOS	Newcastle Ottawa Scale
OR	Odds ratio. The OR measures the ratio of the odds that an event or result will occur compared to the odds of the event not happening. Clinically, that often means that the researcher measures the ratio of the odds of a disease occurring or a death from a specific injury or illness happening versus the odds of the disease or death not occurring
PANCARE	A multidisciplinary pan-European network of professionals, survivors and families aiming to reduce the frequency, severity and impact of late side-effects of childhood and adolescent cancer
Parturition	The action of giving birth
PDF	Portable Document Format
Pelvis	The lower part of the trunk of the body between the abdomen and the thighs
Placenta praevia	A pregnancy condition where the placenta lies low in the uterus and partially or completely covers the cervix
PPIE	Patient and Public Involvement and Engagement
PRISMA	An evidence-based set of reporting guidelines for systematic reviews and meta-analysis
PROM	Premature rupture of membranes
PROSPERO	An international database of prospectively registered systematic reviews in health and social care
Proton Beam therapy	Type of radiotherapy that uses protons to treat cancer
RCM	Royal College of Midwives
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
Retinoblastoma	A rare malignant tumour of the retina, usually in childhood

Rhabdomyosarcoma	A type of sarcoma
RR	Risk ratio. In statistics and epidemiology, relative risk or risk ratio (RR) is the ratio or probability of an event occurring (for example, developing a disease, being injured) in an exposed group versus the probability of the event occurring in a comparison, non-exposed group
Sarcoma	Rare cancers that develop in the muscle, bone, nerves, cartilage, tendons, blood vessels and fibrous tissues
SIGN	Scottish Intercollegiate Guidelines Network
TYA	Teenage and Young Adult
USA	United States of America
UK	United Kingdom
Wilms tumour	Also known as nephroblastoma is a kidney cancer usually associated with childhood

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v) Acknowledgments

I would like to take this opportunity to thank everyone that has contributed to the completion of this thesis and for the ongoing support and encouragement. This journey has ignited a passion for research that I wasn't aware I had, and I am excited for the future.

First, I would like to thank my supervisory team, especially my director of studies, Dr Elizabeth Bailey who has been a constant source of reassurance and an inspirational figure to aspire to. To Professor Jane Coad, for your wealth of experience and knowledge, and Dr Bob Phillips for being my mentor, cheerleader and long-term supporter both as a parent advocate and a baby researcher. To Dr Alex Toft, who since joining my supervisory team has been a steady and reassuring voice and Nic Aldridge for offering to help in my hour of need. I would also like to thank Dr Daniel Saunders who has been an invaluable resource for radiotherapy aspects of my project and last but not least Neil Ranasinghe for his ongoing support, advice and shoulder to lean on.

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Most of all I would like to acknowledge my beautiful daughter Bethany, who without the memory of I would not have the strength, passion and determination that I do today to try and make a difference in her name. This thesis is dedicated to her and all the children with cancer.

Chapter 1 – Introduction

The survival rate for Children and Teenagers and Young Adults (TYA's) with cancer is now approximately 80 percent (Clic Sargent 2016). Despite this, cancer treatments delivered to a child or young person are known to cause significant long-term* chronic health problems in adulthood (Clic Sargent 2016, Aslett et al. 2007).

Many female childhood cancer survivors (CCS) now maintain their fertility in adulthood (Reulen et al. 2017). Research has not adequately addressed the impact of chronic and treatment-related health conditions, combined with anatomical and physiological pressures of pregnancy and birth on the female CCS and their babies. There is an important and vital knowledge gap for health care providers who provide obstetric care to a CCS to ensure optimal outcomes for both mother and baby are achieved.

This thesis provides a systematic review and meta-analysis of the existing evidence investigating the long-term effect of radiotherapy on outcome of live birth and associated pregnancy adverse events. The researcher, a midwife by profession, has employed extensive experience in being involved and running Patient and public involvement and engagement (PPIE) events and has aimed to incorporate a patient-centred approach to the review with the inclusion of a PPIE survey.

**Long-term in this review is defined as an outcome or clinical health or psychological health issue of a CCS still alive >5 years since diagnosis.*

1.1 Background

This chapter will outline the incidence of childhood cancer and survival rates, the biology underlying the disease and the effects of radiotherapy on the female anatomy, and an overview of survivorship research. The chapter will then consider the challenge of addressing complex health conditions in maternity services and conclude with the aim, rationale and outline of this review.

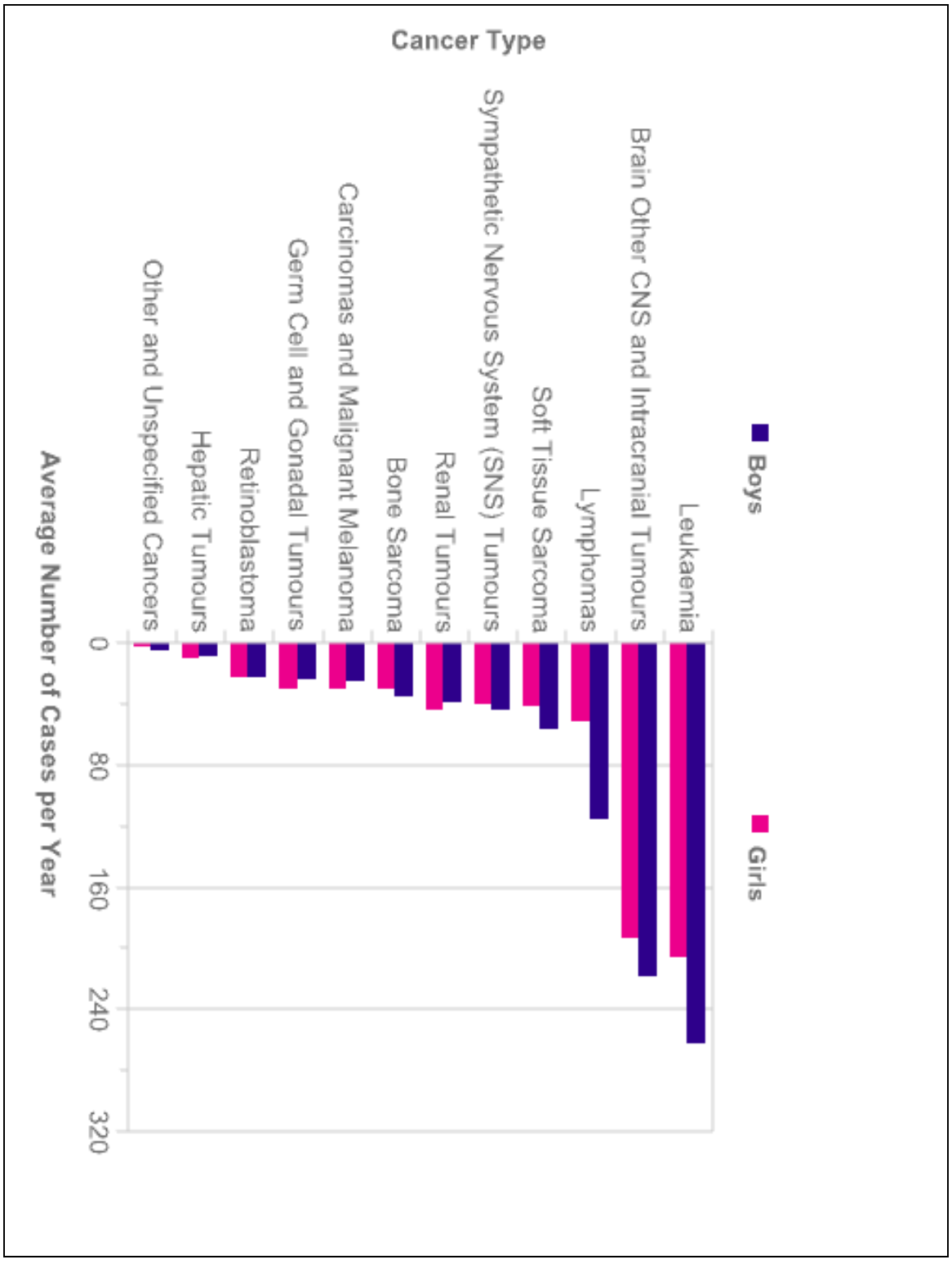
1.1.1 Childhood Cancer – Incidence and survival rates

Annually, 1800 children under 15 and around 2,200 15 to 24-year-olds are diagnosed with cancer every year in the UK (Children with Cancer UK 2018). The 15-24-year age group is referred to as 'teenage and young adult' or 'TYA'. Childhood cancers are classified into cancer types using the International Classification of Childhood Cancer (ICCC) (Steliarova-Foucher 2005) **.

***In this review, the researcher has chosen to include children and TYA groups with cancer (0-24 years) within the term 'childhood' to provide an accurate and extensive representation of all childhood/teenage/young adult specific cancers which may arise until age 24.*

Figure 1 - Childhood cancer incidence by type

(Childhood Cancers by Cancer Type, Average Number of New Cases per Year, Ages 0-14, Great Britain, 2006-2008, Cancer Research UK 2018, accessed on 30th April 2018)



Advances in childhood cancer treatment have evolved dramatically since 1960, where survival rates were less than 30 percent at five years' post treatment (Cancer Research UK 2018). The rise in survival is largely attributed to the introduction of chemotherapy, a greater understanding of the aetiology of cancer and risk stratification methods (Cancer Research 2018). Despite survival rates across all malignancies at around 80% (Children with Cancer UK 2018), there is still a marked variation in survival rates between malignancies such as DIPG or bone cancer (Children with Cancer UK 2018).

Improved survival rates now provide the opportunity for CCS to lead a life that is comparable to the general population, including having a family of their own (Fallat and Hutter 2008, Wallace, Thompson and Anderson 2013).

1.1.2 Biological features of childhood cancer

There are multiple and complex types and subtypes of childhood cancers. Biologically, childhood cancer develops, mutates and reacts differently to treatment than adult cancer; therefore, treatments, dosages, protocols and toxicity of treatments for children vary greatly from adults (Cancer Research UK (CRUK) 2018).

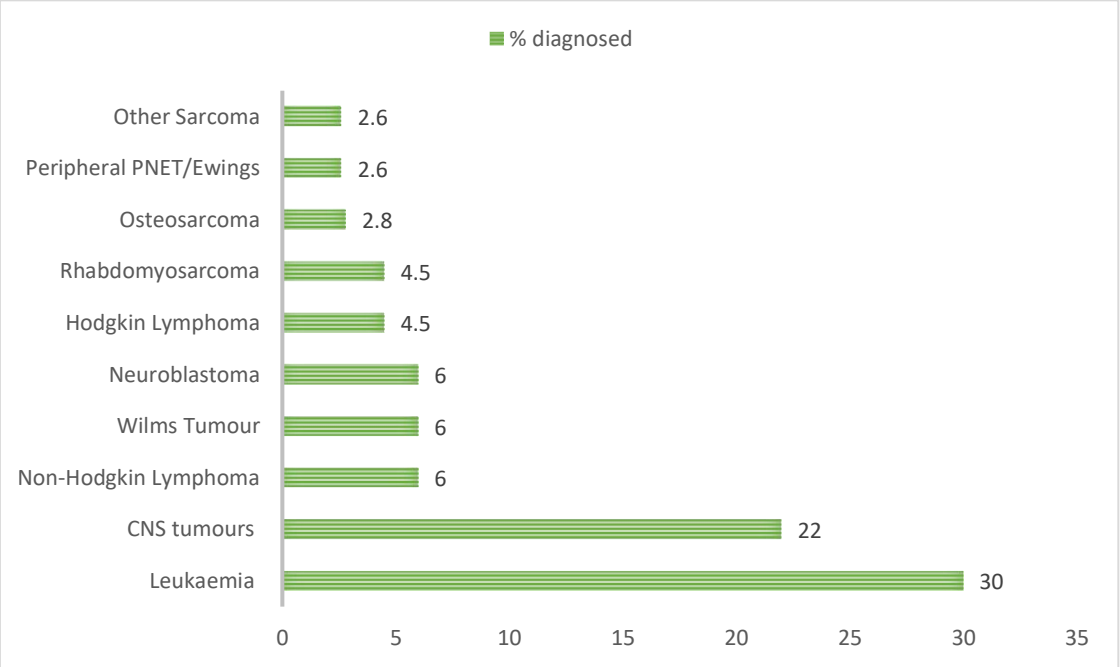
Treatment for childhood cancer typically includes a combination of chemotherapy, radiotherapy, surgery and immunotherapy treatments (CRUK 2018). Chemotherapy works by mutating the deoxyribonucleic acid (DNA) of the child to stop the cancer from replicating (CRUK 2018). Radiotherapy can be used in treatment of targeted areas of the body including the entire chest, abdomen and brain to control disease and prevent relapse (CRUK 2018) and

surgery can include organ removal and amputation. Some childhood cancer treatment protocols also now include autologous or donor bone marrow transplantation and novel immunotherapy treatments (CRUK 2018).

Not all childhood cancers receive all treatment modalities, however almost all receive chemotherapy as a standard treatment (CRUK 2018). The Royal College of Radiologists (RCOR) (source Saunders via RCOR members update 2018) surmises that out of an approximate 1800 new cases of childhood cancer per annum, 40 percent of children will receive radiotherapy (conventional or proton) as part of their treatment (RCOR, source Saunders via RCOR members update 2018). Figure 2 illustrates the percentage of childhood cancer malignancies that are likely to receive radiotherapy as standard treatment:

Figure 2 - Childhood malignancies that receive radiotherapy

(Adapted from Saunders 2015)



The use of radiotherapy to the flank, abdomen or pelvic areas is dependent on the site and type of tumour, the location of any tumour deposits and often sub-classifications related to risk of recurrence and degree of response to other treatments (Saunders 2015).

Tumours that often receive radiotherapy to the flank, abdomen or pelvis include Wilms tumour, neuroblastoma, leukaemia (when total body irradiation is used), Hodgkin lymphoma, sarcomas and germ cell tumours. This list is not exhaustive or exclusive and is dependent on the site of the tumour and/or metastases and the recommended treatment protocols (Saunders 2015).

1.1.3 Biological effects of radiotherapy on the uterus

During puberty, the growth of the uterus commences before the appearance of external sexual characteristics and is not completed until around 7 years after menarche (Teh et al. 2014:2). Radiotherapy delivered to the uterine area in a child that has yet to reach puberty, has been suggested by Revelli et al. (2007) to increase the likelihood of abnormal organ development and growth, increasing likelihood of adverse pregnancy and birth outcomes. The pre-menarche uterus has also been suggested to be more sensitive to radiation-induced adverse effects (Revelli et al. 2007). Larsen et al. (2004) equally supported the view that uterine radiotherapy at a young age reduces adult uterine volume and that the radiotherapy-induced damage is probably irreversible. The timing of treatment and dosages was also suggested to be an important variable for perinatal risk by Signorello et al. (2006), Reulen et al. (2009) and Lie Fong (2010).

Biological indicators of radiotherapy damage to the uterus include decreased uterine blood flow, endometrial and myometrial atrophy, decreased uterine elasticity and uterine fibrosis (Critchley et al. 1992:394). This type of damage to the uterus has been linked to adverse perinatal outcomes (Critchley et al. 1992). It has also been suggested that abnormal placental formation and abnormal conversion of uterine spiral and distal arteries (due to radiotherapy damage), could subsequently increase the risk of abnormal placentation (placenta praevia, percreta or accreta), uterine rupture, miscarriage, preterm and low birth weight babies and cervical insufficiency leading to late miscarriage during pregnancy (Revelli et al. 2007:805, Kalapurakal et al. 2004:1366, Critchley et al. 1992:395). Signorello et al. (2006) further supports these findings by linking female CCS treated with flank, abdominal and pelvic radiotherapy with an increased risk of premature delivery, miscarriage, stillbirth and delivering low birth weight babies.

Reulen et al. (2009:2245) reported that although pregnancy rates of CCS were found to be less than sibling and general population controls and that they produced fewer offspring in total, female CCS, that subsequently became pregnant and who had prior exposure to abdominal radiotherapy, carried a significant biological risk in pregnancy due to increasing myometrial fibrosis of the uterus. This echoes previous research by Revelli et al. (2007), linking abnormal vascular and/or muscular development of the uterus to radiotherapy exposure as a child. Reulen et al. (2009:2243) also linked this abnormal development of the uterine muscles to an increased inability of a female CCS to carry a pregnancy to full term.

Although this evidence is limited and largely out-dated case-study evidence, it strongly suggests that damage caused by radiotherapy might be a key factor to adverse pregnancy and birth outcomes, impacting on the live birth rate and associated adverse outcomes of CCS. As the authors suggest, more research is desperately needed to be conclusive for accurate claims of long-term damage to the uterus caused by radiotherapy and the impact upon female CCS in pregnancy.

1.1.4 Survivorship research – An overview

The population of CCS in society has grown significantly. In 2005 it was reported that 26,000 people in the UK were long-term*** CCS, (CRUK 2018). Children with Cancer UK (2018) also estimate that there are now over 35,000 CCS in the UK and this is growing by 1,300 per year.

Long-term (>5 years post treatment completion) health outcomes of CCS is a rapidly growing area of interest for both CCS, their families and professionals (Aslett et. al 2007:1782). Up to 30 percent of CCS are left with long-term effects caused by either the cancer itself or the treatment required to cure the cancer (Clic Sargent 2016).

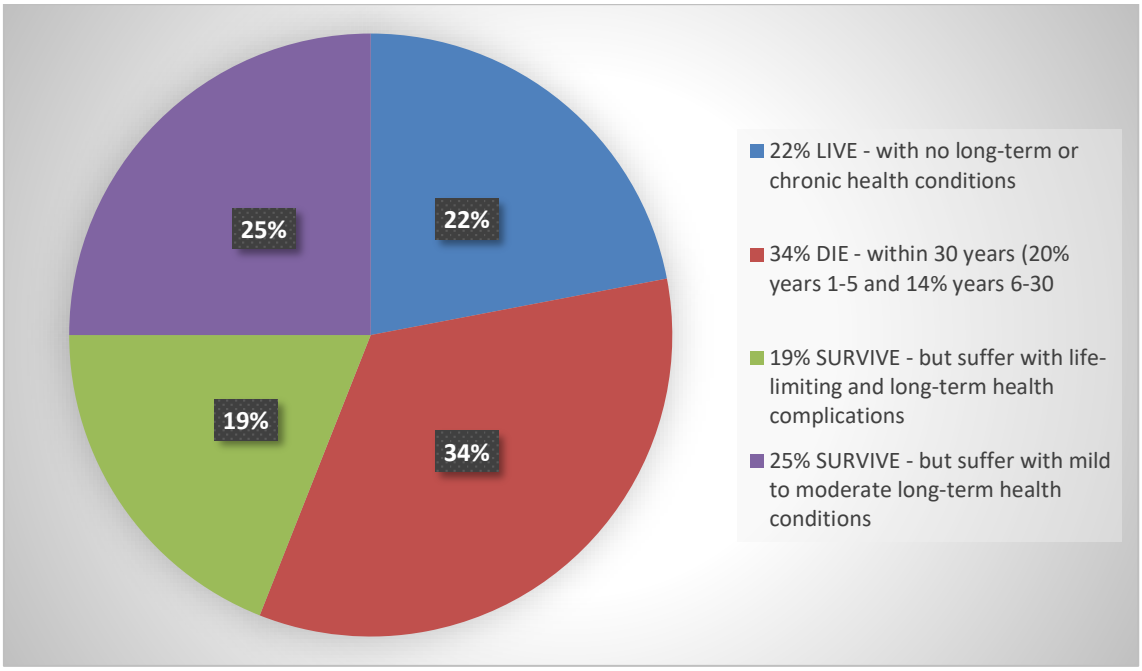
****A Long-term CCS is defined in this review as a survivor of childhood/teenage/young adult cancer still alive >5 years since diagnosis.*

Late effects can include problems with growth, mobility, organ function, fertility, cognition and academic achievement (Aslett 2007:1782). At least two thirds of

CCS develop at least one late-onset treatment-related complication in adulthood (Aslett 2007:1782).

Figure 3 - Long term outcomes CCS

(Reproduced from PAC2 (adapted from Hudson 2013, accessed on 30th April 2018)



Although research into the long-term effects of childhood cancer treatments is an emerging area of interest both in the USA and Europe (Aslett et. al 2007:1782), research into pregnancy outcomes of CCS has been limited. This is despite fertility and pregnancy being reported as a significant concern for CCS and their families (Benedict, Shuk and Ford 2016, Teh et al. 2014).

Research into pregnancy outcomes of CCS has largely compromised of epidemiological studies, which have used small sample sizes; varied greatly in methodological approach, have varied greatly in the selection of patient/control group samples and often contain data which cannot be extrapolated for

treatment modality analysis (Chiarelli et al. 2000, Melin et al. 2015, Meuller et al. 2009 and Winther et al. 2008).

An organisation specifically set up to address issues of CCS (Multidisciplinary, pan-European network for survivors of childhood cancer (PANCARE)), has resulted in an array of international guidelines and published work into long-term health outcomes of CCS, including guidance for antenatal screening and pregnancy care of CCS at risk of heart disease from chemotherapy treatments (Armenian et al. 2015). Despite acknowledging cardiovascular disease as an important issue for CCS in pregnancy, there has not been a guideline published to date addressing the needs of CCS who have received radiotherapy treatment. This is despite several international retrospective cohort studies demonstrating an increased risk of premature delivery and low birth weight babies for female CCS treated with radiotherapy (Signorello et al. 2006, Reulen et al. 2009).

Survivorship research investigating long-term outcomes of CCS is an emerging area if interest for both professionals and CCS, however pregnancy and birth outcomes of CCS has been shown to be an area that requires further work.

1.1.5 Complex health conditions in maternity services

An increasing number of physically complex pregnant women with pre-existing co-morbidities now routinely present for maternity care (NHS England 2016a:3). Specific care pathways to meet the complex medical and psychological needs of women in pregnancy and birth have been published for conditions such as diabetes, epilepsy and women with complex cardiovascular conditions (Smith,

Dixon and Page 2009: 21). These pathways have been successfully introduced into the National Health Service (NHS) with National Institute of Health and Care Excellence (NICE) accreditation and adoption by the Royal College of Midwives (RCM) and Royal College of Obstetricians and Gynaecologists (RCOG). This has allowed for quick clinical implementation and patient impact, optimising care and outcomes for families based upon evidence-based research.

There are no maternity guidelines for the management of care for CCS in pregnancy, or for any women who present with a history of adult cancer (except for breast cancer where a clinical guideline does exist (Dow 2000)). This could be explained by a lack of awareness of specific needs within this rare disease group or a lack high-quality, collated evidence for this issue.

1.2 Rationale for the review

This systematic review and meta-analysis are unique, as no clinician with a maternity or obstetric background has attempted to answer this question with a systematic approach. Despite acknowledgement of data that highlights the increased likelihood of adverse pregnancy outcomes in female CCS, research has been largely conducted by epidemiologists and paediatric oncology specialists. This has led to a lack of clear and focused recommendations when attempting to address exactly what is needed in a maternity care package for female CCS. This review is also the first to include patient and public involvement and engagement (PPIE), which was used to align patient needs or concerns in this area with selected outcomes by the researcher. The researcher has also ensured that PPIE involvement within the dissemination plan and with

a lay-summary for findings is included, which has not been employed into previous systematic review design.

As a midwife by profession, the researcher understands the need for accurate and evidence-based information for maternity care services, empowering women to make informed choices and providing evidence for obstetricians and midwives to enable birth choices and screening choices. The researcher aims to share results from this review not only paediatric oncology care specialists but also maternity organisations and stakeholders, allowing for wider dissemination between clinical specialities with the intent to allow quicker patient impact and implementation of findings. This might allow for further research in this field and an evidence base to support interventional research projects.

The existing evidence suggests that childhood cancer survivorship research is of importance to both health care professionals, researchers and CCS and their families (Benedict, Shuk and Ford 2016, Teh et al. 2014). CCS represent a patient cohort susceptible not only to increased likelihood of co-morbidities throughout the life span (directly attributable to prior cancer treatment), but who are also at an increased likelihood of adverse pregnancy and birth outcome.

Further research into this patient cohort is pertinent for maternity services to enable effective planning of midwifery and obstetric care for female CCS, which improves care and outcomes for CCS and their families.

1.3 Aims and questions for this review

The aim of this research is to search for, evaluate and synthesise the existing data relating to live births of pregnant women who have received flank, abdominal or pelvic radiotherapy as treatment for childhood cancer. The findings will provide clinical and research recommendations based on the evidence to adequately inform both professionals and patients accessing maternity services with a history of childhood cancer.

Table 1 - Aims of the review

Title of the review:	
Female childhood cancer survivors and the impact of flank, abdominal or pelvic radiotherapy on live birth: A systematic review and meta-analysis	
Research questions:	
(1)	What is the impact of flank, abdominal or pelvic radiotherapy for female CCS on live birth outcome and associated adverse pregnancy outcomes?
(2)	Are any associated adverse outcomes in pregnancy and childbirth directly attributable to flank, abdominal or pelvic radiotherapy as a child?
Objectives:	
•	To identify publications that investigate live birth and birth outcome of female CCS that have received radiotherapy to the flank, abdomen or pelvis as part of their treatment as a child
•	To critically appraise the methodological quality of publications
•	To synthesise data from identified publications to establish whether likelihood of live birth and adverse pregnancy outcomes are affected in this patient group and if this is attributable to their radiotherapy treatment as a child
PICO	
P	Childhood cancer survivors
I	Treatment for childhood cancer with radiotherapy to the flank,

	abdomen or pelvic region
C	General Population, siblings or non-exposed control group
O	Live birth

1.4 Outline of the review

This systematic review compromises of six chapters. The PRISMA reporting guidelines for systematic reviews (Moher et al. 2009) have been used to structure and present the review and is included in Appendix 1. However, the researcher notes the use of the PPIE survey is a deviation from this guideline but is a novel element which strengthens the applicability of the findings.

Chapter two explores PPIE in research, rationale for use in this review, methods and results. Chapter three discusses methodological underpinning of the researcher, the steps of the review, including search and selection processes, data management and synthesis. Chapter four presents the results of the review with summary tables, meta-analysis and narrative synthesis of additional outcomes and risk of bias assessment. Chapter five discusses the findings, the researcher's personal learning, scope for further research bringing together methodological limitations, implications for practice and generalisability of findings. Chapter six concludes the discussion and will revisit the research question and aims of the review.

Chapter 2 – Patient and Public Involvement and Engagement

2.1 PPIE in maternity and health care

PPIE in healthcare was introduced to provide a platform for patient opinion, experience and voice to be used as a valuable tool in shaping health care service provision (National Institute of Health Research (NIHR) 2012). It reinforces the ideology of making patients 'partners' in their care and is being prioritised by many health care trusts as an effective way to address key patient concerns through collaborative working (NIHR 2012).

Likewise, PPIE in healthcare research is fast becoming the gold-standard approach to development of patient-centred projects and an integral part to funding applications (NIHR 2012). Cancer is a specialist area that has actively involved survivors, parents and people affected by cancer in their prioritisation of research priorities, project delivery and evaluation of services (e.g. National Cancer Research Institute (NCRI) 2013). Through this approach, long term effects of cancer treatment have emerged as an area of interest for survivors and parents, driving the agenda for future research and international collaborations such as PANCARE SURFUP (Gibson et al. 2005).

Maternity services actively promote a patient and family centred approach to healthcare delivery, making women active partners in their birth choices, antenatal care and in accessing services throughout the peripartum period (NHS England 2016a:5). However, the concept of PPIE in developing research priorities within maternity services is novel and relatively unexplored with only

one example of best practice in the UK (The London Maternity Strategic Clinical Network 2015). Despite the lack of PPIE driven research activity in UK maternity services, midwives have long been strong advocates for women during pregnancy and childbirth and are ideally placed to directly influence the research focus of multi-disciplinary projects and research priorities.

The researcher has attempted to bridge this gap in clinical practice and has lead and developed a maternity based research involvement group called PIPR (Patients Involved in Pregnancy Research) which meets on a bi-monthly basis. The group have contributed to the research priorities in maternity research and been integral to research trial applications within the local trust.

2.2 PPIE in this review

The researcher has a strong background and appreciation for PPIE in research and healthcare provision and utilised the principles of INVOLVE and previous experience of delivery and participation in PPIE groups to adopt a patient-led approach to the alignment of the research outcomes with the use of an online PPIE survey.

This is a rare feature in systematic reviews, which traditionally concentrate on data from existing sources and research questions and aims are researcher driven. However, clinical academic researchers are encouraged to prioritise the needs and views of the patients in their research to allow for faster translational impact into clinical practice (NIHR 2012). This is an approach supported by the James Lind Alliance, who set priorities for key areas of health care. They use a priority setting partnership model with multi-disciplinary and multi-stakeholder

groups to prioritise research questions which are of direct relevance and potential benefit to patients and the clinicians who treat them (James Lind Alliance 2018).

> "The idea of bringing together clinicians, patients and carers to discuss research priorities seems obvious – why shouldn't all those affected have a chance to jointly discuss frustrations about the things we don't know, and aspirations for the future?"

(Ekkeshis 2018 (Quoted in James Lind Alliance 2018)

The researcher was keen to incorporate past personal experience of being involved in PPIE initiatives into the design of the review. A PPIE survey was created to gauge survivor's thoughts about the topic and the important issues they face as survivors of childhood cancer related to pregnancy, fertility and birth. The researcher wanted to align the outcomes selected for the review with the priorities of the survivors and involve PPIE groups into the plans for dissemination to ensure that full impact of findings can be shared with those who they affect.

2.3 The PPIE Survey

2.3.1 Aims and approach

Table 2 - Aims of PPIE survey

To verify justification of the review with CCS and their families
To evaluate and reinforce the primary and secondary outcomes of the review
To ensure the outcomes reflected the concerns and priorities identified by CCS and their families

PPIE was not used to formulate the research question or selection of search terms as this had already been selected by the researcher using the PICO tool

and in the scoping review. The survey was also used to identify existing knowledge surrounding any possible implications for pregnancy and birth following radiotherapy and how this had been communicated to them.

PPIE was aligned with the dissemination plan for the review, to allow wide communication of findings to all stakeholder groups including participants of the PPIE survey upon completion.

2.3.2 Methods

An online anonymous survey was sent to CCS (aged ≥16 years old), survivors who have had their own children and parents of survivors who have yet to have children. They were asked to complete a short survey to help identify and rank importance of a variety of selected outcomes used in this review. *Qualtrics* Survey tool was used to design the survey (Appendix 2) as a secure and easy to use format. Questions to assess background demographic information and a ranked question style were used and results subsequently compared to the selection of the primary and secondary outcomes used for the review.

Participants for the PPIE survey were approached by the researcher using existing links to affected groups and social media platforms. Parent and survivor groups (My Kid has cancer support group, Wilms Tumour parents support group, Make September Gold for Childhood Cancer Awareness page, Childhood Cancer International Survivors Group, Twitter) and charity groups with access to parents of children with cancer (Childhood cancer and Leukaemia Group, Childhood Cancer Parents Alliance) were all approached. IRAS or NHS ethics was not required for this purpose and participation was

entirely voluntary, anonymous and participants had the option to withdraw at any time by emailing or telephoning the researcher within two weeks of participation.

2.3.3 Results of the PPIE survey

The PPIE survey used in this review was answered by 24 participants. Not all the questions were answered, however sufficient responses were given to support the outcomes used in this review.

The background of the participants was primarily parents of children that have had cancer (19 out of 23) (Figure 4). Interestingly, three of the responses were from CCS that have already had a child. Only one participant failed to answer this question. Out of the 24 responses, 16 recorded that they or their child had received radiotherapy to the ‘tummy’ which was the lay term used by the researcher to encompass the target area of the review (Figure 5).

In question four, 16 participants did not know the dosage of radiotherapy given and out of the seven that did or who selected ‘maybe’, only three could accurately record a figure (Gy) (Figure 6 and Table 3). This finding supports research by Green et al. (2010:2827) suggesting CCS and their parents do not remember or have accurate documentation of treatment dosages to be able to effectively answer patient reported outcome research questions.

Figure 4 - Q2 What is your background?

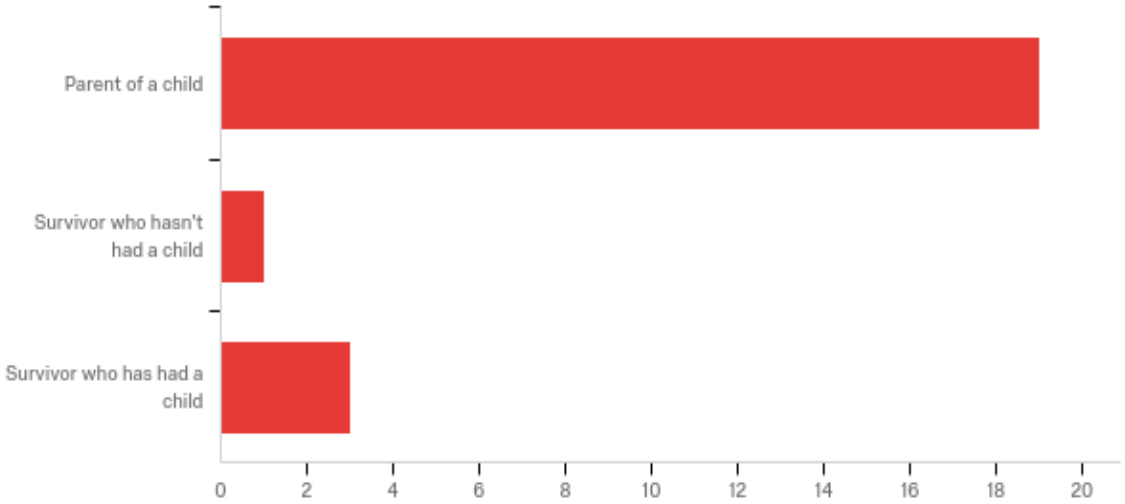


Figure 5 -Q3 As part of your/your child's treatment, did you/they receive radiotherapy to the tummy?

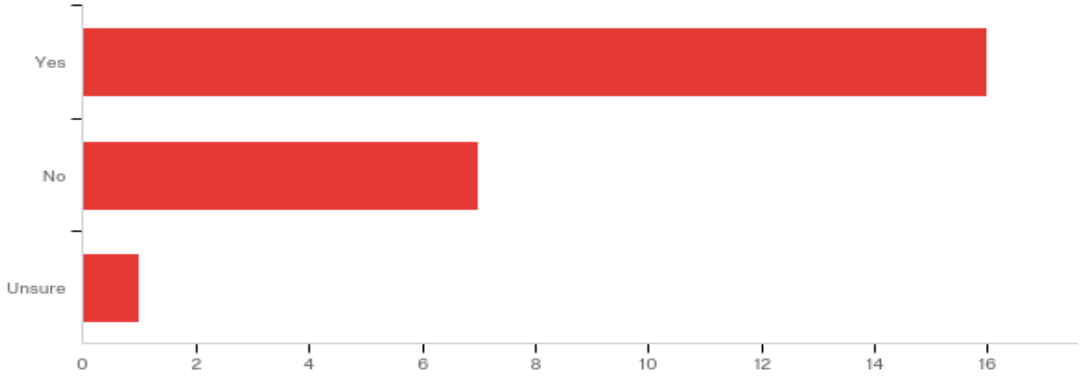


Figure 6 - Q4 - Do you know how much radiotherapy you/your child received?

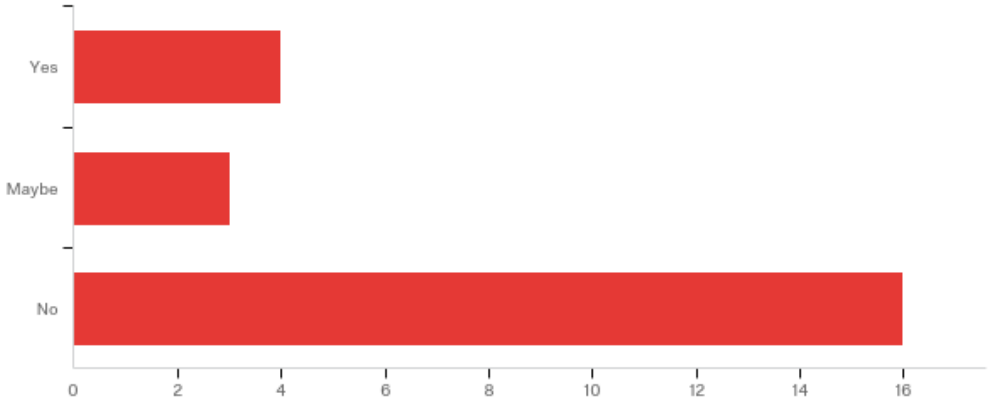


Table 3 - Q5 - If you do know how much radiotherapy was given, please write below (total Gy)

If you do know how much radiotherapy was given, please write below (total Gy)
28 sessions
3600
6 weeks daily doses
64
Total body radiation
15 days
10.80

Only 18 responses were recorded for question six, which depicted an even spread of age of treatment between one to sixteen years old (Figure 7).

Question seven related to awareness of any fertility issues due to cancer treatments as a child and 19 participants recorded that they had been told that 'definitely yes' or 'probably yes' that they or their child would have implications for fertility (ability to have a baby) (Figure 8).

Figure 7 - Q6 - If you/your child received radiotherapy to the tummy, at what age did you/they receive this?

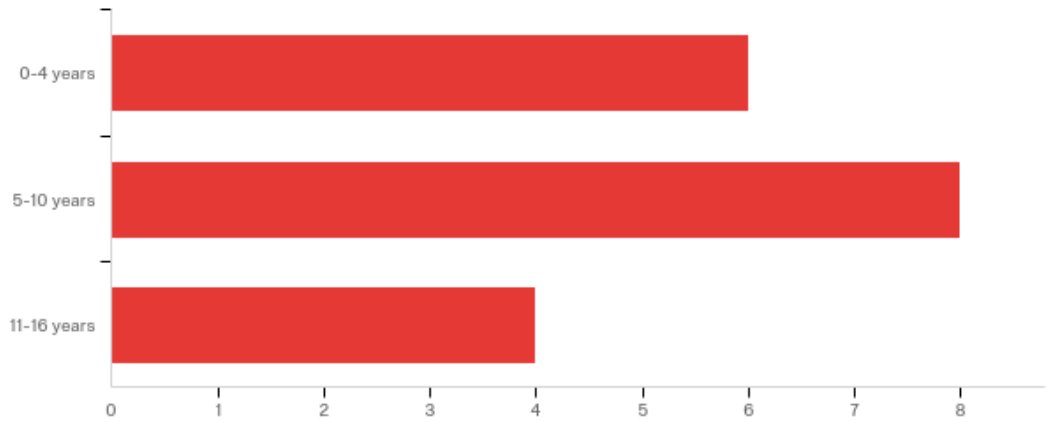
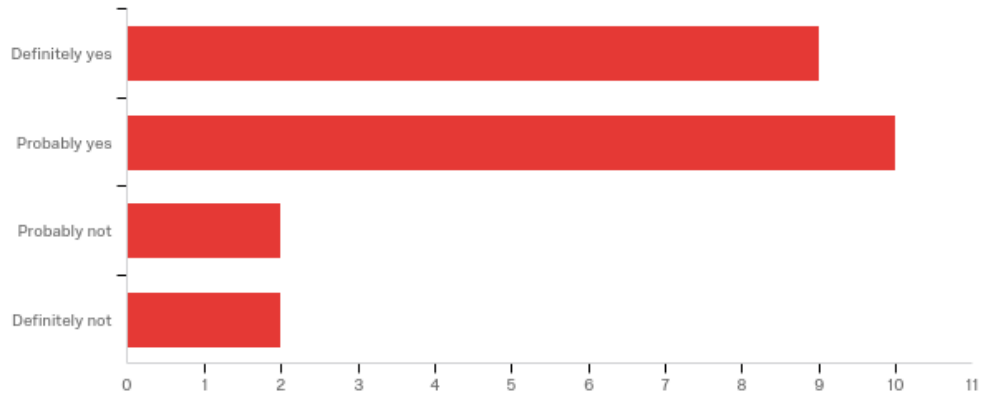


Figure 8 - Q7 - Have you been told that your/your child's treatment for cancer is likely to affect fertility (ability to have a baby)?



In question 8, the participants were asked to rank from most important to least important, what they would be concerned about during a pregnancy of a CCS that has had treatment including radiotherapy, the results ranked in Figure 9:

Figure 9 - PPIE rankings

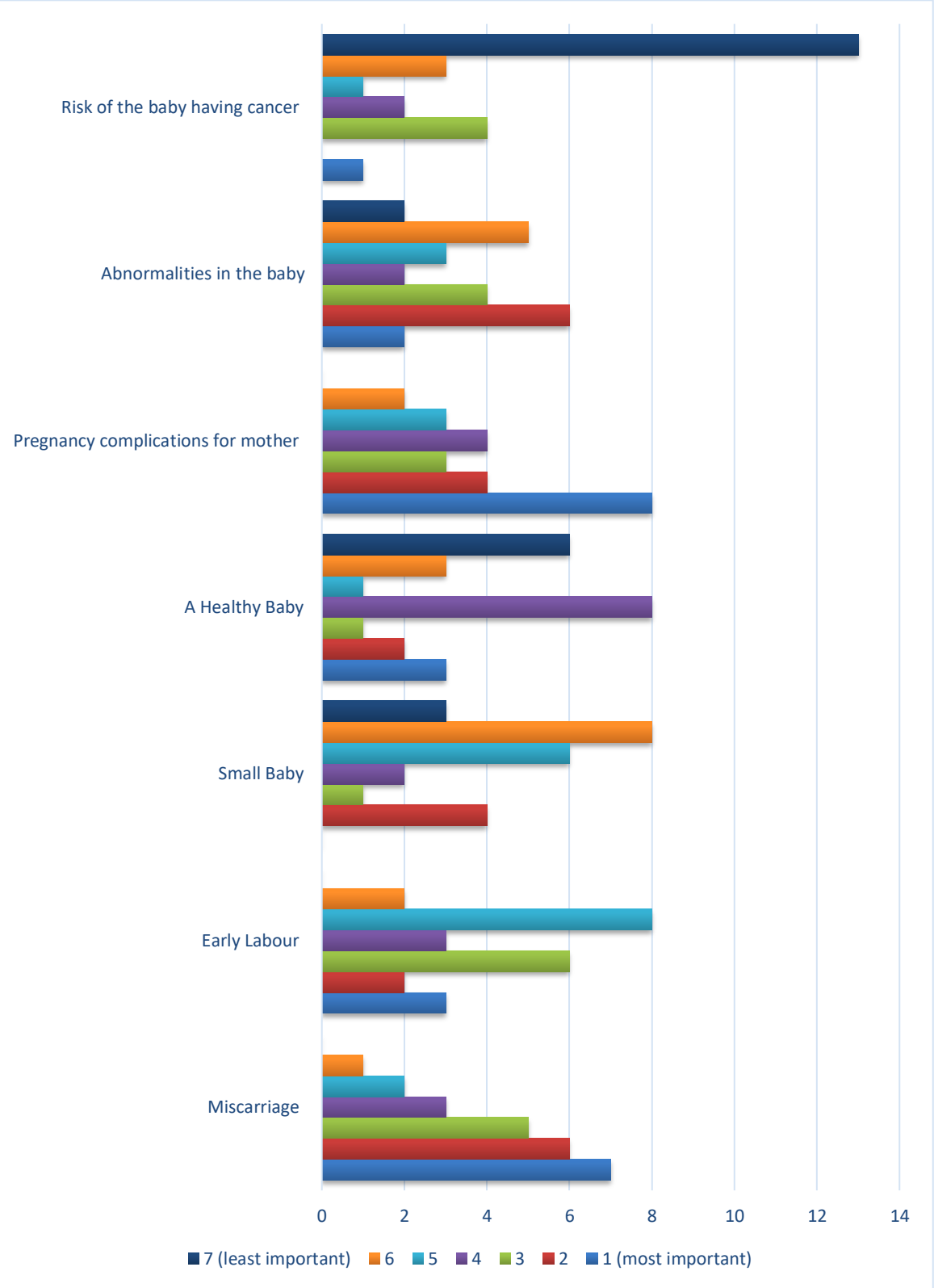


Figure 10 - Most important concern PPIE survey

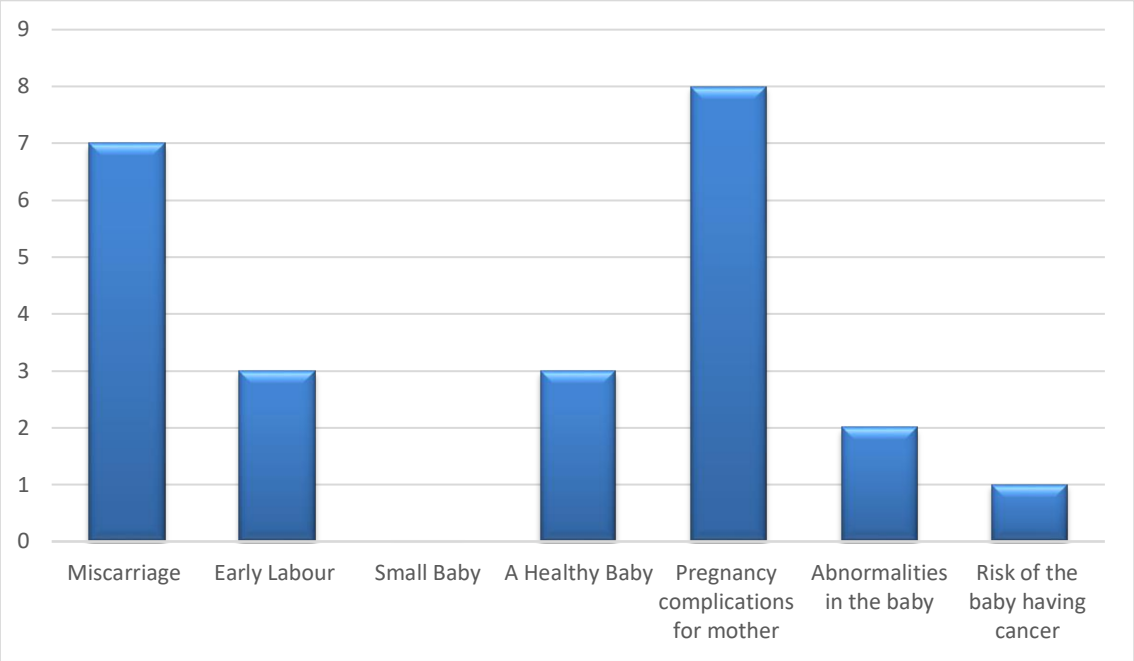
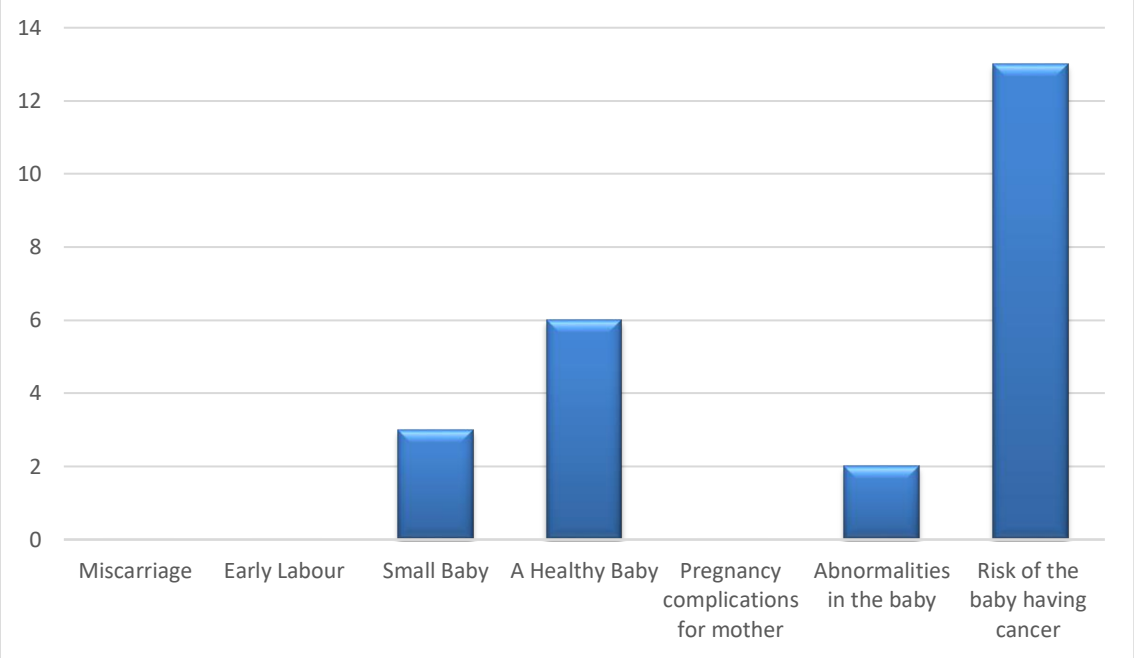


Figure 11 - Least important concern PPIE survey



The remaining questions related to additional concerns not already asked and knowledge of information surrounding the issue (Table 4, Figure 12 and Figure 13). This information will be used for dissemination to professionals in the field

of paediatric oncology and survivorship and taken forward for potential future research projects to ensure that key issues are not overlooked.

Table 4 - Q9 - Are there any other issues during pregnancy or birth that you think might be important?

Are there any other issues during pregnancy or birth that you think might be important?
No
No
Hormonal imbalances
She will be trying ivf with egg donor. Unsure whether womb capable of carrying to full-term. She has lung condition so needs further tests before to see if lungs and heart will cope.
Strain on remaining kidney
I got told I couldn't have children and a traumatic birth
My daughter surviving pregnancy with one kidney and scarring of the abdomen
Hormone issue while pregnant- she would have to conceive via in vitro- radiation ruined her ovaries.
Emotional and psychological effect on mother

Figure 12 - Q10 - Are you aware of any information given to survivors of childhood cancer about pregnancy after treatment has finished?

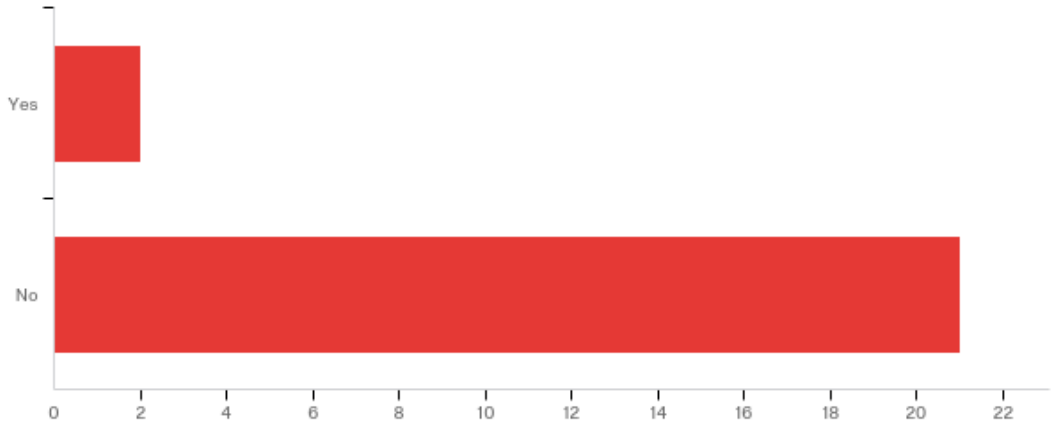
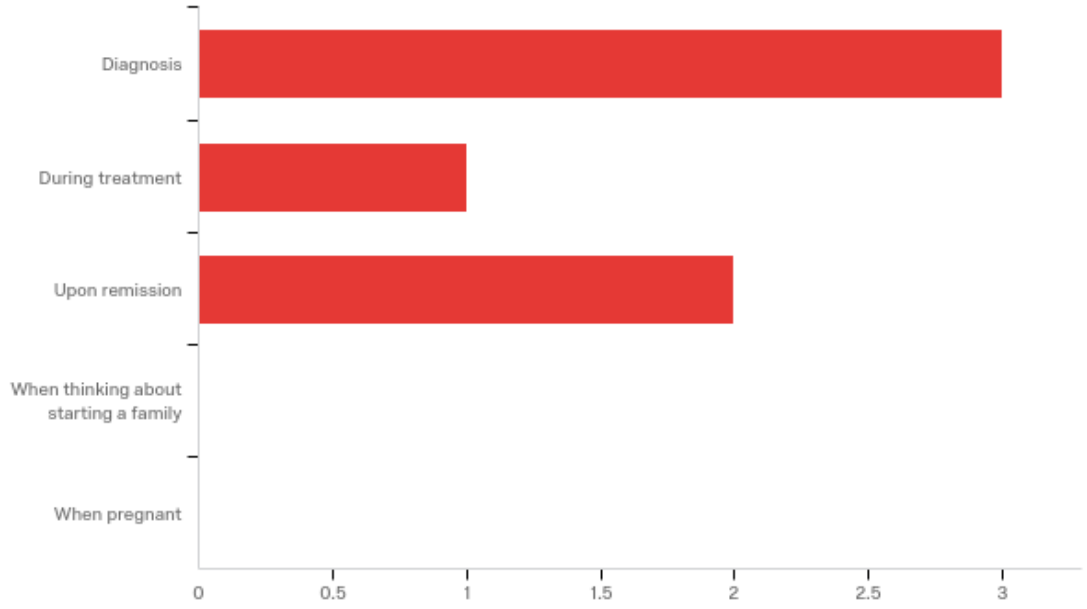


Figure 13 - Q11 - If you/your child have been given such information, at what point were you given this?



2.3.4 PPIE rankings – applicability to the review

The results of the PPIE survey helped to validate the selected outcomes of the review. The three top-ranking concerns by CCS survivors, their parents or CCS that had been pregnant before were identified as:

1. Pregnancy complications of the mother
2. Miscarriage and abnormality in the baby
3. Early labour

The highest-ranking concern was ‘pregnancy complications for mother’ with ‘abnormalities’ ‘miscarriage’ and ‘early labours’ being the next highest-ranking concerns. These outcomes have been included in the secondary outcomes of

the review, therefore reflection of the patient point of view and incorporating patient-verified outcomes into the review have been shown.

The outcome of a live birth was not directly asked to participants, however relates to ‘A healthy baby’ which was ranked fourth in the survey. The outcome of a live birth is assumed as the intended outcome of all pregnancies. The researcher felt it was important to answer the question surrounding ‘a live birth’ and how this might be affected by radiotherapy treatment first and foremost, as this is what the desired outcome of pregnancy is. The selection of the primary outcome is further supported by the fact that live birth has not yet been addressed as a primary outcome in any research paper in this area.

The additional questions provide an insight into possible future research projects, including how CCS and their families should be counselled to the potential odds of long term adverse effects on their health and consideration as to when this information is discussed.

By placing PPIE into a systematic review design, the researcher has demonstrated how PPIE can be integrated into any research design and not simply large scale RCT’s. Dissemination of this patient-based approach will aim to raise awareness and encourage implementation of similar approaches in future research in this field.

The next chapter, Chapter 3 will address the methodology and methods used to conduct the shape and conduct the systematic review following PPIE.

Chapter 3 – Methods

3.1 Scoping review

As part of the review, the researcher used a scoping review of the literature in the chosen topic area, based upon a framework by Arksey and O'Malley (2005). This was used to inform and refine the systematic review protocol and to avoid duplication of any existing review and ensure that sufficient evidence existed in this field of research to allow a systematic review methodological approach.

Scoping reviews help identify appropriate parameters of a review (i.e. define the targeted population, intervention, comparison, outcomes- otherwise known as PICO) and explore terminology to be used in the research topic (Armstrong et al. 2011). Scoping reviews have a great utility for synthesizing research evidence and are often used to map existing literature (Armstrong et al. 2011). Therefore, they are of use when a body of literature has not yet been comprehensively reviewed or exhibits a heterogeneous nature such as in CCS and pregnancy outcomes.

The research question and search terms used for the scoping review were:

Table 5 - PICO for the scoping review

P – Childhood cancer survivors
I – Radiotherapy
C – Nil
O – Pregnancy outcome, birth

Search terms were inputted into Medline and Cinahl databases. The results were collated, and abstract/titles were appraised by the researcher for relevance to the research question and quality appraisal by using the Critical Appraisal Skills Programme (CASP) checklists (CASP 2014), which the researcher was familiar with using.

3.1.1 Findings from the scoping review

The results from the scoping review provided 55,697 studies. Inclusion criteria were then applied that included:

Table 6 - Inclusion criteria (scoping review)

Studies from 2000 onwards
Studies published in the English language
In peer-reviewed journals
Female childhood cancer survivors

This produced 10 results, which verified that there were no randomised controlled trials (RCT's), systematic reviews or UK/European clinical guidelines found for care of CCS treated with radiotherapy in pregnancy and birth. Similarly, no articles that addressed the needs of CCS when accessing obstetric healthcare in the UK were found. The studies identified were in the majority, retrospective cohort-studies based upon large registry data such as the British Childhood Cancer Survivorship Study (BCCSS) (Hawkins et al. 2008) and the American Childhood Cancer Survivorship study (CCSS) (Robison et. al 2009).

The researcher discovered that the Scottish Intercollegiate Guidelines Network (SIGN) have produced one of the most comprehensive resources for CCS for

long-term health risks (Wallace, Thompson and Anderson 2013). They highlighted that pregnancy in a CCS is a risk factor for long-term adverse outcome and recommended that women who have had radiotherapy to an area which includes the uterus, should have pre-conception counselling and be supervised in a high risk obstetric unit (Wallace, Thompson and Anderson 2013). However, this guideline is not specific to maternity service care provision or does not provide any detail as to the level of radiotherapy dosage needed to cause long-term effect.

A resource from data in the CCSS was also discovered, which consisted of a table of outcomes and risks for pregnancy in relation to treatment and cancer type (St Jude Children's Research Hospital 2017). Although this serves as an excellent reference tool, differences in population demographics, health care systems and access to health care in the UK and Europe means that applicability of these outcomes and attributed risks, would be limited in applicability or generalisability to the UK population.

It was evident from the results of the scoping review that pregnancy outcomes of CCS were an important aspect of survivorship research. The scoping review revealed studies which suggested a link between childhood cancer treatment and pre-term labour, restricted intrauterine growth or low birth weight and stillbirth (Reulen et al. 2009: 2246, Wallace, Thompson and Anderson 2013:31, Green et al. 2009:2684). Evidence also pointed to abdominal radiotherapy received as treatment for childhood cancer as the most significant factor relating to adverse outcomes in pregnancy (Signorello et al. 2006, Reulen et al. 2017).

Chemotherapy use, and anthracycline exposure is well documented as having significant long-term risks for cardiovascular disease, heart failure and stroke for CCS (Armenian et al. 2015). Evidence suggests that there is a low risk of complications for women in pregnancy and birth if existing heart disease is not present before pregnancy and does not impact on live birth rates or outcomes (Armenian et al. 2015, Metzger et al. 2013).

Also evident from the existing research, was the impact of childhood cancer treatment on male CCS and their partners. Chow (2009), Green et al. (2003) and Signorello (2010) found no significant adverse effects in fertility or subsequent pregnancy for male CCS or their spouses, therefore, the justification for this review to focus on female CCS and radiotherapy as the main intervention was valid.

3.2 Methodology

3.2.1 Epistemology, Ontology and Paradigm of the research

As the researcher is a midwife by background, it is important to acknowledge and consider any principles, beliefs or assumptions to limit bias and reliability of the research and to support or refute pre-defined conclusions of other researchers when appraising the project (Finlay and Gough 2008).

Research into new cancer treatments and survival rates is traditionally viewed with a positivistic approach. The belief in a diagnosis, cause and effect, data collection, analysis and dissemination to inform which treatment arm or procedure is more effective for survival of patients is aggregative, and therefore suits a quantitative approach. Quantitative researchers believe that data will

confirm or refute a hypothesis, therefore answering a clinical problem, which could lead to improved outcomes for patients. Methodological designs such as interventional; RCT's, Clinical Trial of Investigational Medicinal Product (CTIMP) and placebo designs are common and outcomes such as disease incidence, survival rates or event free time periods are often measured.

In this systematic review, the researcher has adopted a positivistic epistemological standpoint, aligning with the paradigm that accepts knowledge and data to be trustworthy. In such a paradigm, knowledge in the form of an authoritative truth is derived from empirical evidence (Gordon 2016). A positivistic approach is appropriate to the research question of this review as 'knowledge' in this instance, derives from empirical evidence collected by health care professionals regarding treatment outcomes of a patient set (CCS). This knowledge has been collated by the researcher with a quantitative and fact-based approach to provide results which sit within this positivistic paradigm as the results are intended to be viewed with a belief that the data used is trustworthy and represents an overall outcome of a population (CCS) in relation to a treatment they have received as a child.

3.2.2 Systematic review process

There are many types of review, however, a systematic review is regarded as 'gold standard' and is defined by its peer-reviewed protocol, ability to replicate, description of sources used, data synthesis, data extraction tools, meta-analysis (if appropriate) and strict inclusion and exclusion criteria and dissemination of results (Hemingway 2009). Alternative reviews such as narrative reviews,

although providing a way to collate information can be open to bias and may not consider all the evidence to be able to generalise to the population.

Systematic reviews aim to identify, evaluate and summarise the findings of available individual studies, providing evidence that is accessible, translatable and robust (Centre for Reviews and Dissemination 2009:3). This systematic follows the steps recommended by The Centre for Reviews and Dissemination (2009) and uses a PRISMA flow chart to chart search results (see Figure 15). The steps taken by the researcher are further detailed in Figure 14 below.

A lack of a previous systematic review published or registered in female CCS and long-term effects of radiotherapy in pregnancy and birth, highlights the need for a systematic review to be undertaken. A systematic approach is the most appropriate and 'gold-standard' design methodology, to provide high quality research in this field and will ensure replicability, providing a resource which is of a higher quality than individual studies.

Figure 14 - Steps to a systematic review

(Adapted from the University of Minnesota 2017, accessed on 1st February 2018)

3.2.3 The Research Question

The PICO model (Population, Intervention, Comparator, Outcome) (Richardson et al. 1995) was used to define the research question, as it is a well-recognised tool for facilitating the search for clinically relevant evidence in the literature and recommended for reviews of interventions in health care. (Full and exhaustive PICO terms used for the database search can be found in Appendix 3).

Table 7 - PICO for the review

P	Childhood cancer survivors
I	Treatment for childhood cancer with radiotherapy to the flank, abdomen or pelvic region
C	General population, siblings or non-exposed control group
O	Live birth

This led to the development of the following research question:

"With adult survivors of childhood cancer does radiotherapy to the flank, abdomen or pelvis effect term live birth rate?"

This was then further developed to become the title of this review.

3.2.4 Ethical approval

Ethical approval was sought from Coventry University Ethics before commencement of the review. The application was approved on the 15th May 2017 with the project number P46688. A further application was made on the 18th July 2017 due to the nature of the PPIE survey used in the review, which was deemed as needing further approval. The second application was approved on the 4th August 2017 with the project number P60599. (Appendix 4).

3.2.5 Protocol and registration

This protocol for this review was registered on PROSPERO – The international prospective register of systematic reviews following ethical approval from Coventry University on the 30th May 2017 with the identification number CRD42017054533 (Appendix 5). The protocol was updated on PROSPERO on the 23rd March 2018 to reflect changes to the supervisory team and a change to the software programme used for data extraction. The review was marked as complete and re-submitted on the 5th April 2018.

3.3 Search strategy

The search strategy was developed using PICO keywords and medical subject headings (MeSH) (title keywords given to published records). This included text words related to childhood cancer, childhood neoplasms, survivor, radiotherapy and pregnancy/birth. A draft MEDLINE strategy was produced and then adapted to the syntax and subject headings of the other databases and replicated (Appendix 6).

The literature search was limited to the English language due to limited translation resources available. To ensure literature saturation, the reference lists of included studies were scanned and forward cited and back-referenced. Expert opinion was utilised, and any additional articles considered against the inclusion/exclusion criteria.

A search of MEDLINE, PubMed, CINAHL, Google Scholar, Scopus, TRIP and ProQuest databases were searched for articles up until 30th September 2017. The researcher enabled alerts on the databases to include recently published studies from the commencement of the review until 31st October 2017. Any additional identified published studies were analysed against the inclusion criteria and results included if applicable. Google Scholar, due to having vast amounts of articles available was subjected to a pre-screen by the researcher to filter through only the results that fitted the research subject.

The selection of databases was decided by the researcher to reflect the most accurate resources, likely to produce results in this field of research. This selection was confirmed as appropriate and extensive by subject librarians and the supervisory team.

3.3.1 Search terms

Keywords, MESH headings and any additional search terms from the scoping review articles were added to the PICO list used for this review (Appendix 3). Keywords were expanded to include synonyms and alternative definitions for each term of reference. This allowed for differences in language, spelling, medical and lay terms and differences in keywords between databases, i.e. childhood cancer and childhood neoplasms.

3.3.2 Eligibility criteria

Inclusion and exclusion criteria for the studies were as follows (Table 8):

Table 8 - Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	• Females aged >=16 years old • Females who have a history of being diagnosed with childhood cancer (up to age 24) • Population for data will be restricted to recognised data registries from list of included countries	• Men • Surrogates of survivors • Females treated for an adult specific cancer • Females treated for cancer during pregnancy or a birth <1yr from end of treatment • Females who have received fertility treatment or IVF to conceive a pregnancy
Intervention	• Radiotherapy to flank, abdomen and pelvis as part of a treatment plan for childhood cancer	• Radiotherapy to other area including head/neck/extremities etc. • Exclusive surgery as treatment • Exclusive chemotherapy as treatment • Exclusive immunotherapy or proton beam therapy as treatment
Comparator	• General population control • Sibling control • Non-exposed control (non-exposure relates to radiotherapy)	• Nil
Outcome	Primary – • Live birth at term (defined as 37 weeks of completed pregnancy) Secondary – • Pregnancy Outcome (Live birth, miscarriage, stillbirth, neonatal death up to 28 days and intrauterine death) • Premature birth (24 weeks to 36+6 weeks gestation) • Growth restriction (birth weight below 2.5kgs or below 10th centile of predicted growth projection) • Caesarean section rate (elective or emergency) • Onset of labour type (spontaneous, induced or augmented)	• Absence of any of the outcomes listed in the inclusion criteria

	• Uterine dysfunction (defined as delayed first stage requiring syntocinon augmentation and postpartum haemorrhage) • Congenital abnormality	
Setting	• USA, Australia, Canada and EU countries	• Non-EU countries • Other countries not identified as being in the inclusion criteria
Design	• Case-control/Cohort studies • Quantitative methodology	• Qualitative methodology • Grounded theory • Ethnography • Narrative • Phenomenological • Case Study • Thematic analysis • Interpretative phenomenological analysis (IPA) • Mixed methodology • Systematic reviews or reviews
Literature	• Published articles in peer-reviewed journals	• Unpublished articles • Conference presentations • Poster presentations • Expert opinion • Case studies of less than 10 participants
Language	• English	• Non-English
Follow-up	• Any follow-up period	• Nil

3.3.3 Data management

RefWorks was used as the primary software for exporting the documents from the databases to the *EPPI Reviewer4* software in RIS format. Duplicates were not removed upon exportation to *RefWorks* as this was undertaken following export to *EPPI Reviewer4*.

RefWorks is a widely recognised software programme for research and suitable for secure data management. *EPPI Reviewer4* software is a recognised software programme used by the Cochrane Collaborative and is password protected. The software choices allowed for restrictive access to articles and review stages to ensure data extraction, screening and meta-analysis were kept confidential and secure. Both *RefWorks* and *EPPI Reviewer4* allowed checking and removing of duplicates and exportation of references into suitable formats that can be used for future publications.

3.3.4 Selection process

The screening process for studies was carried out electronically using *EPPI Reviewer4* as per inclusion/exclusion criteria:

Table 9 - Review selection stages

Stage 1: Title and abstract screening for inclusion criteria (first reviewer)
Stage 2: Full-text documents in PDF form obtained and uploaded (first reviewer)
Stage 3: Full-text screening against inclusion criteria (first reviewer)
Stage 4: Review and agreement of a random selection of title/abstract papers (10% of total included) and all full-text included studies (second reviewer)

Full text PDF versions were obtained for all studies included for full text screening. Records that were not available via the *ATHENS* gateway or Coventry University gateways were obtained by the researcher via the local trust library ordering system. The PDF versions were then uploaded to *EPPI Reviewer4*.

Discrepancies in screening for title/abstract and full text stage were discussed between reviewers and a consensus was reached. Although a plan to include a third independent reviewer was made, this was not necessary to resolve any discrepancies. Authors of papers were contacted by the researcher if there was insufficient or unclear detail reported in the publication and if no response was received within two weeks, the articles were excluded from the review. All screening decisions were recorded and accounted for and study selection reported as per PRISMA flow diagram guidance (Moher et al. 2009) (Figure 15).

3.4 Data Analysis plan

3.4.1 Data extraction

EPPI Reviewer4 was used to extract data from the included studies alongside a *Microsoft Excel* data sheet to record key patient demographics and outcomes. The *Microsoft Excel* sheet was needed as an additional resource to the software, to assist with an easy visual reference data source for the researcher and second reviewer as the software did not provide an easy to use example of this.

Data extraction headings were created by using a modified Cochrane data extraction template (Appendix 7) and subsequently inputted into *EPPI Reviewer4* software to record features such as cancer type, treatment and dose, age at treatment, ethnic background, and age at pregnancy, adverse events and other key data.

Crude binary data were then extracted from the individual studies for outcomes by the first reviewer using a 2x2 contingency table. If crude data could not be

found in the paper, then the authors were contacted to provide this information. If this could not be provided within two weeks or the author did not respond in this time, then the study was not used for meta-analysis. Data from the binary tables were then transferred to the *EPPI Reviewer4* software for meta-analysis following calculation of odds ratio for each outcome.

Odds ratios (see glossary) were selected as the most appropriate measure for the review due to a more symmetrical representation of the outcome definition, i.e. the odds ratio for outcome Y is the inverse of the odds ratio for the outcome not Y and is representational of each outcome without the need for amending to suit clinical applicability, i.e. applies to premature labour, miscarriage, live birth equally. Risk ratios lack this symmetry, therefore necessitating adjustments to present one risk ratio for outcome Y and another for outcome not Y. However, the researcher accepts that by using odds ratios and not relative risk or risk ratios, then it can be more difficult to translate risk in clinical practice as the 'risk' of an event happening is traditionally discussed in comparison to 'odds' of an event happening. This is usually regardless of the measurement for data used in the original research, despite the clear mathematical differences in calculation.

3.4.2 Synthesis of results

Measures of outcomes from studies were recorded and tabulated and feasibility of meta-analysis considered. To accurately test for statistical heterogeneity, a chi-squared test (also known as χ^2) was used with an I^2 test used to confirm results and ensure rigour of findings. Parameters of I^2 of > 50% and a chi-squared p value of <0.05 were used to identify significant heterogeneity as

recognised standard measures within statistical analysis. A plan for narrative review was made for outcomes deemed too heterogeneous and sub-group analysis was planned for but was not undertaken due to limitation of available studies and heterogeneity in and between included studies. Narrative synthesis was used to summarise and explain the results of each study, quality of the evidence and the relationship of the findings between the included studies.

The narrative review was based upon guidance from Cochrane (Ryan 2013), however did not follow this specific framework. The researcher believed that this approach to presenting key elements of the review combined with the added benefit of applicability to clinical practice demonstrated a more rounded view to the narrative synthesis of findings not applicable for meta-analysis.

3.4.3 Assessment for meta-analysis

Meta-analysis is intended to use statistical methods to summarise the results of combined studies. Data is analysed for strength and consistency of the evidence and investigate reasons for any inconsistencies. The two most common statistical models for meta-analysis are the fixed-effect model and the random effects model (Borenstein et al. 2010:97)

The fixed-effects model represents a one true effect size encompassing all the studies in the analysis. Any differences in effects are presumed to be due to sampling error and the data derives from one population rather than multiple variable populations. A choice of model should reflect the sampling frame and not the test for heterogeneity used (Borenstein et al. 2010:98).

In contrast, the random-effects model follows the belief that true effect size might differ from study to study due to variables in population demographics. Random effects models reflect data where all or some of the model parameters are considered as random variables. In this review the researcher chose to use a random effects model for analysis and chose the headings of 'binary odds' to represent the type of data included by studies and to reflect the variety of geographical locations and population variances in the data.

Assessment and suitability of the included papers for meta-analysis was made by the researcher and confirmed by the second reviewer. An initial consideration of clinical homogeneity was undertaken by the researcher with guidance from the supervisory team, by deciding if there were not more than three of the same outcomes from included studies that matched a control group (sibling, general population or non-exposed CCS), then meta-analysis would not be possible to do with the software.

Following this assessment, *EPPI Reviewer4* software was used to run the meta-analysis for the following outcomes of:

Table 10 - Meta-analysis outcomes

Live birth (non-exposed CCS and sibling)
Miscarriage (non-exposed CCS)
Pre-mature birth (non-exposed CCS)
Stillbirth (non-exposed CCS)

The researcher was assisted by supervisory team to assess for final inclusion based upon the outcome of statistical pre-defined heterogeneity markers and by

assessment of a forest plot visualisation to determine if the overlap was in favour of effect or non-effect of the intervention (radiotherapy to the flank, abdomen or pelvis). Once meta-analysis was completed, if there were multiple outliers, the spread was too broad or not to one side of the scale, significant statistical heterogeneity was considered likely.

3.4.4 Quality appraisal

Quality of the studies and their risk of bias were assessed at the individual study level using a quality index suitable for cohort or case-control studies. For this review, the Newcastle Ottawa Scale was used as a recognised and reputable tool for health care research appraisal of non-randomised studies (Appendix 8). Following data extraction and synthesis, the recommended scoring system was used to categorise studies, with the most robust achieving up to nine stars. They were then classified as ‘good’ ‘fair’ or ‘poor’ quality reflecting selection, comparability and outcome classifications.

Low quality studies can lead to a distortion of the summary effect estimate and it remains a challenge for researchers to find a tool which can critically assess cohort and case-control designs effectively. The NOS is star-based visual tool which works in a similar way to Grade (Guyatt et al. 2008), to give a quick overview of the study for the researcher. The tool used for this review was the cohort study template (Appendix 8).

The researcher aimed to address systematic bias of the review by ensuring the following:

Table 11 - Systematic bias in the review

• Using Cochrane guidance of the steps to a systematic review
• Registering the review on PROSPERO
• The use of an independent reviewer to assess and analyse studies included in the review
• The use of an independent reviewer to second check data extraction and risk of bias
• The use of EPPI Reviewer4 software in the review and meta-analysis

Reporting bias, an important consideration for systematic reviews, was addressed by the researcher in the following ways:

Table 12 - Reporting bias in the review

• All outcomes recorded and tabulated
• Meta-analysis of results and sensitivity analysis considered although high likelihood of extreme heterogeneity
• Use of EPPI Reviewer4 to show all tabulated results
• Limitations of the review discussed
• Conflict of interest of the authors made transparent
• Rationale for the approach and methodology used for the review clear
• Absence of data or any outcomes that were looked for but were not reported by included studies will be reported
• Non-significant results discussed
• Clear plan for dissemination identified by the researcher

3.4.5 Allocation of roles

The second independent reviewer confirmed/disputed inclusion of papers for title and abstract screening. As recommended in systematic review process

(Centre for Reviews and Dissemination 2009), a random sample of 10 percent of the entire selection was provided to the second reviewer.

The Data collection and extraction process was completed by the first reviewer independently. The second reviewer (external to the supervisory team) then confirmed validity of the data and agreed consensus on all included papers. Any discrepancies were discussed and although planned for, a third independent reviewer was not required for arbitration.

3.5 Protocol amendments

During the review, amendments were noted from the original protocol. These are identified as follows (Table 13):

Table 13 - Protocol amendments

• The inclusion criteria published on PROSPERO stated, “Population for dataset will be restricted to participants of the British Childhood Cancer Survivorship Study”. This was changed to “Population for dataset will be restricted to data from a recognised data registry from the list of included countries” as the researcher accepted that papers would be published outside of the UK/United States of America (USA) and would use alternative data registries
• Exclusion criteria defined as “Radiotherapy to head/neck/extremities i.e. legs” was amended to ‘Radiotherapy to other areas’ to assist clarity for screening purposes for first and second reviewer
• Comparator was amended from “nil” to include general population, siblings or non-exposed control group to allow meta-analysis of data
• Inclusion criteria for studies were amended to exclude systematic reviews and reviews as it was felt that these publications did not provide original raw data. It was also decided that case studies would not be included as this would bias the data due to small sample sizes and results that are not translatable

• The supervisory team was amended during the review; however, this did not affect the researcher's role or the role of the secondary reviewer
• Software choices of *Revman* and *RefWorks* as detailed in the protocol were changed to *EPPI Reviewer4* software programme

3.6 Time management and costs

Costs for the review can be found in Appendix 9. The researcher has conducted the review and meta-analysis as part of a Health Education England (HEE) and NIHR funded Masters by Research Programme at Coventry University. Funding to attend national and international conferences through the Global Researchers Programme at the home institution to support plans for dissemination and impact of the results were also planned for.

The review has followed a time planned approach by use of a Gantt chart (Appendix 10), which was amended during the programme.

3.7 Dissemination and impact

Dissemination for the review is intended with publication in peer-reviewed publications and journals and via conference and poster submissions. Outputs will be promoted on social media platforms and the review will be made public on Research Gate, Research Fish and to the NIHR. Pre-existing links with specialists in the field will be maintained and the results from the review shared amongst interested parties/collaborators for future projects and specialists in this area. The review will also be published on PROSPERO. A lay summary, produced in conjunction with PPIE and CCS/parent groups will be disseminated to local, national and international stakeholders and groups that have an interest in long-term effects and survivorship issues. Contact will also be made

with the midwifery organisations RCM, NMC and RCOG to ensure that results are widely and appropriately disseminated, allowing for clinical impact and awareness of the public.

3.8 Summary

Following the scoping review and construction of the research question, a clear and focussed protocol was published on PROSPERO which enabled a robust systematic review to be undertaken by the researcher. The results of the review will now be presented in the following chapter.

Chapter 4 – Results

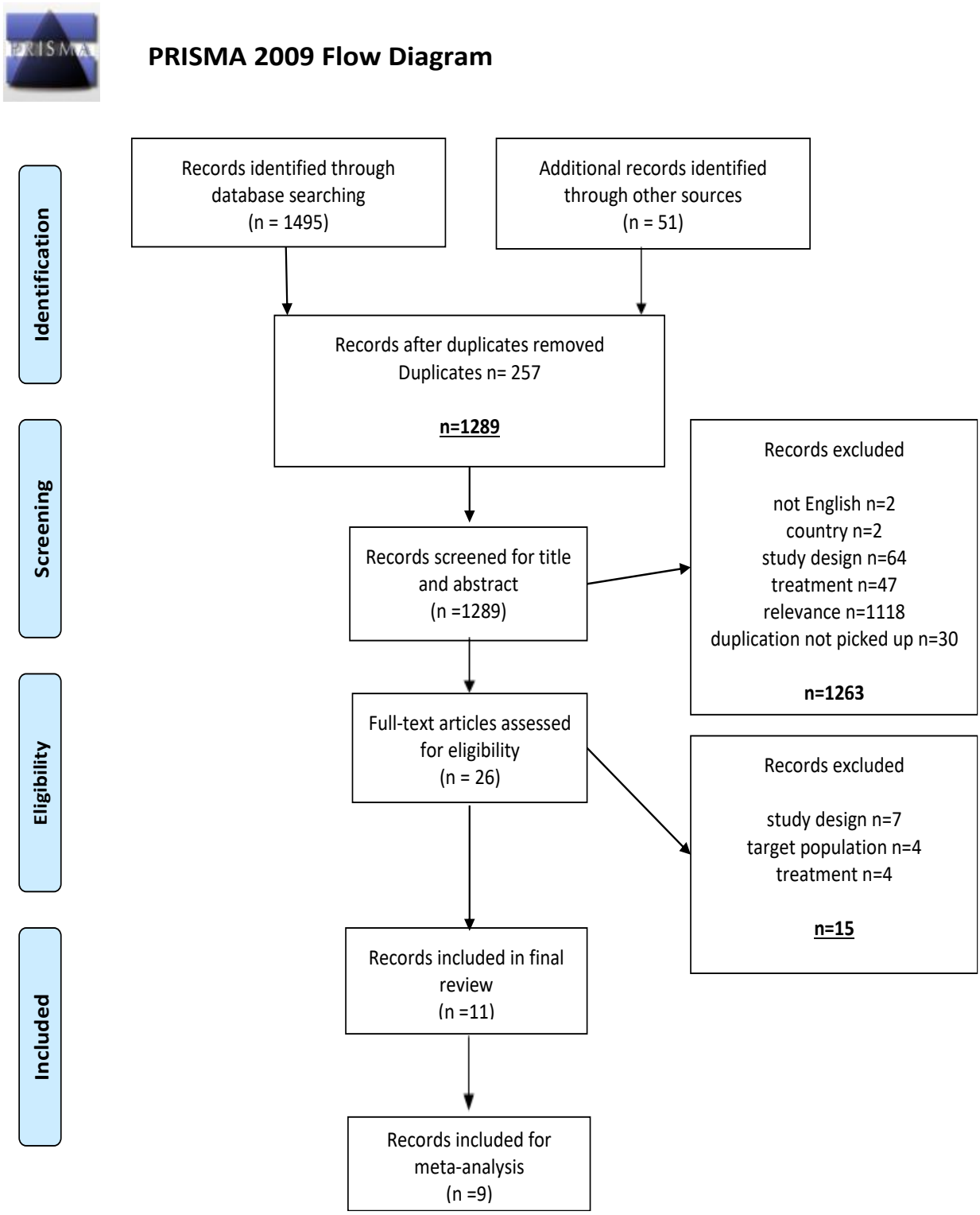
4.1 Introduction

This chapter will present the results of the review, including meta-analysis where data could be extracted, narrative synthesis and an outline to the characteristics and methodological approach of the included papers. Applicability and clinical impact of the results for key findings is also described.

4.2 Results of search

A search of MEDLINE, PubMed, CINAHL, Google Scholar, Scopus, TRIP and ProQuest databases for published records up until 30th September 2017 in the week commencing 14th August 2017. This returned a total of 1495 records taken forward for the screening stage of the review. The PRISMA flow diagram (Figure 15) illustrates the total records and reasons for exclusion.

Figure 15 - PRISMA flow diagram



The diagram shows 51 records were located from other sources. These sources included references and citations from forward citing and back referencing, records used in the scoping review and studies forwarded from specialists in the

field of long term CCS survivorship research with whom the researcher had existing links.

Duplicate checking found 257 records. Despite this step another 30 records were excluded at the title and abstract screening stage due to being duplicates. The researcher was unable to identify why they had been missed in the original scanning action and could not correct the error by adding them manually. After contacting the software owners, the researcher created an exclusion category 'duplicates' to ensure the records were accounted for.

Features which lead to exclusion by the researcher were:

Table 14 - Exclusion features (Screening and abstract stage)

Two records written in another language other than English
Two records originating from a country not in the inclusion criteria (India and South America)
64 records did not fit the inclusion criteria for study design, e.g. conference papers or qualitative methodology
47 records excluded for treatment modality (chemotherapy treatment only or records that reported on populations where treatment modality could not be separated or established)
1118 excluded for relevance to the PICO and research area (e.g. treatment for breast cancer, male CCS and biology focused records)

This left 26 records taken forward for full text screening. At the full-text screening stage the following records were excluded:

Table 15 - Exclusion features (full text stage)

Seven records due to study design (e.g. abstract from conference proceedings or opinion piece)
Four, due to target population (e.g. male and female CCS data unable to be extrapolated or from a data source that was not a recognised registry)
Four, due to treatment modality (radiotherapy was not given or not able to be separated from other data)

This left 11 records for data extraction and risk of bias assessment.

The second reviewer agreed that records taken forward for full text review met the criteria for the inclusion/exclusion restrictions. There were no disagreements. The second reviewer was then allocated the 26 full text records to review for inclusion into the data extraction stage. There were no disagreements at this stage for inclusion and exclusion although two records were marked by the researcher as ‘unsure’ to include as male/female data could not be separated easily, the second reviewer agreed that this should be excluded in line with the exclusion criteria of the review.

Data were extracted using modified Cochrane data extraction template (Appendix 7) headings for the 11 remaining records. Then studies were appraised using the NOS for case-control or cohort studies (Appendix 8). Two records contained data that could not be extracted due to usage of percentages or odds ratio/risk ratio (OR/RR) without raw data. The authors of the studies were contacted by the researcher to provide raw data to be used for meta-analysis, however one author replied to say that he could not access the data any longer and no response was recorded from the other author after two weeks, therefore excluded as per the protocol.

The second reviewer was asked to confirm two records for accuracy of data extraction and risk of bias assessment. The second reviewer also confirmed if two records identified as unsuitable for meta-analysis should be included in the narrative synthesis of the review. The decision was made to include these in the final review but not in the meta-analysis as they fitted the inclusion criteria. This left nine records suitable for meta-analysis.

The final included studies were (Table 16):

Table 16 - Included studies

Chiarelli et al. 2000	Green et al. 2002
Green et al. 2010	Reulen et al. 2017
Lie Fong et al. 2010	Signorello et al. 2006
Reulen et al. 2009	Signorello et al. 2010
Winther et al. 2008	Haggar et al. 2014 (not used for meta-analysis)
Mueller et al. 2009 (not used for meta-analysis)	

4.2.1 Outcomes

Outcomes from the included studies have been tabulated below (Table 17) demonstrating odds ratios of events.

Table 17 - Primary and secondary outcomes from review

Chiarelli et al. 2000	
Perinatal death OR 4.8	Live birth OR 0.85
Low birth weight OR 8.09	Congenital abnormality OR 2.38
Miscarriage OR 0.85	
Green et. al 2002	
Sibling control	
Live birth OR 0.53	Stillbirth OR 1.26
Miscarriage OR 1.43	Abortion OR 1.54
Low birth weight OR 2.64	
Non-exposed CCS control	
Live birth OR 0.91	Miscarriage OR 1.48
Stillbirth OR 1.27	Abortion OR 1.1
Green et. al 2010	
Congenital abnormality OR 1.06	Live birth OR 2.78
Hypertension OR 3.6	Premature labour OR 3.16
Malposition OR 4.06	Obstructed labour OR 1.96
Abnormality of force OR 1.29	Cord complications OR 2.34
Premature birth OR 3.58	PROM OR 1
Reulen et al. 2017	
Hypertension (pre-existing and not) 0.33	Caesarean (emergency and elective) OR 0.16
Live birth OR 0.29	Gestational Diabetes OR 0.36
Anaemia OR 0.21	Growth issues OR 0.14
Post-term OR 0.11	Labour complications OR 0.06
PROM OR 0.09	Malpresentation OR 0.13
	Haemorrhage OR 0.15
Lie Fong et al. 2010	
Congenital abnormality OR 4.67	Low birth weight -1.07 (SMD)
Pre-eclampsia OR 17.07	Manual removal of placenta OR 6.71

The primary outcome, live birth, showed eight studies which reported this as an outcome. Odds ratios have been presented as crude numerical data and not been adjusted for confounders. Therefore, there are slight variations in the odds ratios recorded by the authors of the studies.

4.2.2 Summary tables

In addition to Table 17, a more detailed summary table including study demographic characteristics and outcomes can be found below. The researcher found it necessary to have a separate *Microsoft Excel* spreadsheet outside of the software to have a visual reference for the results as it was felt that the software did not produce this effectively.

Table 18 - Summary table for included studies

Author	Data set	General Information	Cancer type	Cases n=	Control n=	Comparison n=	Control background
Chiarelli et al. 2000	Canada	Publication type - Journal	Not given	97	0	113	CCS exposed vs CCS non-exposed
		Study funding source - public					
		Conflicts of interest - not given					
		Age of participants - 18-49					
		setting of population - community					
		Age at diagnosis - before 20yrs					
		Withdrawals/exclusions - accounted for					
		Patient demographics - yes					
		Control age matched - yes					
Green et al. 2002	USA	Publication type - journal	Sarcoma (soft tissue and bone)	4029	1903	1680 pregnancies	Siblings
		Study funding source - public/academic	Wilms				CCS exposed vs CCS non-exposed
		Conflicts of interest - not given	Hodgkin's lymphoma				
		Age of participants - 16-40+	Neuroblastoma				
		Setting of population - community	Leukaemia				
		Age at diagnosis - <21yrs	Non-Hodgkin's lymphoma				
		Withdrawals/exclusions - accounted for in CCSS	Central nervous system tumours (CNS)				
		Patient demographics - yes					
		Control age matched - no					
Green et al. 2010	USA	publication type - journal	Wilms	312		187	CCS exposed vs CCS non-exposed
		study funding source - public/private/charity/academic					
		conflicts of interest - no					
		age of participants - not given					
		NB - WTLTFU 32.9 +- 5.5 years at follow up.					
		setting of population - community/long term clinic					
		age at diagnosis - not given					
		NB - Wilms known to be cancer of childhood <11 yrs.					
		withdrawals/exclusions - accounted for WTLTFU					
		Patient demographics - no					
		Control age matched - no					
Reulen et al 2017	UK	Publication type - journal	Non-Hodgkin's lymphoma	2783	25000		General population
		Study funding source - academic/private/charity	Wilms				
		Conflicts of interest - no	Hodgkin's lymphoma				
		Age of participants - 16-49 yrs.	Neuroblastoma				
		Setting of population - community	Leukaemia				
		Age at diagnosis - 0-17 yrs.	CNS				
		Withdrawals/exclusions - accounted for	Retinoblastoma (hereditary and non-hereditary)				
		Patient demographics - not given	Bone				
		Control age matched - no	Soft tissue sarcoma				

Lie Fong et al. 2010	Netherlands	Publication type - journal	ALL	40 (6 in RT)	9031		General population
		Study funding source - public	Wilms				
		Conflicts of interest - not given	Hodgkin's lymphoma				
		Age of participants - 26-49yrs	Neuroblastoma				
		Setting of population - community/long term clinic	Sarcoma				
		Age at diagnosis - 0-12yrs	Germ cell				
		Withdrawals/exclusions - accounted for	Langerhans cell histiocytosis (LCH)				
		Patient demographics - not given					
		Control age matched - no					
Signorello et al.2006	USA	Publication type - journal	Leukaemia	1264 (2201 births)	601 (1175 births)		Siblings
		Study funding source - public	Wilms				
		Conflicts of interest - not given	Hodgkin's lymphoma				
		Age of participants - 16-40yrs	Neuroblastoma				
		Setting of population - community	Bone				
		Age at diagnosis - not defined	Sarcoma				
		Withdrawals/exclusions - accounted for in CCSS	Soft tissue sarcoma				
		Patient demographics - not given	Non-Hodgkin's lymphoma				
		Control age matched - no	CNS				
Reulen et al. 2009	UK	Publication type - journal	Non-Hodgkin's lymphoma	509		1422	CCS exposed vs CCS non-exposed
		Study funding source - academic/charity/private	Wilms				
		Conflicts of interest - not given	Hodgkin's lymphoma				
		Age of participants - 16-49yrs	Neuroblastoma				
		Setting of population - community	Leukaemia				
		Age at diagnosis - not given	CNS				
		Withdrawals/exclusions - accounted for	Retinoblastoma (hereditary and non-hereditary)				
		Patient demographics - not given	Bone				
		Age matched control - no	Soft tissue sarcoma				
Signorello et al. 2010	USA	Publication type - journal	leukaemia	1014		596	CCS exposed vs CCS non-exposed
		Study funding source - public/academic	Wilms				
		Conflicts of interest - no	Hodgkin's lymphoma				
		Age of participants - not given	neuroblastoma				
		Age at diagnosis - 0-24yrs	non-Hodgkin's lymphoma				
		Setting of population - community	sarcoma				
		Withdrawals/exclusions - accounted for	bone				
		Patient demographics - not given	soft tissue sarcoma				
		Age matched control - no	CNS				

Winther et al. 2008	Denmark	Publication type - journal	Leukaemia	1688	16700	2737 siblings	General population
		Study funding source - public	Wilms				Siblings
		Conflicts of interest - no	Lymphoma				
		Age of participants - not given (approx. 13-46yrs)	CNS				
		Age at diagnosis - 0-24yrs	Nervous system tumours				
		Setting of population - community	Retinoblastoma				
		Withdrawals/exclusions - not given	Bone tumours				
		Patient demographics - not given	Soft tissue sarcoma				
		Age matched control - yes	Germ cell carcinoma				
Haggar et al. 2014	Australia	Publication type - journal	Leukaemia	1894	4138		General population
		Study funding source - public/academic	Lymphoma				
		Conflicts of interest - no	CNS				
		Age of participants - 16-49yrs	Bone				
		Age at diagnosis - 13-24yrs	Soft tissue sarcoma				
		Setting of population - community	Germ cell				
		Withdrawals/exclusions - not given	Melanoma				
		Patient demographics - not given	Carcinoma				
		Age matched control - yes					
Mueller et al. 2009	USA	Publication type - journal	Leukaemia	1898	14278		General population
		Study funding source - public/academic	Lymphoma				
		Conflicts of interest - no	CNS				
		Age of participants - 16-49yrs	Embryonal (Wilms, neuroblastoma etc.)				
		Age at diagnosis - 0-24yrs	Malignant bone				
		Setting of population - community	Soft tissue sarcoma				
		Withdrawals/exclusions - accounted for	Thyroid				
		Patient demographics - given	Skin carcinoma				
		Age matched control - yes					

Outcome	Crude data results	Crude data results control	Calculated OR	Main findings
Miscarriage	19/78	25/88	0.85	No increase in miscarriage
Perinatal death	4//93	1/112	4.81	No increase in congenital abnormality
Live birth	19/78	25/88	0.85	Radiotherapy CCS more likely LBW infant
Low birth weight	12//63	2//85	8.09	Radiotherapy CCS more likely premature birth and low birth weight babies
Congenital abnormality	4//93	2/111	2.38	Radiotherapy CCS more likely to have neonatal death
SIBLING CONTROL				No significant results in outcome by treatment
Live birth	131/101	1349/554	0.53	Higher risk of miscarriage for CCS with ovarian radiotherapy
Stillbirth	2/230	13/1890	1.26	Radiotherapy CCS more likely to have LBW infant
Miscarriage	46/186	279/1624	1.43	
LBW all CCS vs siblings (not treatment specific)	172/2376	36/1313	2.64	
Abortion	39/193	220/1683	1.54	
NON EXPOSED CONTROL				
Live birth	1472/877	1076/604	0.91	
Miscarriage	463/1886	239/1441	1.48	
Stillbirth	25/2326	14/1666	1.27	
Abortion	460/1889	304/1376	1.1	
Live birth	312/187	187/312	2.78	Increase in LBW and premature labour increased in CCS with radiotherapy
Hypertension	74/425	23/476	3.6	No trend in congenital abnormalities
Premature labour	79/420	28/471	3.16	Increased hypertension, malposition of fetus, increased with radiation dose
Malposition	31/468	8/491	4.06	
Obstructed labour	23/476	12/487	1.96	
Abnormality of force	18/481	14/485	1.29	
Cord complications	77/422	36/463	2.34	
Premature birth	62/437	19/480	3.58	
PROM	11/488	11/488	1	
Congenital abnormality	28/284	16/171	1.06	
Hypertension (pre-existing and not)	101/2682	2508/22492	0.33	3 fold increase in hypertension
Live birth (EXPOSED VS NON-EXPOSED CCS)	326/2457	860/1923	0.29	Increased risk of GDM, anaemia for CCS with radiotherapy
GDM	16/2767	390/24610	0.36	CCS more likely to have caesarean
Anaemia	27/2756	1099/23901	0.21	
Growth issues	24/2759	1431/23569	0.14	
Post-term pregnancy	18/2765	1349/23651	0.11	
Labour complications	127/2656	10448/14552	0.06	
PROM	21/2762	1913/23087	0.09	
Malpresentation	17/2766	1058/23942	0.13	
Caesarean (emergency+elective)	122/2661	5423/19577	0.16	
Haemorrhage	41/2742	2179/22821	0.15	

Congenital abnormality	0//6	145/8834	4.67	Pregnancy outcome not different
Pre-eclampsia	0//6	40/8991	17.07	CCS exposed to abdominal radiotherapy had more preterm and haemorrhage
Birth weight	n=6, mean 2503, SD 1026	n=9031, mean 3271, SD 714	-1.07	Normal birthweight after adjustment for age of CCS babies
Haemorrhage	2//4	449/8232	9.16	
Manual removal	1//5	251/8430	6.71	
Caesarean (emergency+elective)	0//6	1296/7735	0.45	
Gestational age (WEEKS)	n= 34.9, mean 34.9, SD 4.3	n=39.2, mean 39.2, SD 3	-1.15	
Live birth (all CCS vs siblings)	2309/1220	1209/491	0.76	CCS more likely to be premature birth
Livebirth CCS exposed vs non exposed	1116/1085	617/558	0.93	CCS treated with abdominal radiotherapy increased risk of premature birth
Premature birth (RT UTERUS)	252/864	145/1007	2.02	increased risk of small for gestational age and low birth weight CCS
Premature birth (RT OVARY)	172/701	145/1007	1.7	
Premature birth (cumulative)	424/1565	145/1007	1.88	
Low birth weight (RT UTERUS)	106/1026	48/1094	2.35	
Low birth weight (RT OVARY)	65/814	48/1094	1.81	
low birth weight (cumulative)	171/945	48/1094	2.11	
SGA (cumulative) (OVARY AND UTERUS RT)	159/1758	101/1002	0.89	
Live birth	351/158	1048/374	0.79	CCS with radiotherapy at increased risk of preterm and low birth weight
Miscarriage	96/413	209/1213	1.34	Small increased risk of miscarriage
Stillbirth	3/506	7/1415	1.19	Live birth rate 2/3 lower than expected for CCS (particularly abdominal radiotherapy exposed)
Premature delivery	90/419	95/1327	3	
Low birth weight	75/276	77/971	3.42	
Termination	59/450	158/1264	1.04	
Livebirth (ALL CCS VS EXPOSED CCS)	3077/60	4853/93	0.98	CCS exposed to abdominal radiotherapy at increased risk of stillbirth and neonatal death.
Stillbirth/neonatal death	39/3098	21/3116	1.86	

Miscarriage (siblings)	44/413	27989/1718	0.006	CCS increased risk of miscarriage
Live birth (ALL CCS VS POPULATION)	1022/666	19335/2635	0.2	No other differences noted
Stillbirth (ALL CCS VS POPULATION)	5/1683	94/16606	0.52	
UNABLE TO DO META-ANALYSIS DUE TO LACK OF DATA				CCS increased risk of miscarriage
				CCS increased risk of GDM, pre-eclampsia, haemorrhage
				CCS increased risk of caesarean and hospitalisation post-partum
				CCS no excess risk of premature labour, antepartum haemorrhage, PROM
				CCS no increased risk of labour prolongation, retained placenta
				CCS offspring increased risk of premature birth and LBW
				No increase of congenital abnormalities, perinatal deaths
				No increase in growth restriction and neonatal complications
				CCS more likely preterm birth and low birth weight
				CCS no increased risk of congenital abnormalities, neonatal death
				CCS bone cancer increased risk for GDM
				CCS brain tumour increased level of anaemia

4.3 Meta-analysis

Following assessment for suitability of meta-analysis, *EPPI Reviewer4* software was used to conduct the meta-analysis with selection of parameter outputs by the researcher. Outcome type was selected as 'binary: odds ratio', model selection was 'DL (DerSimonian-Laird estimator), significance level was set to 95 and 4 decimal places selected. Confidence intervals and forest plot/funnel plot selections were made which produced the reports for five outcomes:

Table 19 - Meta-analysis report categories

Pre-term labour (control non-exposed CCS group)
Stillbirth (control non-exposed CCS group)
Live birth (control non-exposed CCS group)
Live birth (control sibling group)
Miscarriage (control non-exposed CCS group)

Out of the five meta-analysis reports, three did not meet the criteria for heterogeneity as described in the review protocol (I^2 result of >50% or χ^2 result with a p value significance of <0.05). Two of the meta-analysis reports, pre-term birth and stillbirth met the criteria and was classed as a significant result. Overall odds ratio of having a pre-term birth when exposed to radiotherapy to the flank, abdomen or pelvic area as a child was 3.27 (95% CI 2.71-3.96) with an I^2 result of 0% and a p value χ^2 result of 0. 0.7633. The odds of having a stillbirth was 1.62 (95% CI1.10-2.40) with and I^2 result of 0% and p value χ^2 result of 0.5943. Full reports from the meta-analysis have been provided in Appendix 11. Summaries are included below:

Figure 16 - Pre-term birth CCS vs non-exposed CCS

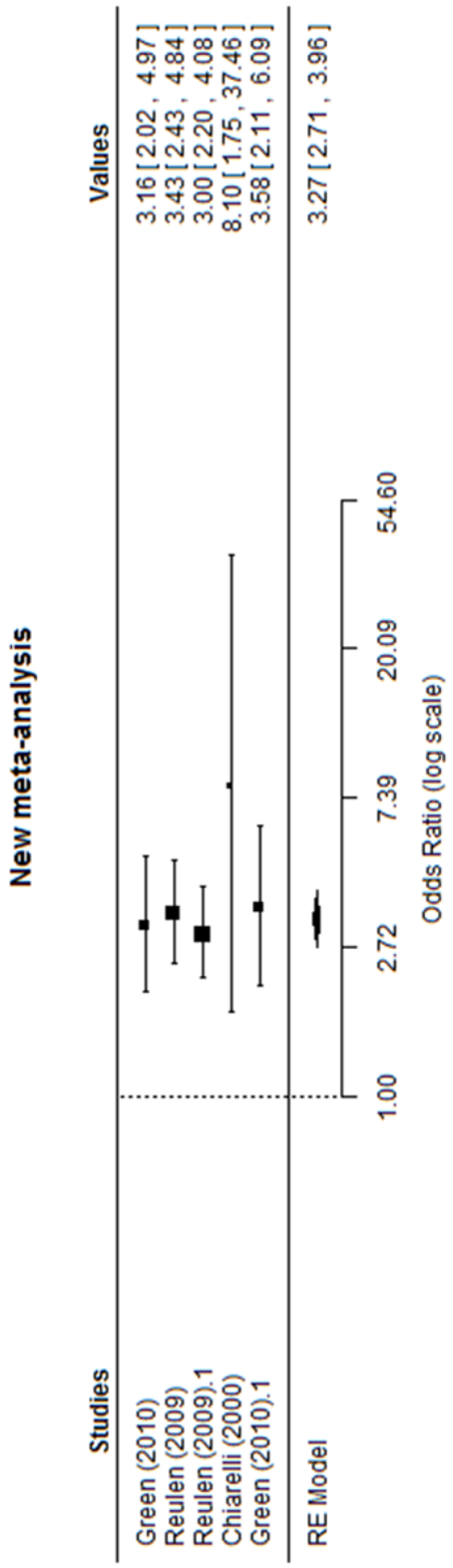


Figure 17 - Stillbirth CCS vs non-exposed CCS

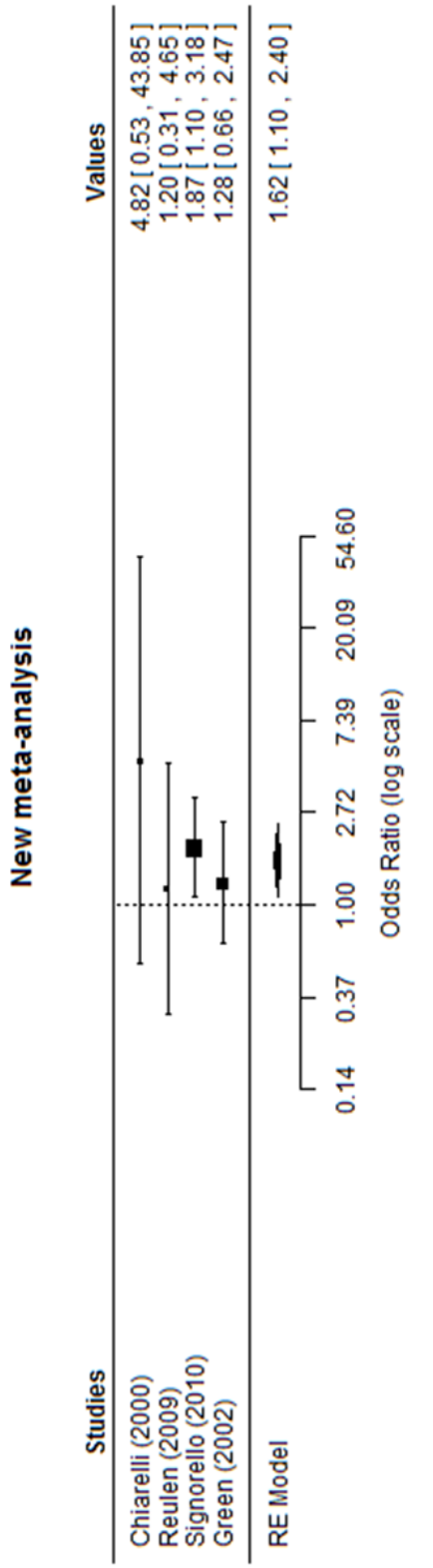


Figure 18 - Live birth CCS vs non-exposed CCS

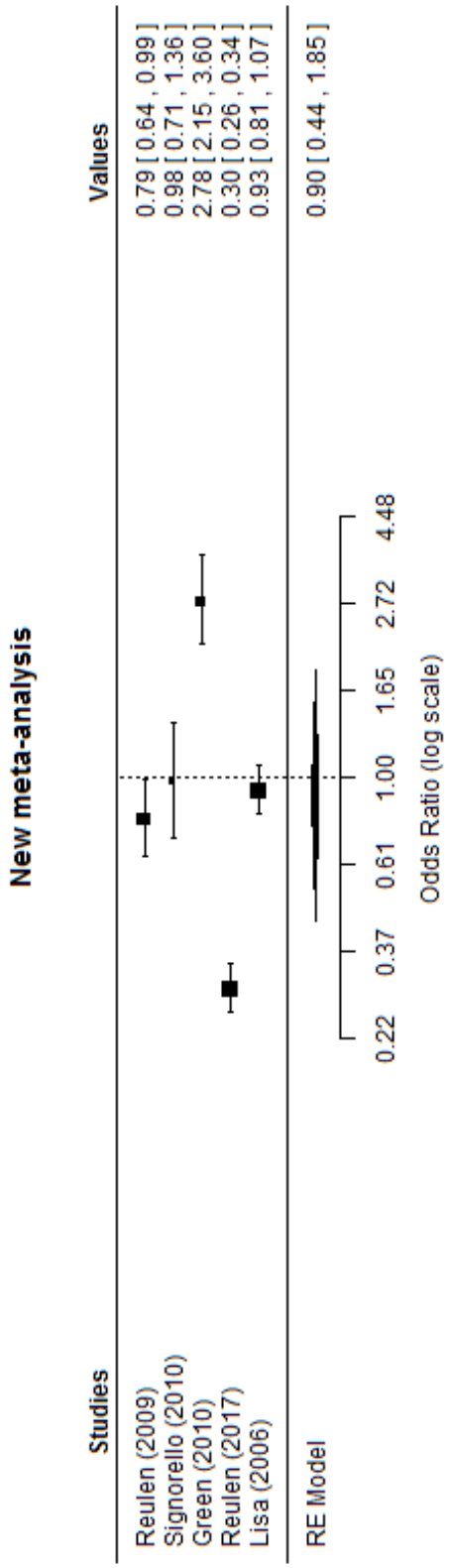


Figure 19 - Live birth CCS vs siblings

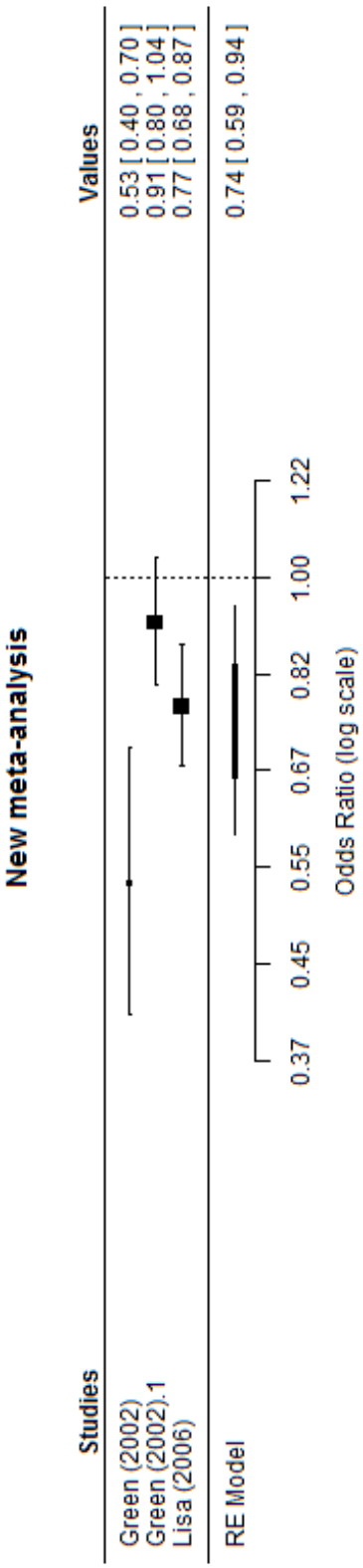
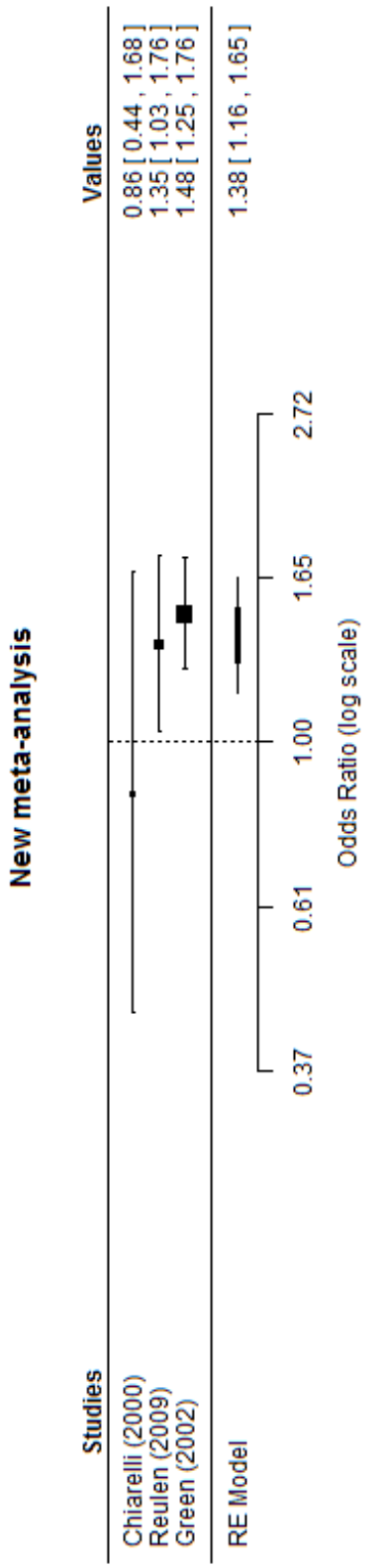


Figure 20 - Miscarriage CCS vs non-exposed CCS



4.3.1 Characteristics of included articles

The included studies included in the review were retrospective cohort studies. The studies utilised established data registries to obtain information, such as the BCCSS and the CCSS. Several studies used medical records to corroborate data provided from patients, however some information was missing.

The included studies were published in peer-reviewed journals, funded with a mixture of academic institutional support and public health grants. Conflict of interest was not declared by any of the included studies; however, five studies did not refer to any conflicts within the text. The age of the participants was not easily found as many authors did not report on the age of the participant upon analysis of the outcomes, however, there was assurance in the inclusion/exclusion criteria and description of the population of the studies that the CCS was post-treatment of at least one to five years and that they were diagnosed in line with the inclusion criteria of the review <24 years.

All original data registry information and citations were checked by the researcher for verification as some authors based their studies on cohorts which are described elsewhere, e.g. BCCSS, CCSS, and WTLTFU. The included studies varied in population size from less than 1000 to more than 34000. Sampling techniques were purposeful and convenience with some studies choosing data linkage techniques to reduce population and sampling bias.

In one study (Green et al. 2010) it was not clear as to the diagnosis age of the CCS to confirm eligibility of the study for inclusion into the review. The author

was contacted by the researcher to confirm that in the patient group used for the study, all CCS were diagnosed before age 24 years. The author confirmed this and provided evidence for the cohort used, this allowed inclusion of the study into the review.

4.3.2 Characteristics of excluded studies

Excluded studies featured patient groups that could not be separated from either their treatment regime or that included collective male and female CCS in the outcome data. Many studies were not relevant to the subject area and included studies of females who had cancer whilst pregnant and fertility or Artificial reproductive treatment (ART) topic focus.

Several excluded studies were found to be conference abstracts, opinion pieces or book chapters upon further investigation and were therefore excluded. One study (Sudour et. al 2010) was excluded at the full text stage of the screening process as the data used did not come from a recognised data registry as specified in the inclusion criteria. The study used hospital records from two state hospitals in France and did not feature a control group. Although methodologically sound, the exclusion criteria for this review states that the data must derive from a recognised resource. France has an existing national childhood cancer registry from which data could have been collated or extracted, however the author did not choose to do this.

Additional features of exclusion included one systematic review, older studies which reported on outcomes but were then superseded by another study using the same data after a period (updated studies were included) and studies where

treatment with radiotherapy to the flank, abdomen or pelvis could not be separated from other areas of the body.

4.3.3 Methodological features of the studies

The included studies were longitudinal retrospective cohort studies. This is the most appropriate design for patient reported and data registry outcomes of this kind as prospective data would prove difficult in terms of length of study and recruitment.

All the included studies used data which had previously been collected by patient reported outcome and hospital treatment records. Consent had been given for future research of this kind by the patients upon recruitment to the registry data study. Therefore, consent was not needed from patients to access their data and treatment history for follow on studies. Chiarelli et. al (2000) recorded their consent process as primary care physicians were approached to consent to sending of information to eligible patients.

Eligibility of the population was confirmed in the exclusion/inclusion criteria of the studies; however, some authors directed the reader to additional data sources such as BCCSS, CCSS to provide further data. All studies used recognised statistical tests and/or software packages to analyse and synthesise data and all but two (Haggar et al. 2014 and Winther et al. 2008) of the studies had clear population demographical data of the affected group and accounted for withdrawals and exclusions within the text.

4.3.4 Control groups

All studies included in the final review had a comparator control group. They were categorised as:

Table 20 - Control group categories

General population (non-cancer match)
Sibling control
CCS who did not receive radiotherapy (non-exposed CCS)

This was to ensure outcome data related to the same type of control. Green et al. 2002, Winther et al. 2008 and Reulen et al. 2009, provided data for two different categories of control (sibling match and general population); therefore, data were recorded for both groups on the data extraction tool.

Sample sizes were of average size and ranged from <1000-3000+ and included a variety of convenience, purposeful (sibling matches) and random (data linkage comparisons from data registry) sampling methods were utilised.

Of the included studies, five studies provided data for exposed versus non-exposed groups and six provided data for the general population or sibling matches. Mueller et al. (2009) and Haggar et al. (2014), despite providing data from the general population comparison groups, could not be taken forward for meta-analysis of data provided due to data extraction problems.

Demographical data were provided for the control group from three authors and the controls were age matched to their affected CCS in three studies. Socioeconomic considerations and parity was recorded by two authors. Type of

cancer, treatment type and age at diagnosis was extracted by the researcher from the studies. Apart from Chiarelli et al. (2000), all authors provided this information. Chiarelli et al. (2000), failed to record the type of cancer of the CCS in the paper.

4.3.5 Risk of bias

The included studies were assessed for risk of bias based upon the Newcastle Ottawa Scale. The ROB results of the studies including the allocation of ‘good’ ‘fair’ or ‘poor’ quality is presented in Appendix 12. Of the included studies, ten were classed as ‘good’ quality and one study classed as ‘poor’ quality (Chiarelli et al. 2000). Out of the studies included in the meta-analysis eight studies were classed as ‘good’ and one classed as ‘poor’.

The researcher made the decision to include the study ranked as ‘poor quality’ (Chiarelli et al. 2000) as the results produced were not reliant on this study for statistical significance. No weighting of studies was used in the analysis and although ranked as ‘poor’ quality, the paper was of sound methodological quality and fitted the inclusion criteria of the review. However, the researcher accepts that this is a limitation or threat to validity as combining studies of poor quality with more rigorous studies may not be useful for recommendations and create a false sense of precision around the truth (Garg, Hackam and Tonelli 2008).

In relation to reporting bias within the findings, there is a risk due to exclusion of unpublished or studies which did not meet the criteria of this review. These studies may hold key data that could be influential to results or that contradicts

results of this review. However, since this is the first systematic review in this area, the researcher does acknowledge this, but is confident that results found are from evidence based and reliable sources subjected to stringent inclusion criteria which is essential for transferability and formulation of clinical recommendations.

There is also a possibility of reporting bias in the results of the studies, with authors choosing to report on the most significant adverse outcomes and not secondary outcomes nor wider clinical data that could be influence and impact upon maternal and child health, e.g. only one author looked into pre-eclampsia, haemorrhage, gestational diabetes or socioeconomic factors such as maternal age at delivery (Reulen et al. 2009, Reulen et al. 2017).

4.4 Narrative synthesis

How narrative syntheses are carried out varies widely, and historically there has been a lack of consensus as to the constituent elements of the approach or the conditions for establishing credibility (Centre for Reviews and Dissemination 2009). Cochrane advises authors to attempt a narrative synthesis that includes investigation of the similarities and the differences between the findings of different studies, as well as exploration of patterns in the data. This might involve examining links between study outcomes and any other factors related to the study design and conduct (Ryan 2013).

Findings from individual studies have been collated to represent outcomes to demonstrate trends of data that would benefit from further research. These

outcomes could not be taken forward due to heterogeneity of control group and classification of outcomes and have been tabulated below:

Table 21 - Common trends narrative synthesis

Congenital abnormality		
Chiarelli et al. 2000	OR 2.38	No increase in congenital abnormality
Green et al. 2010	OR 1.06	No trend
Low birth weight (LBW) infant		
Chiarelli et al. 2000	OR 8.09	CCS more likely LBW infant
Green et al. 2002	OR 2.64	Radiotherapy CCS more likely to have LBW
Green et al. 2010	Not calculated	Increase in LBW increased in RT CCS
Lie Fong et al. 2010	-1.07 (SMD)	Normal birthweight after adjustment for age of CCS babies
Signorello et al. 2006	Uterus OR 2.35 Ovary OR 1.81 Cumulative OR 2.11	Radiotherapy CCS increased risk of LBW
Reulen et al. 2009	OR 3.42	RT CCS increased LBW
Neonatal death		
Chiarelli et al. 2000	OR 4.81	Radiotherapy CCS more likely to have neonatal death
Signorello et al. 2010	OR 1.86	Radiotherapy increased risk of neonatal death.
Maternal complications		
Green et al. 2010	Hypertension OR 3.6 Malposition OR 4.06 Obstructed labour OR 1.96	Increased hypertension, malposition with

	Abnormality of force OR 1.29 PROM OR 1	increasing radiation dose
Reulen et al. 2017	Hypertension OR 0.33 GDM OR 0.36 Anaemia OR 0.21 Post-term pregnancy OR 0.11 labour complications OR 0.06 PROM OR 0.09 Malpresentation OR 0.13 caesarean (emergency+elective) OR 0.16 Hemorrhage OR 0.15	3-fold increase in hypertension, increased risk of GDM, anaemia, caesarean section for CCS who receive radiotherapy
Lie Fong et al. 2010	Pre-eclampsia OR 17.07 Haemorrhage OR 9.16 Manual removal OR 6.71 caesarean (emergency+elective) OR 0.45	pregnancy outcomes not different CCS with radiotherapy had more haemorrhage

The above findings corroborate existing evidence from authors who suggest that CCS who receive radiotherapy are at risk of a variety of maternal complications during pregnancy and birth and neonatal death, low birth weight infants (Reulen et al. 2009: 2246, Wallace, Thompson and Anderson 2013:31, Green et al. 2009:2684). It also supports evidence that congenital abnormalities and genetic effects upon the baby after birth are not linked to childhood cancer treatments (Winther et al. 2009, Boice et al. 2003).

In relation to reporting of the primary outcome of this review, the likelihood of live birth or an effect on live birth rates in the included studies did not feature as a primary outcome in any but was discussed by authors within the discussion part of the studies. This would suggest that further research surrounding live births of female CCS is warranted and that it is an area of interest for researchers and clinicians in this field.

4.5 Applicability to clinical practice

4.5.1 Radiotherapy delivery and toxicity

Loss of fertility is a key issue for younger cancer survivors (Teh et al. 2014:1). Direct irradiation of the ovaries is known to induce ovarian failure in up to 90 percent of women and ovarian treatment thresholds have been well documented with protective treatments such as transposition, shielding, or transplantation offered to try and reduce the risk of radiation-induced ovarian damage (Future Fertility Trust 2018). However, the efficacy of such interventions is variable (Revelli 2007).

Little evidence exists to investigate treatment toxicity thresholds of the uterus as an organ, unlike their ovarian counterparts and implications of dosages and relation to age at delivery is unknown. Larsen et al. (2004) suggested that a direct high dose radiation (>25 Gy) to the uterus in children commonly leads to irreversible damage to both vasculature and muscular function. Sudour et al. (2014) suggests that a dose of below 4Gy appears to be the threshold dose, depending on the associated treatment plan. However, even low doses may

affect future fertility and pregnancy sustainability, but research to support or refute these claims is not apparent (Sudour et al. 2014).

Teh et al. (2014) also agrees that the threshold radiation dose for uterine damage to occur such that pregnancy is not sustainable is unknown and alludes to the suggestion that younger age at uterine radiation leads to greater adverse effects on uterine reproductive capacity, particularly in pre-pubertal girls. This is corroborated by Reulen et. al 2009, Revelli et al. 2007, Sudour et al. 2010 who infer that radiation doses of >25Gy directly to the uterus in childhood appears to induce irreversible damage, however research is so limited in this area that conclusions cannot be carried forward to clinical practice.

An example of a childhood malignancy that receives direct uterine radiotherapy is Wilms tumour. The table below illustrates treatment doses related to stage (Adapted from Saunders 2015).

Table 22 - Radiotherapy treatment dose for Wilms Tumour

Stage II high risk	flank RT: 25.2Gy with a boost of 10.8Gy for extensive residual disease
Stage III intermediate risk	flank RT: 14.4Gy with a boost of 10.8Gy for extensive residual disease
Stage III high risk	flank RT: 25.2Gy with an extensive residual disease boost 10.8Gy
Diffuse intraperitoneal. Spread/major rupture	whole abdomen 20Gy

This example suggests that children treated for Wilms tumour would receive on average close to the 25 Gy marker that is suggested to cause irreversible damage, yet no known communication of this damage, awareness or organ

protection for the uterus in childhood cancer radiotherapy planning exists. Therefore, female CCS and their families are not aware of any potential damage that could be caused from their or their child's treatment, which is unacceptable and demands closer consideration so that families are fully informed of long-term treatment related effects.

Paediatric radiotherapists and paediatric oncologists involved in treatment planning, should be aware of the long-term effects to the uterus caused by radiotherapy and communicate these to CCS and the long-term follow up team. Considerations to protect the uterus at the time of delivery or a more precise method of delivery which does not adversely affect reoccurrence or survival could be introduced to protect long-term pregnancy adverse outcomes.

4.5.2 Pregnancy rates of CCS and live birth

Pregnancy rates of CCS, have been found to be less than the general population and in sibling comparator groups by Reulen et al. (2009:2245). This provides insight into the non-significant result for the primary outcome of live birth in this review. If the pregnancy rates themselves are reduced in an already small population, then the effect size may be too small to accurately predict or measure an effect or non-effect. This is often known as a type II reporting error where a non-effect may be found, but this is due to bias within the data and the population size (Lieberman and Cunningham 2009)

Reporting bias is an important factor to results and relates to the under-reporting or non-reporting of all outcomes as authors favour to report outcomes which show adverse effect. Live birth would be a positive outcome for a CCS,

therefore it would not be considered as a reportable outcome for assessment of effect on adverse outcome. In the papers included in the review, although live birth was measured in eight of them, the researcher did encounter difficulty in extracting data for live birth. This suggests that more longitudinal prospective design research project is needed investigating this outcome with adequately powered sample sizes to determine exact effect or non-effect.

4.5.3 Pre-term birth

A pre-term birth occurs before the 37th week of pregnancy and carries an incidence rate of 60,000 per year in the UK. The UK has a pre-term birth rate of 7-8% of all pregnancies, higher than most European counterparts (Tommy's 2018a). Pre-term infants are at an increased risk of long-term illness, disability and death which directly correlates to the gestation at which they are born. Some pre-term births are planned due to pregnancy complications (iatrogenic), however the rate of pre-term birth from spontaneous pre-term labour is an issue for health care providers in the UK.

Prevention of pre-term birth is defined as one of the key strategic priorities in obstetrics and carries great economic and health care implications for health care services in the UK (NICE 2015:2). The best intervention for the prevention of pre-term birth is still unclear despite vast research in this area to try and attempt to answer the question as to what causes pre-term birth (World Health Organisation 2018).

Risk stratification is key to ensure that woman at an increased risk of pre-term birth are referred for high-risk obstetric care and receive a detailed pregnancy

plan including screening and interventional planning to avoid a pre-term birth. Pre-term birth carries significant maternal and fetal mortality and morbidity risk, with the costs of caring for pre-term infants reaching approximately one billion pounds per year in England and Wales (Tommy's 2018a). Tests such as the 'fetal fibronectin' test have assisted with the prediction if pre-term labour and birth are likely to occur in the next 24 hours. However, obstetric professionals, researchers and health care professionals still do not know what causes pre-term labour (Tommy's 2018a).

Table 23 - Current risk factors for pre-term birth

(Adapted from NICE 2015)

Clinical History	Imaging
History of mid-trimester loss	Short cervix <25mm on transvaginal ultrasound
PPROM in previous pregnancy	Cervical funnelling
Previous pre-term birth	
History of cervical treatment for cervical intraepithelial neoplasia	
Multiple births	

NICE, the leading body for health care guidelines, recommends identification of women at risk of pre-term labour, surveillance and intervention to ensure optimal outcomes (NICE 2015). Treatment with radiotherapy or a history of childhood cancer is not featured in this list, nor is a broader patient history of cancer treatment. This is a gap in risk stratification highlighted by the significant results of this review that could adversely affect the outcomes for both mother and baby with this patient history if not addressed and recognised.

4.5.4 Stillbirth

When a baby dies after 24 weeks of pregnancy it is defined as a stillbirth. Before this gestation it is called a late miscarriage or miscarriage. Some authors also report this outcome as ‘spontaneous abortion’. In the UK there are 3,430 stillbirths each year which equates to nine per day (Tommy’s 2018b). Like pre-term birth, often the cause is unknown, however risk factors exist, and health care professionals seek to identify and raise awareness of the risks of stillbirth to prevent and increase surveillance during pregnancy. The highest population attributed risk factor associated with stillbirth is fetal growth restriction (Gardosi 2013). Although fetal growth restriction was not identified as a significant result in this review, perhaps due to reporting and classification variances and non-measurement of this outcome preventing meta-analysis. Stillbirth however, was found to be at increased odds for female CCS who have been treated with radiotherapy to the flank, abdomen or pelvic areas as children, therefore assessment of growth restriction is an important variable that needs to be considered in future research.

Saving Babies’ Lives (NHS England 2016b) is a care bundle aimed at health care professionals to enable a reduction in stillbirths in the UK and highlights the issue as a priority for the NHS. An algorithm was produced to detail risk factors for pregnancies with classifications of ‘low’ and ‘high’ risk (Appendix 13). This guidance does not include any information relating to prior treatment as a child with radiotherapy for cancer or even a broader history of cancer before pregnancy. This again illustrates that the results of this review can be used to

highlight and acknowledge a significant impact upon neonatal health of a patient group which has not been acknowledged previously.

4.6 Relevance to research question

The research questions asked in this review are:

(1) What is the impact of flank, abdominal or pelvic radiotherapy for female CCS on live birth outcome and associated adverse pregnancy outcomes?

(2) Are any associated adverse outcomes in pregnancy and childbirth directly attributable to flank, abdominal or pelvic radiotherapy as a child?

From the results of the systematic review, a significant result to suggest impact on likelihood of live birth for CCS treated with radiotherapy to the flank, abdomen or pelvic regions could not be found. However, due to heterogeneous results, non-reporting of the primary outcome or inability to extract raw data, a conclusion that this is not a significant factor for CCS cannot be justified.

A statistically significant result linking risk of pre-term birth to radiotherapy treatment as a child to the flank, abdomen and pelvic regions with an odds ratio of 3.27 (95% CI 2.71-3.96) was found, which supports previous studies by Reulen et al. (2017), Green et al. (2010) and Signorello et al. (2006). Equally a significant result was found linking stillbirth to this patient group with an odds ratio of 1.62 (95% CI1.10-2.40) supporting previous research by Signorello et al. 2010. This demonstrates that female CCS who have received radiotherapy to the flank, abdomen and pelvic regions are at increased odds of adverse outcomes in pregnancy. This finding warrants further research into additional

adverse effects and a clinical need for interventional planning by obstetric professionals and paediatric oncologists to ensure optimal care and outcome for this patient group.

4.7 Summary

This chapter has presented the results of the systematic review, meta-analysis in the context of the characteristics, metalogical rigour and the applicability to both radiotherapy and pregnancy care.

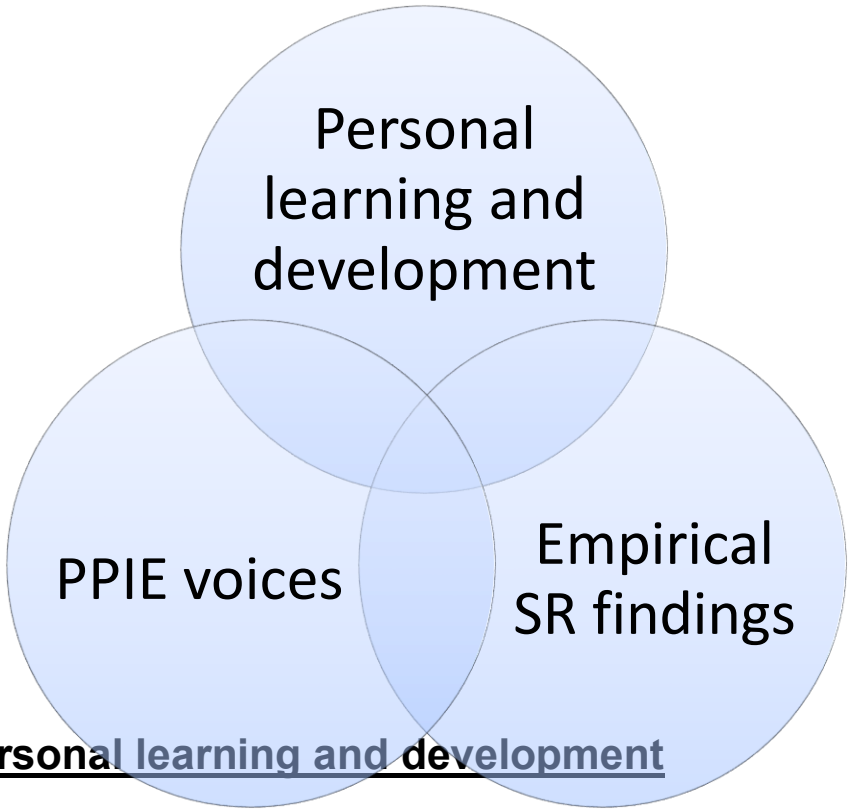
Chapter five will draw together the results of the review alongside personal learning, the impact of PPIE in the review and provide a synthesised information resource with research and practice recommendations.

Chapter 5 – Discussion

5.1 Introduction

This chapter will draw together the learning process from undertaking this review in three key areas. Firstly, personal learning and development of the researcher (which will be documented in the first person), secondly additional validity and insight gained through PPIE work from Chapter 2, and finally, the empirical new knowledge drawn from the results of the systematic review including reliability and limitations. Findings will be placed in context within existing knowledge and followed by clinical practice implications and recommendations for further research.

Figure 21 - Levels of knowledge



5.2 Personal learning and development

5.2.1 Reflection on learning

(Based on Gibbs 1988)

5.2.1.1 Description

During the Masters by Research programme, I have continued to work as a clinical research midwife, which has been challenging to manage two frames of mind and dedicate time to each discipline. The knowledge gained through my clinical role of 10 years, has provided a unique perspective for me when commencing a programme of study for clinical academic research.

Prior to this programme of study, I completed the Interdisciplinary Non-medical Clinical Academic Programme (INCA). This provided an excellent foundation to the distinct differences of working as a clinical academic and the importance of remaining clinically focused to accelerate the impact of results into clinical practice for the benefit of patients.

The opportunity provided during the programme to take part in specialist workshops, conferences, training days and spending time with experts in the field of the relevant subject area, was fundamental to the development of this review. I was also able to sound out ideas and discuss how to incorporate my personal experience in patient and public involvement groups into this systematic review design, something which hadn't been attempted before.

5.2.1.2 Feelings

The apprehension of a 'non-medic' undertaking this type of research and actively working to be a recognised professional in this field was great. I had

countless reservations about the research area and topic being too ‘niche’ to have clinical impact. Despite this, peer and colleague validation and increasing publications in this area encouraged and motivated me to move forward and continued reassurance that the topic was relevant, would have clinical impact and that it was important not only to clinicians but also to CCS and their families really helped to cement my motivation and passion to complete the project.

Self-directed learning and time management proved difficult to navigate at first, with revisions of Gannt charts and setbacks with new learning needed for the *EPPI4 Reviewer* software programme. However, by using a needs-based analysis and with regular supervisory support and guidance, this ensured the project as completed on time. The home institution study peer group also created a passionate and focused environment, which helped me to develop a positive and determined mind-set, which was necessary for independent study.

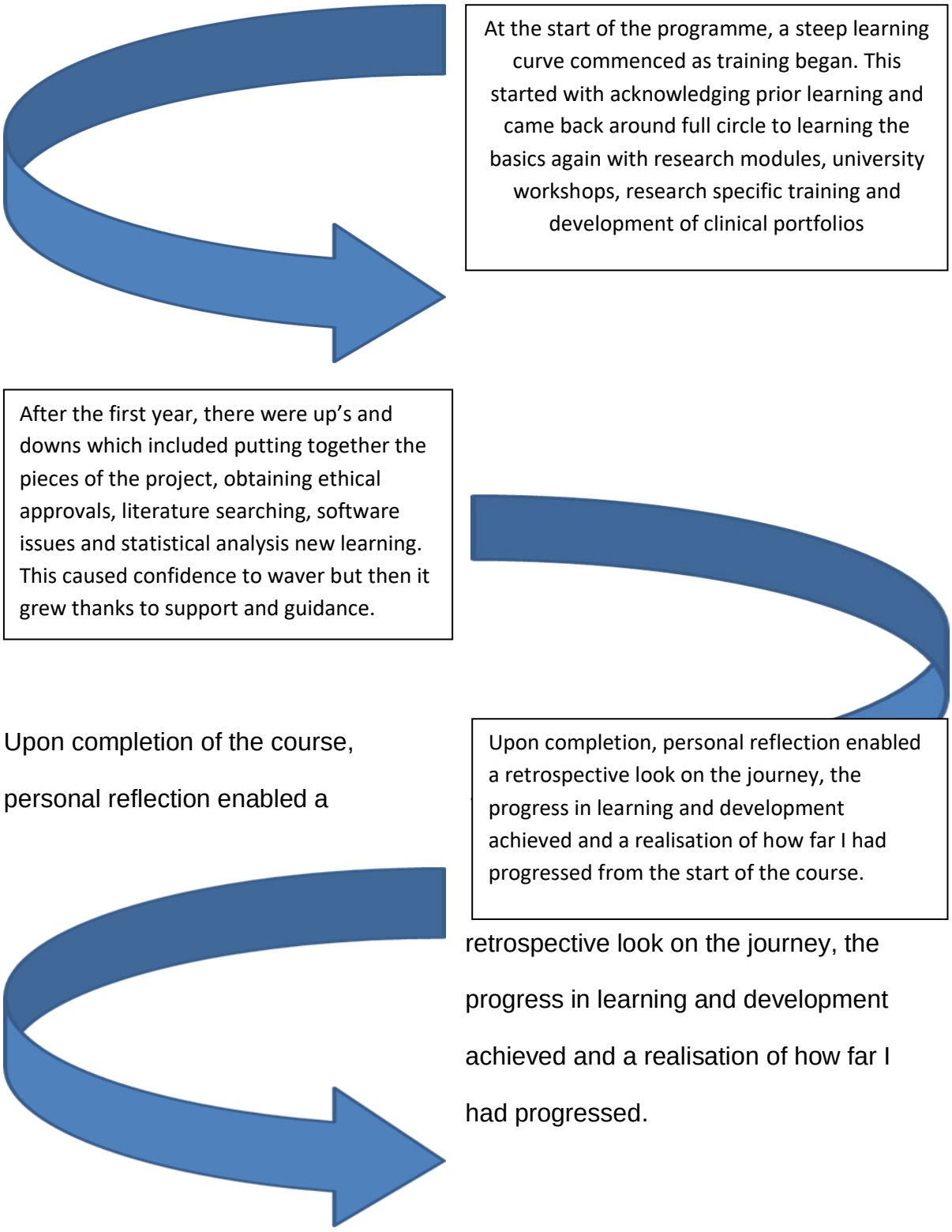
As the project progressed, my confidence to engage in informed conversations with other academics and the ability to explain and defend my results grew. This also developed into colleague discussions and learning sessions about the importance of research in clinical practice with presentations in mandatory training days and journal club.

5.2.1.3 Evaluation

My clinical academic journey has represented an evolving circular process of building upon prior learning, adding in new learning and then reflection on what

I had achieved. A pictorial representation of this process has been represented in Figure 23.

Figure 22 - Process of learning and development



Upon completion of the course, personal reflection enabled a retrospective look on the journey, the progress in learning and development achieved and a realisation of how far I had progressed.

5.2.1.4 Conclusion

Through completion of the programme and personal development as a midwife, I have felt that my journey into the clinical academic world has been commenced and future aspirations will include the opportunity to develop, lead and facilitate research which helps to really change the way healthcare is practised. I plan to continue academic studies alongside clinical practice and seek new opportunities to further clinical academic ability and experience.

Dissemination and raising awareness around my results and keeping close collaboration with professionals in this field of research will be continued. This will aim to assist new learning, pave the way for further research collaborations and assist the translation of new evidence into clinical practice, improving patient outcomes.

5.2.1.5 Action Plan

Table 24 - Action plan for learning and development

• Complete dissemination and impact plan to ensure results from research are translated
• Submit abstracts, posters and publications to disseminate results
• Work alongside clinical colleagues and maintain links with professional groups
• Work with obstetric colleagues to increase awareness of results and discuss future projects to improve patient care
• Apply for future funding to enable continued study and develop clinical academic career pathway

5.3 PPIE voices

5.3.1 PPIE in the review

Including PPIE in the review was a novel approach, as it is often never included in a systematic review as outlined in Chapter 2. Limitations to the PPIE activity and the level of involvement exist, which could be improved if this approach were to be replicated. PPIE is advised from initiation of idea through to dissemination and impact of results (NIHR 2012). The researcher acknowledges that PPIE could have been used in the design of the research question and the selection of the outcomes, rather than the justification or alignment of them with the PPIE priorities. Also, PPIE could be incorporated into the review activities, for example using a lay member to help select and extract data from texts and confirm eligibility. PPIE could also be incorporated into the writing of the results and the creation of the abstract to ensure clarity, readability and patient need is reflected.

Barriers to this level of engagement included time frame and funding for the project. Learning from the PPIE went beyond the framing of the systematic review and the researcher would recommend exploration of this via further PPIE in future work to align with the ethos of INVOLVE (NIHR 2012) and James Lind Alliance (2018) and their priority setting partnerships.

5.4 Empirical review findings

5.4.1 Summary of evidence

As presented in Chapter 4, this systematic review provided a statistically significant link between pre-term birth (birth occurring before 37 completed weeks of pregnancy) in pregnancies of female CCS treated with radiotherapy to the flank, abdomen or pelvic area (odds ratio 3.27, 95% CI 2.71-3.96). The odds of having a stillbirth were also significant with an odds ratio of 1.62 (95% CI1.10-2.40). Although not a primary outcome of the review, this result carries huge clinical impact for patients, babies and healthcare providers.

In the primary outcome of impact on live birth rate, data could be analysed by meta-analysis in both the CCS versus non-exposed CCS control group and the CCS versus sibling comparator group. However, the results were not deemed suitable for inclusion due to heterogeneity. Equally, likelihood of live birth for female CCS versus sibling controls found that the odds ratio favoured a non-effect. Despite this result, the heterogeneity was assessed to be significant, therefore could not be used as a conclusive result for the review.

Low birth weight, although identified as a significant result authors of studies included in the review, could not be analysed as an outcome using meta-analysis due to lack of comparable studies with this outcome. However, more research with the same control group comparator and standardised terminology and categorisation is needed to achieve this might produce an alternative finding.

Data from included studies suggested significant links to maternal complications during pregnancy such as haemorrhage, miscarriage and pre-eclampsia and is suggested by the researcher as an area that would benefit from further research. Maternal complications carry significant maternal morbidity and

mortality and notable fits within the top ranked PPIE concern about ‘pregnancy complications in the mother’ (See 2.3.4)

5.5 Strength of evidence

5.5.1 Systematic Process

The systematic review was conducted in accordance within recommended practices (Centre for Reviews and Dissemination 2009) and meets PRISMA recommended guidelines (Moher et al. 2009). Ethical approval was attained, and an independent reviewer used for screening and selection of texts. Recognised software *(EPPI Reviewer4)* and statistical software programmes were used, and secure data management employed by the researcher *(RefWorks).*

A pre-defined research protocol was submitted to PROSPERO before commencement of the review and the review updated as completed. Meta-analysis results were measured against heterogeneity measures to ensure that any significant results were comparable to evidence-based reporting parameters of acceptance. Results were identified and presented, and a dissemination and impact plan outlined by the researcher.

A recognised risk of bias assessment tool (NOS) was used to appraise the included studies and all findings tabulated and presented within the review.

5.5.2 Reliability of the evidence

As the included studies for this review are cohort studies, the applicability and ‘quality’ of the evidence may be criticised by some researchers and is

acknowledged by the researcher. Due to the existence of no randomised control trials (RCT's) in this field, a systematic review of cohort studies might be viewed negatively in the respect of applicability, rigour and hierarchical importance of the results, which typically favours RCT's, systematic reviews of RCTs, or RCTs with a very low risk of bias (Bowling 2014:203).

Despite this, cohort study methodology is the most appropriate design in this rare disease type. Constraints with obtaining adequate sample size, comparators and ensuring children are provided with the most effective treatment to cure their cancer is of upmost importance and prevents a randomised control trial design.

5.6 Discussion of limitations

Limitations to research are important to acknowledge for transparency of the research, contextualisation of the results, assessing the validity of the research and assigning credibility of the research team.

5.6.1 Limitations of the data

Although 11 studies were obtained in this review, there is a notable limitation of available evidence in this field. There is also acknowledgement from the authors of the included studies that some of the data, vital to the results, is missing due to inability to obtain accurate treatment modality and dosage information.

The data also relies heavily on self-reported data outcomes, which produces adequate sample sizes for research, however, longitudinal cohort studies are often criticised due to the potential for significant recall bias of participants (e.g.

participants in many registries were asked to recall information about miscarriages and pregnancies). Chow et. al (2016:575) highlights that self-reported data might not be the most representative and could lead to significant loss of data.

Furthermore, the data used in most of the studies derives from the BCCSS and CCSS. Despite this extensive and reliable resource, it does not reflect recent novel drug and immunotherapy developments and risk stratification methods allowing for toxicity reducing treatments or high- risk pathways based upon genetic and biological information now used in modern practice.

Patient cohorts used in these registries were relatively young when they were approached; therefore, perhaps limited numbers of participants would have reached an age where reproduction was likely, and many more participants may have data available now which has not been analysed. The data analysed in the studies is more than ten years old, which could be deemed non-representative of the true cohort of patients now completing treatment.

5.6.2 Software limitations

The software used by the researcher to assist with the data management and conducting of the review *(EPPI Reviewer4)* required new learning and familiarisation of processes by the researcher. This impacted upon the time management of the review and led to difficulties when attempting to allocate screening and full text allocations and removing duplicates. It also required an additional purchase to allow access by the second reviewer, which was unforeseen at the commencement of the review. The researcher soon became

familiar with the format and sought assistance with the software providers which allowed for successful completion of the review.

5.6.3 Analysis of data

Meta-analysis could be conducted in five outcomes within the review. Significant results which satisfied the heterogeneity markers were found in pre-term birth and stillbirth. The other outcomes did not satisfy the heterogeneity measures; however, the results can be used to strengthen findings from independent studies suggesting that live birth of female CCS exposed to radiotherapy to the flank, abdomen and pelvis as children is affected (Reulen et al. 2017) and that miscarriage is an area of research that requires further analysis, especially as this was identified in the PPIE survey as the second most important outcome for pregnancy of female CCS (Appendix 2)

Limitations within the review from data extraction and analysis were acknowledged by the researcher as more sophisticated statistical packages were not used due to timeframe or cost restrictions. Therefore, raw data were used for extraction and odds ratios calculated without the ability to adjust for cofounders or adjust for sociodemographic variables. Also, two studies were not able to be used for meta-analysis due to the availability of data, which may have impacted upon the results of the review.

The researcher also acknowledges that there is a limitation in the results found due to a possible type II reporting error, with non-significant findings of live birth both in the CCS versus sibling and non-exposed comparator groups. The data extracted for the studies relies upon accurate data collection, adjustment of

variables and adequate population size to power the study and it is of note that none of the included studies in this review were powered to capture live birth as a primary outcome.

If the sample size is not adequate to demonstrate an effect, then the results cannot be confidently upheld. Some studies were also not able to be included in the meta-analysis due to missing data, which in turn may have influenced the results. The reliance on self-reported data and non-reporting of events such as miscarriage could also be a key variable, as people may have perceived early pregnancy events or minor ailments as being classed as insignificant by others, or distressing to report, which may bias data collected. This may impact the live birth rate effect, as with more accuracy through outcome validation, or with increased sample sizes and statistical powering for live birth as a primary outcome, it is possible an effect may have been seen, or if the non-effect continued to be observed there would be more confidence in its reliability.

5.6.4 Heterogeneity of data

The included studies demonstrated heterogeneity within and across studies, which impacts upon clinical recommendations and synthesis of data, e.g. three out of the five meta-analysis reports were deemed too heterogeneous to be classified as a significant result.

Likelihood of live birth for female CCS versus non-exposed CCS provided an odds ratio of 0.90 (95% CI 0.44-1.86). This suggests that likelihood of live birth is neither effected nor non-effected by prior treatment with radiotherapy to the areas mentioned due to wide distribution and significant heterogeneity between

papers. Heterogeneity was found to be (I^2 of 98.54% and χ^2 p value of < .0001) which implies that authors reported and measured this outcome with such variation that more research would be needed to be conclusive in this assumption.

In likelihood of live birth for female CCS versus sibling comparators an odds ratio of 0.74 (95% CI 0.59-0.94) was found. This suggests that live birth is less likely in female CCS. However, the heterogeneity measure revealed an I^2 value of 84.12% and χ^2 p value of 0.0018, determining that the result cannot be conclusive. More studies would be needed with measurement of this outcome to determine true effect or non-effect.

5.7 Similar research ongoing in this field

As mentioned in chapter one, (see 1.1.4), There are currently no systematic reviews with the same research question as this review. There have been various attempts to collate evidence from international studies investigating pregnancy outcomes of CCS (Van Dorp et al. 2018, Shliakhtsitsava et al. 2017, Kalapurakal et al. 2004, and Nagarajan et al. 2005). However, authors have not used a recognised systematic methodology or have provided any specific clinical recommendations for health care professionals providing maternity care to CCS. Data have also been reliant on self-reported outcomes, with acknowledgment of missing data for treatment modality and dosage within studies (Van Dorp et al. 2018, Nagarajan et al. 2005).

Shliakhtsitsava et al. 2017 published a systematic review into pregnancy outcomes of paediatric and young adult leukaemia survivors and highlighted

gaps in research for CCS, specifically for sub-populations at the highest risks of adverse perinatal outcomes. The review, although investigating key outcomes for CCS such as likelihood of live birth and pregnancy complications, did not contain treatment modality data that were extractable, therefore it was difficult to establish if and adverse outcome was related to either chemotherapy, radiotherapy or surgery. It also failed to distinguish CCS data from their population who had been diagnosed before age 24. The review also focuses on chemotherapy toxicity of treatment and maternal cardiopulmonary risk in pregnancy, therefore does not conflict with this review and was excluded by the researcher.

A review by Van Dorp et al. (2018) (published after the literature search of this review and therefore not included), investigated the reproductive outcomes of female cancer survivors. The review was not registered, nor did it provide replicable systematic methodology. However, the findings are of importance and reported that female CCS who maintain fertility had an overall pregnancy relative risk of 0.67 to 0.81 and live birth rates lower than the general public (hazard ratio, 0.79 to 0.82). The authors supported findings from previous research that suggest pregnancy in CCS may be associated with risks to both the mother and the fetus such as miscarriage and preterm birth and advised that women at risk of complications in pregnancy require preconception assessment and counseling from both obstetricians and oncology providers. Notably, there is also a gap in this research from the patient or CCS voice.

Future work of interest to the researcher, includes an international harmonization guideline project investigating the obstetric care needs of CCS in

pregnancy and birth. Work is ongoing and unpublished; however, the researcher is a member of the working group and will disseminate results of this review to contribute to the guideline and will consider results in relation to applicability to the UK health care system once published.

The researcher also acknowledges a systematic review registration on PROSPERO from Australia entitled “Reproductive outcomes in female childhood cancer survivors”. This review is not completed or published and aims to investigate wider effects of both chemotherapy and radiotherapy in pregnancy and birth of female CCS, therefore not specifically replicating the review in this thesis.

A notable consideration for future research in this field is the rapid advancements in medical technology and expertise. Radiotherapy techniques and new therapies such as IMRT and Proton beam radiotherapy (The Christie NHS Trust 2018) are constantly evolving and improving, which may change the impact that radiotherapy may have on long term likelihood of adverse pregnancy and birth outcome. Green et al. (2009) agreed by suggesting that future research should consider newer chemotherapeutic agents and should evaluate risk for genetic disease of offspring of CCS. Edgar and Wallace (2007) also highlighted that prospective cohorts treated with contemporary therapies are needed to determine actual risk for CCS in pregnancy.

5.8 Contextualisation of results

Results of the review carry significant clinical implications and health care economic considerations. Pre-term birth and stillbirth have been identified by the NHS as key priorities in health care for pregnant women (NICE 2015).

Health care costs related to a pre-mature baby cost the NHS millions per year and the psychological distress and associated maternal morbidity rates caused by pre-term birth and stillbirth carry multi-factorial consequences for mothers including birth trauma, susceptibility to infection, perineal trauma and depression (Tommy's 2018a).

Communication of adverse outcomes or late-effects is paramount to ensure that children affected by cancer and their families are aware of risk and benefit before consenting to clinical procedures. Health care professionals involved in the immediate treatment of childhood cancer and long-term care of CCS, have a responsibility to be aware of potential short and long-term complications and communicate this to health care professionals and CCS and their families. A call for clearer threshold for toxicities of organs such as the uterus should also be made to ensure that practitioners responsible for delivering the treatment are aware of the long and short-term effects to organs in the field of radiotherapy.

Obstetrics and midwifery care planning needs to balance clinical need and patient preference and satisfaction to provide optimal outcomes and to maintain the woman-centred care approach. If health care professionals are not adequately informed of increased odds of an adverse outcome or the need for additional surveillance, then this puts at risk the health of the mother and the baby.

5.9 Future research and recommendations

Recommendations for future research and clinically focused recommendations arising from the included studies of the review include:

Table 25 - Research recommendations from the review

• A generic need for more longitudinal research and research into education of CCS and their families surrounding fertility and pregnancy likelihood after treatment
• Investigation into transition of care between the Paediatric and the adult care services as it is an important factor to the communication of long-term effects and appropriate care including surveillance for co-morbidities
• Exploration of geographical variances in service provision and uptake of long-term follow up services by CCS and TYA's
• Investigation into long-term health outcomes of children born to CCS. It has been suggested that possible mutagenic effects of cancer treatment could predispose children of CCS to congenital abnormalities or even cancer itself. (Although notably this was ranked as a low priority concern for CCS responding to the survey presented in Chapter 2. If further research identified a link, then this priority could change)
• Investigation into whether any additional clinical impact exists when fertility preservation techniques are used in CCS to conceive. Assisted-reproduction techniques (ART) such as IVF already carries increased risk during pregnancy and there may be scope to investigate if this existing risk is further heightened by having a background of childhood cancer treatment.
• Fetal exposure to medications, regardless of previous treatment exposures has been linked to a risk of cancer in offspring and further highlights the need for research into long-term outcomes of offspring in current medical trials in a pregnant population (Hoover et al. 2011)

Research by Kelly and Levine (2017) highlighted the inadequate high-risk referral rate of CCS for obstetric care. They found that pregnancies of female CCS treated with abdominal radiotherapy, were not correctly identified as high-risk pregnancies needing greater supervision and suggested that health care systems are not uniform in their approach in correctly identifying CCS in need of referral to high-risk maternal-fetal medicine programmes (Kelly and Levine

2017). Therefore, the researcher has highlighted key areas for research that are applicable to clinical practice:

Table 26 - Clinical recommendations from the review

• Review of current radiotherapy practice as very little is known surrounding maximum and minimum treatment thresholds for the uterus. Organ sparing measures, longitudinal prospective studies of CCS who have been exposed to radiotherapy in the uterine region and developing more targeted treatments considering the findings of this review are areas where health care professionals delivering childhood cancer treatments could improve the care they provide to children with cancer and have direct patient impact.
• Exploration of how information should be communicated to CCS (in relation to the odds of having an adverse event in pregnancy and birth directly attributable to radiotherapy as a child). Information regarding who is best placed to communicate this information, where and when, could translate into improved high-risk referral rates and improved patient care and outcomes. This was highlighted within the PPIE survey in Chapter 2 and supported by Edgar and Wallace (2007:1893) who recommended that more communication should be given to CCS about the impact of their treatment on fertility and pregnancy/birth outcomes. The researcher aims to consider and take these recommendations forward with future research projects.
• Exploration of medical interventions during pregnancy and childbirth in this patient set that might improve outcomes based upon supporting evidence. For example, Revelli et al. (2007) suggested that female CCS should be monitored for myometrial thickness and features of abnormal placentation at obstetrical ultrasound examinations in pregnancy.

Chapter 6 – Conclusion

6.1 Research aims and question

The aim of this review was to search, evaluate and synthesise existing data relating to live births of pregnant women who have received flank, abdominal or pelvic radiotherapy as treatment for childhood cancer. This has been achieved with the completion of a systematic review and meta-analysis and the provision of a synthesised information resource.

The research questions proposed by the researcher were:

(1) What is the impact of flank, abdominal or pelvic radiotherapy on female CCS on live birth and associated adverse pregnancy outcomes?

(2) Are any associated adverse outcomes in pregnancy and childbirth directly attributable to flank, abdominal or pelvic radiotherapy as a child?

This systematic review has provided statistically significant results to demonstrate that there is an increased odds of pre-term birth and still birth for CCS in pregnancy and birth and that this is directly attributable to cancer treatment as a child (0-24 years) with radiotherapy to the flank, abdomen or pelvis.

The impact upon live birth for female CCS treated with radiotherapy to the flank, abdomen and pelvis were inconclusive with more research, comparable samples and specific outcome measures needed in future studies.

6.2 Impact and dissemination plan

Upon completion of the masters' course, the researcher intends to continue further studies. The researcher intends to apply for PhD study either with an academic institution or via the NIHR clinical academic pathway to build upon and address key gaps identified within this review. They would also like to develop leadership skills and further understanding of research methods that are unfamiliar and statistical packages and health economics experience.

The researcher intends to disseminate results from the review within the clinical area and the wider paediatric oncology and obstetric communities. They will work to publish results in key publications and apply to present the work at conference and events in this field of research. They will also aim to publish a lay-summary of the results and share this with PPIE groups and parent and survivor communities to widen the impact of the results. The researcher also aims to showcase research findings at key meetings in the childhood cancer long-term effects arena.

Connections that have been made throughout the programme with the supervisory team, mentors and specialists in the field will prove to be key resources for developing and furthering the research journey and the researcher hopes to include and share with them key developments and successes.

The main measure of impact and dissemination for this review is to educate, raise awareness and instigate change in the care of female childhood cancer survivors who become pregnant, so that they are aware of the likelihood of any adverse outcome and so that professionals involved in their care can advise,

plan and intervene based upon evidence-based resource. This will in turn optimise outcomes and provide a tailor-made care approach for CCS.

6.3 Final conclusions to review

The population of adults in society that have a history of childhood cancer is growing by 1,300 per year (Children with Cancer UK 2018). Studies have identified that female CCS are at an increased risk of complications during pregnancy and childbirth, a risk directly attributable to treatment for childhood cancer (Signorello et al. 2006, Reulen et al. 2017, Mueller et al. 2009). Treatment for childhood cancer with radiotherapy has been identified as the most significant risk for adverse outcomes in pregnancy and birth, particularly when received to the flank, abdomen and pelvic areas (Reulen et al. 2017).

A systematic review of the evidence investigating the impact of radiotherapy to the flank, abdomen or pelvis on live birth outcome for female CCS was conducted. The purpose of this review and its results was to provide a synthesised information resource for researchers and professionals, based on evidence which has been subject to a systematic methodology and risk of bias assessment addressing the long-term implications for pregnancy and birth outcome of CCS.

PPIE was used to help shape and reinforce the selected outcomes of the review with the use of an online survey. The results of which were considered by the researcher throughout the review process, ensuring a patient-focused approach. PPIE was integrated into the dissemination plan of the review, to ensure wide-scale dissemination of results to all stakeholders, with the aim to have maximum applicability and impact upon clinical practice.

Female CCS that have received radiotherapy to the flank, abdomen or pelvis are at a significantly increased odds of pre-term birth (odds ratio 3.27, 95% CI 2.71-3.96) and stillbirth (odds ratio 1.62, 95% CI1.10-2.40) in pregnancy. A lack of effect for the impact of live birth rate could not be verified due to a lack of data, equally in relation to additional adverse pregnancy outcomes suggests that more research is needed in this area to confidently define impact or effect.

The increased odds of a premature birth and stillbirth in this review demonstrate that health care professionals involved in the obstetric care of female CCS, should ensure that a high-risk pregnancy care plan is in place and that an early referral to an obstetric team is made. Clinicians should also consider the evidence from this review and supporting publications in relation to surveillance and interventional measures for pre-term birth and stillbirth. Interventions such as early pregnancy surveillance, serial ultrasound scanning, cervical length assessment and early induction of labour are pertinent considerations for the obstetric team in charge of pregnancy care of the female CCS. Further research is needed however, to prove that any suggested interventions might influence perinatal outcomes of CCS.

Communication of potential adverse outcomes for CCS in pregnancy and birth is also an important issue for care. Female CCS and their families should feel informed and empowered to be active partners in their pregnancy care, provided with a full clinical picture of evidence-based research to make their care choices. More research is needed to find the most appropriate time to provide female CCS with pregnancy and birth long-term effects information, including an exploration of how to increase the awareness of potential adverse

outcomes for health care professionals from paediatric oncology, long-term follow up and maternity care providers responsible for the care of the female CCS.

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vii) Appendices

Appendix 1 – PRISMA reporting guidelines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Appendix 2 – PPIE survey

Female childhood cancer survivors and birth outcomes

Q1 Thank you for agreeing to take part in this questionnaire. We want to have a better understanding of the effects of radiotherapy given to children with cancer from a patient/parent point of view. If you/your child received: - Radiotherapy as part of their cancer treatment and they are a girl, we would like to know what issues you/your child would consider to be important for a mother and baby during pregnancy and birth.

We are also interested in any thoughts about issues that may concern you/your child when thinking of planning a family. As part of a masters by research programme (funded by the HEE/NIHR and Coventry University), Angela Polanco (Research midwife and bereaved parent) will be undertaking a review of the evidence to see if there is any links with radiotherapy, given in childhood for cancer, on live birth and looking at any associated complications for women/babies during pregnancy and birth. Many thanks for your time.

Q2 What is your background...

- Parent of a child (1)
- Survivor who hasn't had a child (2)
- Survivor who has had a child (3)

Q3 As part of your/your child's treatment, did you/they receive radiotherapy to the tummy?

- Yes (1)

□ No (2)

□ Unsure (3)

Q4 Do you know how much radiation you/your child received?

□ Yes (1)

□ Maybe (2)

□ No (3)

Q5 If you do know how much radiotherapy was given please write below (total Gy)

Q6 If you/your child received radiotherapy to the tummy, at what age did you/they receive this?

□ 0-4 years (1)

□ 5-10 years (2)

□ 11-16 years (3)

Q7 Have you been told that your/your child's treatments for cancer are likely to affect fertility (ability to have a baby)?

□ Definitely yes (1)

□ Probably yes (2)

□ Probably not (3)

□ Definitely not (4)

Q8 After completing treatment for cancer (including radiotherapy), what would you/your child be most concerned about during a pregnancy? Please rank your answers from most important to least important.

_____ Miscarriage (1)

_____ Early Labour (2)

_____ Small Baby (3)

_____ A healthy baby (4)

_____ Pregnancy complications for mother (5)

_____ Abnormalities in the baby (6)

_____ Risk of the baby having cancer (7)

Q9 Are there any other issues during pregnancy or birth that you think might be important?

Q10 Are you aware of any information given to survivors of childhood cancer about pregnancy after treatment has finished?

□ Yes (1)

□ No (2)

Q11 If you/your child have been given such information, at what point were you given this?

□ Diagnosis (1)

□ During treatment (2)

- Upon remission (3)
- When thinking about starting a family (4)
- When pregnant (5)

Q12 Thank you for participating in this questionnaire. Your responses will be used anonymously to help shape a master's research project into the possible impact of radiotherapy, given for childhood for cancer, on live birth and any associated complications or for women with this history.

You have the right not to take part in this survey at any time, and/or withdraw your responses at any time within 2 weeks of taking part. You do not need to give a reason for this and this will not affect any care or support provided by your clinical team.

Content removed due to data protection considerations.

Appendix 3 – PICO used for review

PICO – Search terms

Patient ***Problem***	**Adult survivors of childhood cancer**
Intervention	Radiotherapy to the flank, abdomen or pelvis
Comparator	General population, siblings
Outcome	Term Live birth rate

Question: With Adult survivors of childhood cancer does Radiotherapy to the abdomen or pelvis effect Term Live birth rate

Patient/Problem	**Intervention**	**Outcomes**	**Not**
Childhood cancer Childhood neoplasm	**Radiotherapy**	Live birth	**miscarriage**	Non-English
Or	Or	Or	Or	Or
Wilms tumour Renal tumour	Abdomen	Full term	stillbirth	IVF
Or	Or	Or	Or	Or
Neuroblastoma	Pelvis	Pregnancy Outcomes	Neonatal death	Radiotherapy to other areas
Or	Or	Or	Or	Or
Hepatoblastoma Liver cancer Hepatic tumours	Flank	Birth rate	Intrauterine death stillbirth	Prostatic Neoplasms
Or	Or	Or	Or	Or

Germ cell						Premature birth		Male
Or		Or		Or		Or		Or
Childhood cancer survivor						Growth restriction Small baby		Breast cancer
Or		Or		Or		Or		Or
Teenage cancer Young adult Adolescent cancer						Caesarean section		
Or						Or		
rhabdomyosarcoma						Labour type		
						Or		
Or Hodgkin's lymphoma						Labour complications		
Or						Or		
Childhood malignancy						Congenital abnormality		

Appendix 4 – Ethics applications

Certificate of Ethical Approval

Applicant:

Angela Polanco

Project Title:

Female childhood cancer survivors and the impact of flank, abdominal or pelvic radiotherapy on live birth: A systematic review.

This is to certify that the above named applicant has completed the Coventry University Ethical Approval process and their project has been confirmed and approved as Low Risk

Date of approval:

16 May 2017

Project Reference Number:

P46688

Certificate of Ethical Approval

Applicant:

Angela Polanco

Project Title:

Female childhood cancer survivors and the impact of flank, abdominal or pelvic radiotherapy on live birth: A systematic review.

This is to certify that the above named applicant has completed the Coventry University Ethical Approval process and their project has been confirmed and approved as Medium Risk

Date of approval:

04 August 2017

Project Reference Number:

P60599

Appendix 5 – PROSPERO registration

Removed due to data protection considerations

Appendix 6 – MEDLINE sample search strategy

Question: With Adult survivors of childhood cancer does Radiotherapy to the abdomen or pelvis effect Term Live birth rate

Childhood cancer Childhood neoplasm		**Radiotherapy**		Live birth		**miscarriage**		English
Or		Or		Or		Or		Or
Wilms tumour Renal tumour		Abdomen		Full term		stillbirth		IVF
Or		Or		Or		Or		Or
neuroblastoma		Pelvis		Pregnancy Outcomes		Neonatal death		Radiotherapy to other areas
Or		Or		Or		Or		Or
Hepatoblastoma Liver cancer Hepatic tumours						Intrauterine death stillbirth		Prostatic Neoplasms
Or		Or		Or		Or		Or
Germ cell						Premature birth		male
Or		Or		Or		Or		Or
Childhood cancer survivor						Growth restriction Small baby		
Or		Or		Or		Or		Or
Teenage cancer Young adult						Caesarean section		

Adolescent cancer								
Or						Or		
rhabdomyosarcoma						Labour type		
						Or		
Or						Labour complications		
						Or		
						Congenital abnormality		

Search ID#	Search Terms	Search Options	Actions	
☐	S1	TI childhood cancer AND TI surviv*	**Search modes** - Boolean/Phrase	**View Results** (1,643) **View Details** **Edit**
☐	S2	AB childhood cancer AND AB surviv*	**Search modes** - Boolean/Phrase	**View Results** (2,701) **View Details** **Edit**
☐	S3	S1 OR S2	**Search modes** - Boolean/Phrase	**View Results** (3,077) **View Details** **Edit**
☐	S4	TX british childhood cancer survivorship study OR TX BCCSS	**Search modes** - Boolean/Phrase	**View Results** (37) **View Details** **Edit**

☐	S5	S3 OR S4	**Search modes** - Boolean/Phrase	**View Results** (3,085) **View Details** **Edit**
☐	S6	(MH "Pregnancy")	**Search modes** - Boolean/Phrase	**View Results** (788,460) **View Details** **Edit**
☐	S7	TI PREGNAN* OR AB PREGNAN*	**Search modes** - Boolean/Phrase	**View Results** (420,448) **View Details** **Edit**
☐	S8	S6 OR S7	**Search modes** - Boolean/Phrase	**View Results** (879,201) **View Details** **Edit**
☐	S9	(MH "Birth Rate") OR (MH "Term Birth") OR (MH "Live Birth") OR (MH "Parturition")	**Search modes** - Boolean/Phrase	**View Results** (19,438) **View Details** **Edit**
☐	S10	S8 OR S9	**Search modes** - Boolean/Phrase	**View Results** (887,993) **View Details** **Edit**
☐	S11	S5 AND S10	**Search modes** - Boolean/Phrase	**View Results** (129)

Infant, Newborn: birth-1 month;

All Infant: birth-23 months;

Infant: 1-23 months;

Child, Preschool: 2-5 years;

Child: 6-12 years;

Adolescent: 13-18 years;

All Child: 0-18 years;

Young Adult: 19-24 years;

Appendix 7 – Modified data extraction template

Data collection form

Angela Polanco –Mres adapted form to be inputted onto EPPI-reviewer for completion by 1st and second reviewer.

Review title or ID

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*

Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

Notes:

General Information

1. **Date form completed** *(dd/mm/yyyy)*	
2. **Name/ID of person extracting data**	
3. **Report title** *(title of paper/ abstract/ report that data are extracted from)*	
4. **Report ID** *(if there are multiple reports of this study)*	
5. **Reference details**	
6. **Report author contact details**	
7. **Publication type** *(e.g. full report, abstract, letter)*	
8. **Study funding source** *(including role of funders)*	

Possible conflicts of interest *(for study authors)*	
9. **Notes:**	

Eligibility

Study Characteristics	**Review Inclusion Criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	**Yes/ No / Unclear**	**Location in text** *(pg & ¶/fig/table)*
10. **Type of study**	Cohort study	...	
	Case-control	...	
	Randomised controlled study	...	
	Other design (specify):	...	
11. **Age of Participants**		...	
12. **Types of intervention**		...	
13. **Types of outcome measures**		...	
14. **Decision:**	...		
15. **Reason for exclusion**			
16. **Notes:**			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & ¶/fig/table)*
17. **Population description** *(from which study participants are drawn)*		
18. **Setting** *(including location and social context)*		
19. **Inclusion criteria**		
20. **Exclusion criteria**		
21. **Method/s of recruitment of participants**		
22. **Control group and method of recruitment**		
23. **Notes:**		

Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
24. **Aim of study**		
25. **Design** *(e.g. parallel, crossover, non-RCT)*		
26. **Data source** ***(registry data, questionnaire)***		

27. **Start date**		
28. **End date**		
29. **Duration of participation** *(from recruitment to last follow-up)*		
30. **Notes:**		

Risk of Bias assessment

Please use attached Newcastle Ottawa Scale form for either cohort or Case-Control study

Scale score	**(stars)**
High or low risk	**High/low**

Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	**Location in text** (pg & ¶/fig/table)
31. **Total no. included** *(or total pop. at start of study for NRCTs)*		
32. **Control population number**		
33. **Baseline data comments**		
34. **Withdrawals and exclusions** *(if not provided below by outcome)*		
35. **Age**		

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
36. **Sex**		
37. **Race/Ethnicity**		
38. **Country of domicile**		
39. **Type of cancer**		
40. **Age at diagnosis**		
41. **Age at birth**		
42. **Treatment received (chemo/radio/combination)**		
43. **Dose of radiotherapy given**		
44. **Other relevant sociodemographic**		
45. **Subgroups measured**		
46. **Subgroups reported**		
47. **Notes:**		

Control groups

Copy and paste table for each intervention and comparison group

Control group (if identified)

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
48. **Group size**		
49. **Method of recruitment**		

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
50. **Description** *(include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention)*		
51. **Duration of observation period**		
52. **Timing** *(e.g. frequency, duration of each episode)*		
53. **Delivery** *(e.g. mechanism, medium, intensity, fidelity)*		
54. **Providers** *(e.g. no., profession, training, ethnicity etc. if relevant)*		
55. **Co-interventions**		
56. **Economic variables** *(i.e. intervention cost, changes in other costs as result of intervention)*		
57. **Resource requirements to replicate intervention** *(e.g. staff numbers, cold chain, equipment)*		
58. **Notes:**		

Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
59. **Outcome name**		
60. **Time points measured** *(specify whether from start or end of intervention)*		
61. **Time points reported**		
62. **Outcome definition** *(with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious)*		
63. **Person measuring/ reporting**		
64. **Unit of measurement** *(if relevant)*		
65. **Scales: upper and lower limits** *(indicate whether high or low score is good)*		
66. **Is outcome/tool validated?**	... *Yes/No/Unclear*	
67. **Consent process**		
68. **Notes:**		

Results

EPPI-Reviewer software will record all results.

Applicability

69. **Have important populations been excluded from the study?**	... *Yes/No/Unclear*	

(consider disadvantaged populations, and possible differences in the intervention effect)		
70. **Does the study directly address the review question?** *(any issues of partial or indirect applicability)*	... *Yes/No/Unclear*	
71. **Notes:**		

Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
72. **Key conclusions of study authors**		
73. **References to other relevant studies**		
74. **Correspondence required for further study information** *(what and from whom)*		
75. **Further study information requested** *(from whom, what and when)*		
76. **Correspondence received** *(from whom, what and when)*		

Appendix 8 - Newcastle Ottawa Scale

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Appendix 9 – Costs of the review

Costings

Economics of Review	Expenditure	Funding Source
	Cost	
Researcher Costs		
Researcher	unknown	NIHR/HEE funding for part time 2 year course NHS band 6
Independent Reviewer	unknown	NIHR/HEE Fellowship
Director of Studies	unknown	Coventry University Salary
Software		
Covidence	250 (approx £200	Coventry University Post Graduate (PGR) Bursary
Printing and consumables		
Miscellaneous	£50 (Parking)	Researcher to fund
Article sourcing	£2 per article or Nil	Coventry University PGR Bursary
Photocopying	Nil	Coventry University/UHCW NHS trust
Printing	Nil	Coventry University printer credit allowance
Training		
Systematic Review Course	£100	Coventry University PGR Bursary
Accomodation	£150	Coventry University PGR Bursary

Appendix 10 – Gantt chart

2016-17	Month	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug
Mres project timeline													
University Induction													
Module 1 study													
Module 2 study													
Research question, methodology and aims - review and develop													
Database and Literature search - pregnancy outcomes													
critical analysis of key publications and data													
identification of key outcomes													
writing up of results from primary search													

Key 2016-17
Month 1 commencing 26/09/2016
Christmas Break
Easter Break
Summer Break

2017-18	Month	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June
Mres project timeline											
Database and literature review - exisitng and similar pregnancy care pathways											
Critical analysis of data											
assessing application of results to prospective client group											
final thesis writing											
submission											
dissemination of results/publication writing											
application for further funding/study											

Key 2017-18
Month 1 commencing 27/09/2017
Christmas Break
Easter Break

Version 2.0 (updated)

2017	Month	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Nov	Dec
Mres project timeline																
University Induction																
Module 1 study																
Module 2 study																
Research question, methodology and aims																
Finalise Protocol																
Ethical Approval, register on Prospero																
Database and Literature search																
Data Extraction and synthesis																
Meta-Analysis																
critical analysis and discussion																
Clinical Portfolio completion																

2018	Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep
Mres project timeline										
critical analysis and discussion										
final thesis writing										
submission										
dissemination of results/publication writing										
application for further funding/study										

Key 2017-2018
Christmas Break
Easter Break
Christmas Break
Summer Break

Appendix 11 – Full Meta-analysis reports

Meta-analysis

Live birth CCS vs non-exposed CCS

Main Summary

```
Random-Effects Model (k = 5; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.6689 (SE =
0.5505)
tau (square root of estimated tau^2 value):      0.8179
I^2 (total heterogeneity / total variability):   98.54%
H^2 (total variability / sampling variability):  68.73

Test for Heterogeneity:
Q(df = 4) = 274.9106, p-val < .0001

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
-0.1069   0.3694  -0.2893   0.7723  -0.8310   0.6172

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

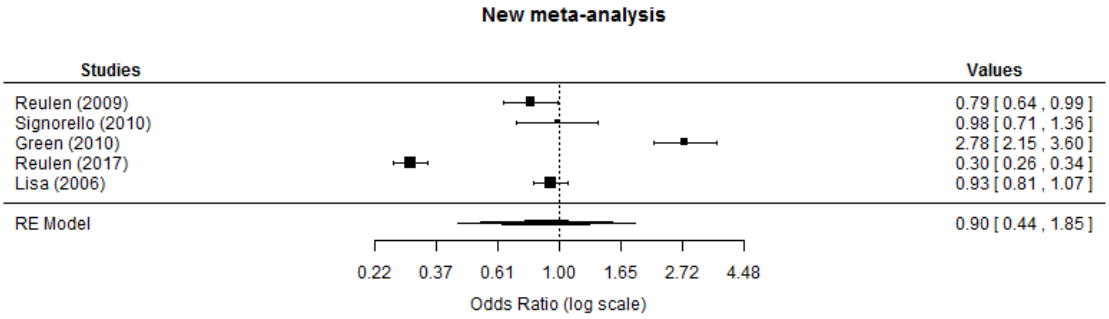
Fit Statistics

```
ML
logLik:   -5.500612
deviance: 24.335929
AIC:      15.001223
BIC:      14.220099
AICc:     21.001223
```

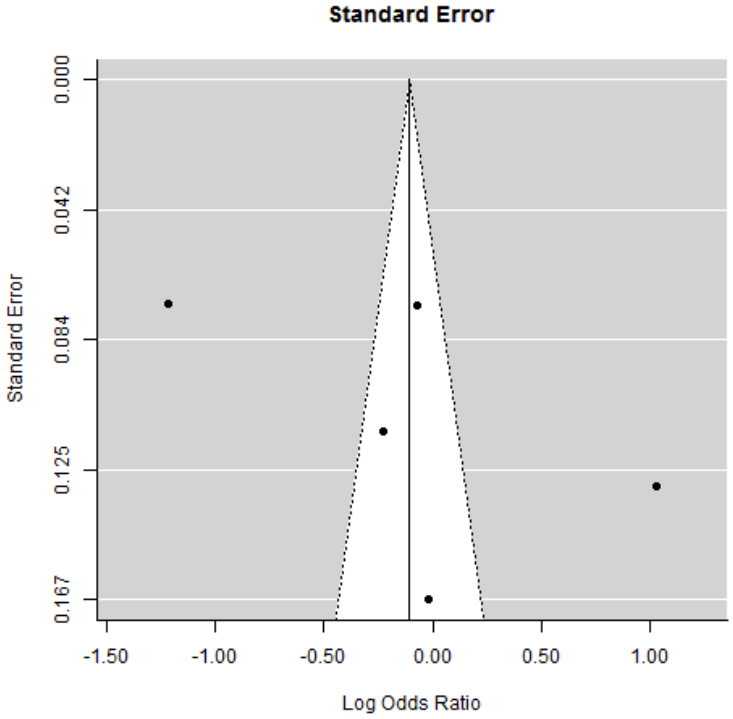
Confidence Intervals

```
estimate   ci.lb    ci.ub
tau^2    0.6689  0.2160   5.2143
tau      0.8179  0.4647   2.2835
I^2(%)  98.5450 95.6269  99.8110
H^2     68.7277 22.8671 528.9734
```

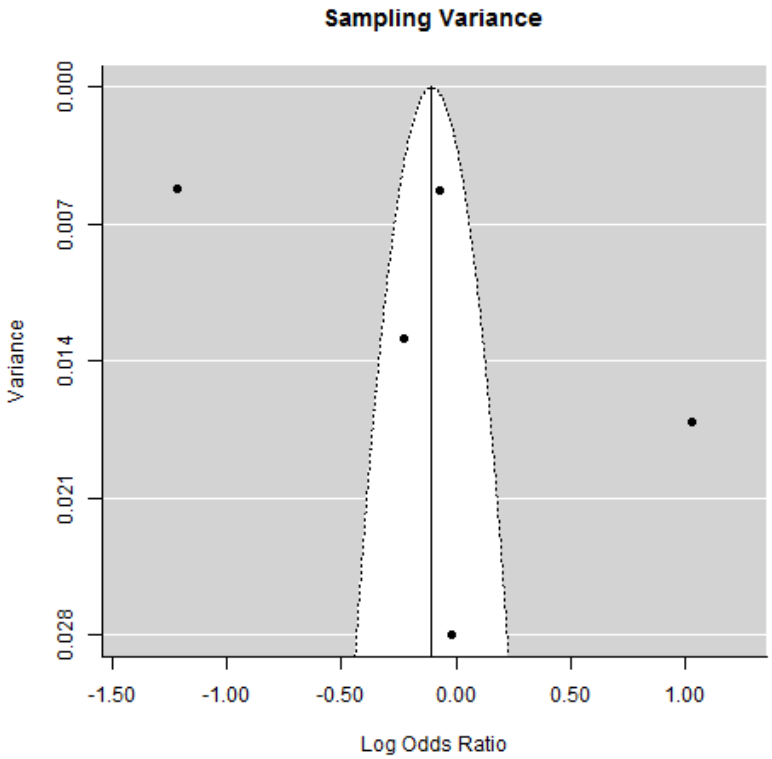
Forest plot



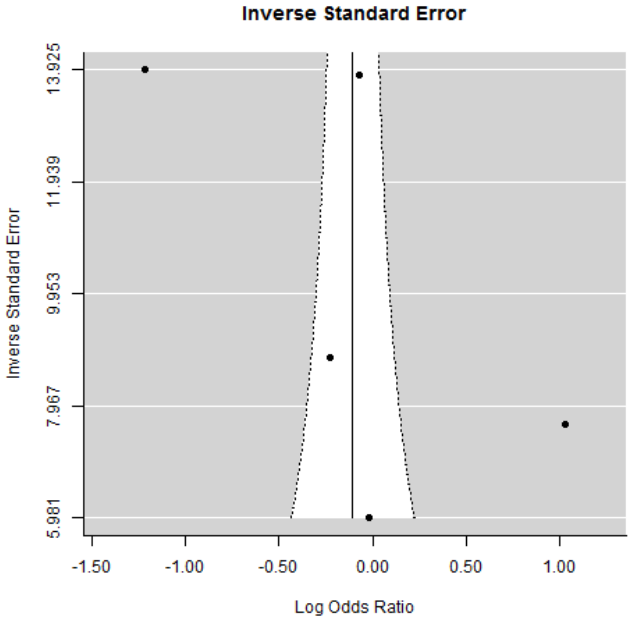
Funnel plot (Standard Error)



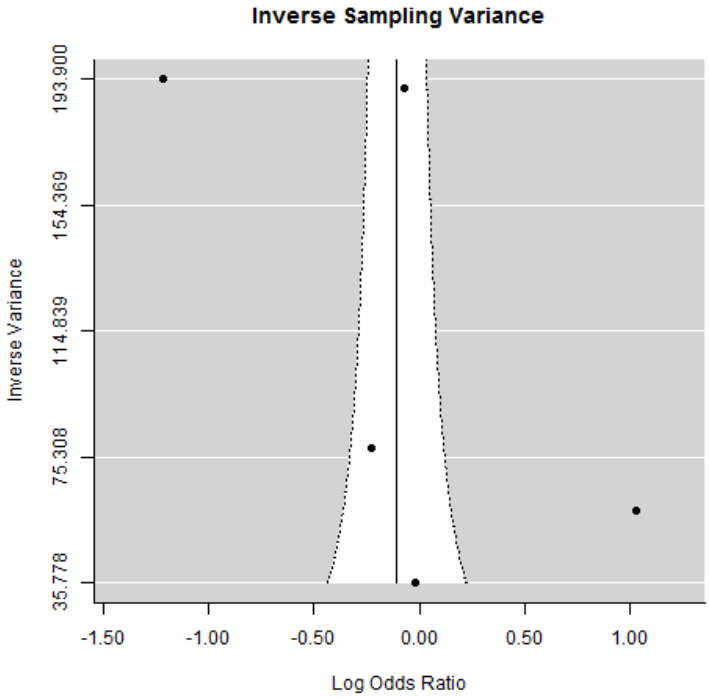
Funnel plot (Sampling Variance)



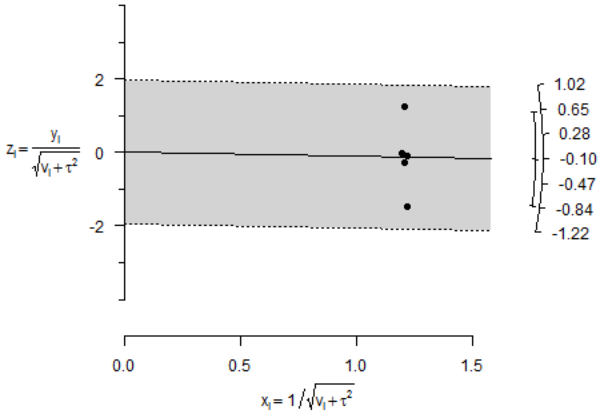
Funnel plot (Inverse Standard Error)



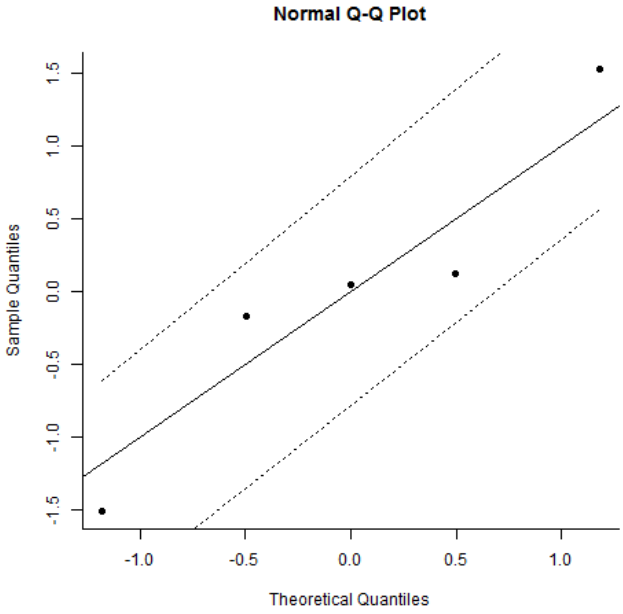
Funnel plot (Inverse Sampling Variance)



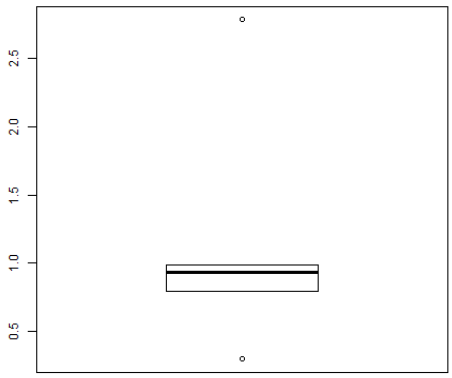
Radial (Galbraith) Plot



Normal QQ Plot (for selected statistical model)



Boxplot of effect size estimates


0.5
1.0
1.5
2.0
2.5

Meta-analysis

Pre term birth CCS vs non-exposed CCS

Main Summary

```
Random-Effects Model (k = 5; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0369)
tau (square root of estimated tau^2 value):      0
I^2 (total heterogeneity / total variability):   0.00%
H^2 (total variability / sampling variability):  1.00

Test for Heterogeneity:
Q(df = 4) = 1.8500, p-val = 0.7633

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
1.1862   0.0967  12.2629   <.0001   0.9966   1.3758      ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

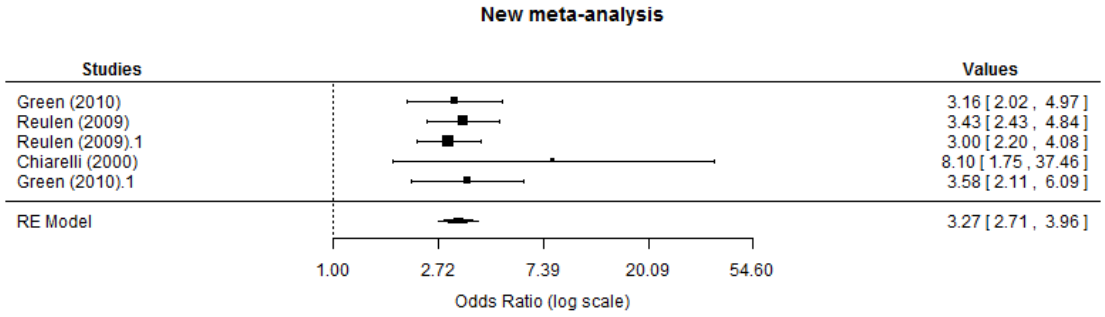
Fit Statistics

```
ML
logLik:   1.090524
deviance: 1.849992
AIC:      1.818952
BIC:      1.037828
AICc:     7.818952
```

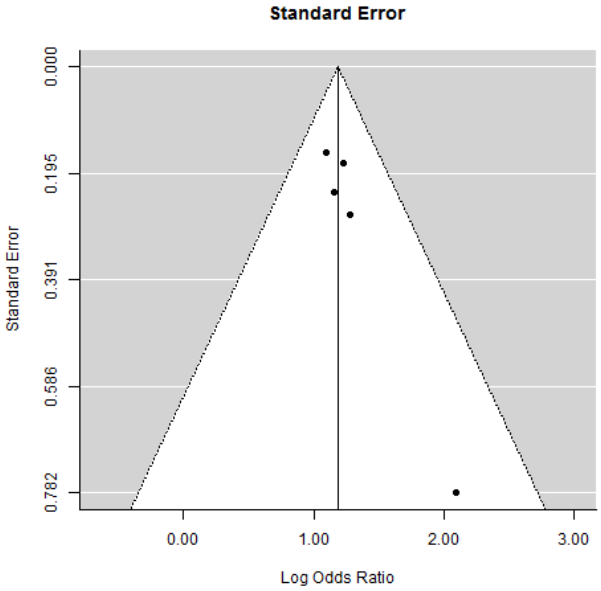
Confidence Intervals

```
estimate  ci.lb   ci.ub
tau^2    0.0000 0.0000  0.9051
tau      0.0000 0.0000  0.9514
I^2(%)   0.0000 0.0000 94.5556
H^2      1.0000 1.0000 18.3675
```

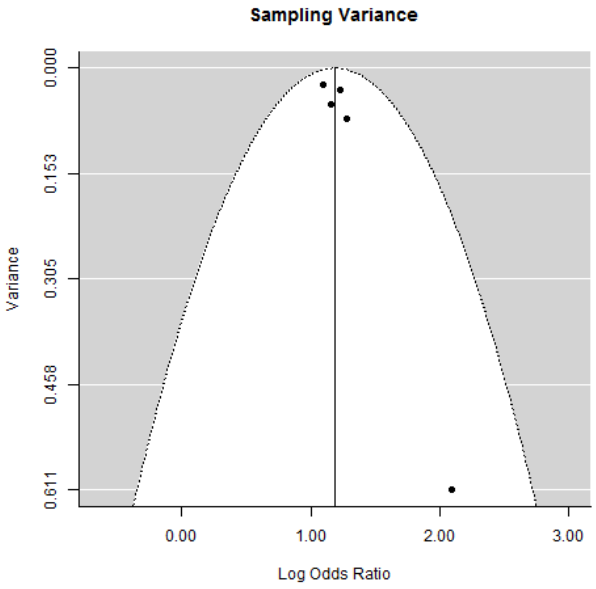
Forest plot



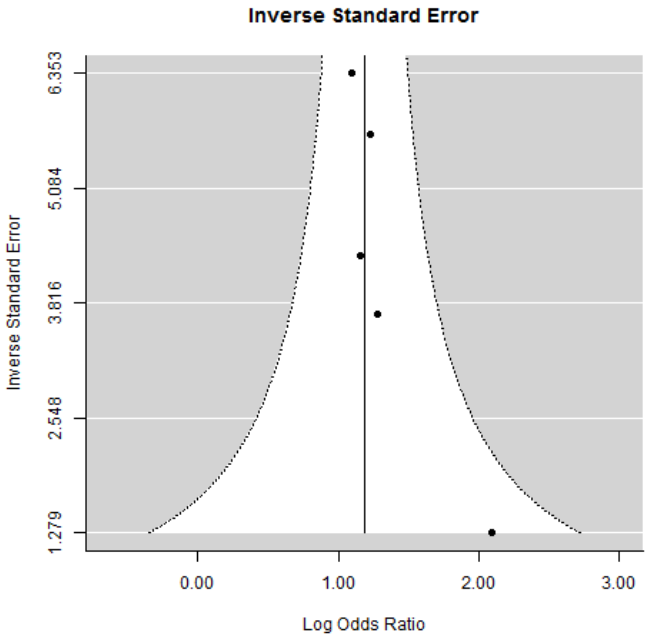
Funnel plot (Standard Error)



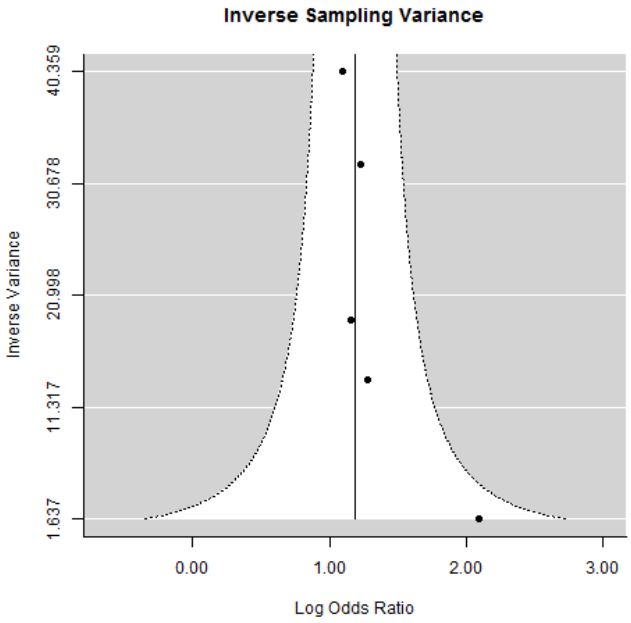
Funnel plot (Sampling Variance)



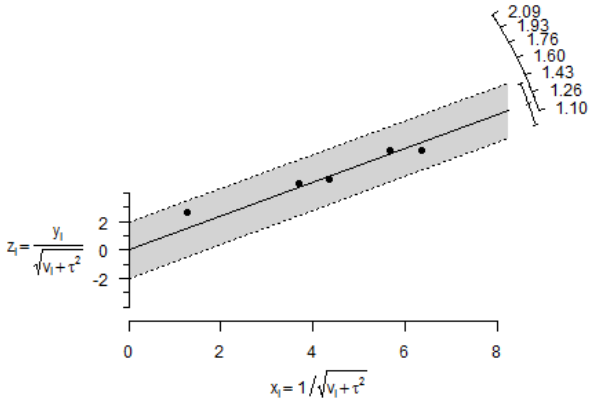
Funnel plot (Inverse Standard Error)



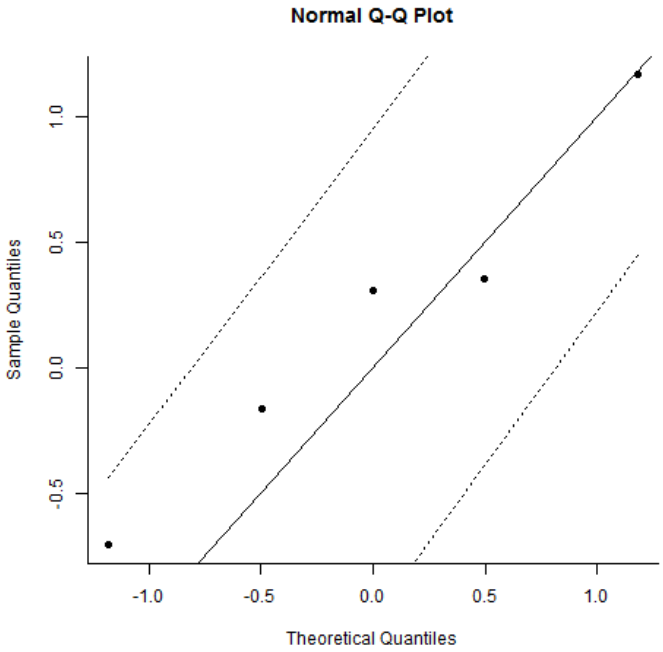
Funnel plot (Inverse Sampling Variance)



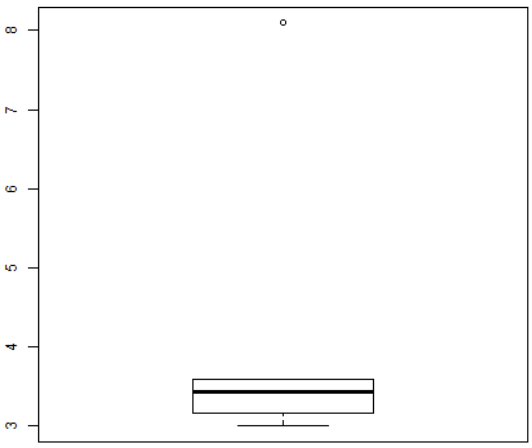
Radial (Galbraith) Plot



Normal QQ Plot (for selected statistical model)



Boxplot of effect size estimates



Meta-analysis

Live birth CCS vs Sibling

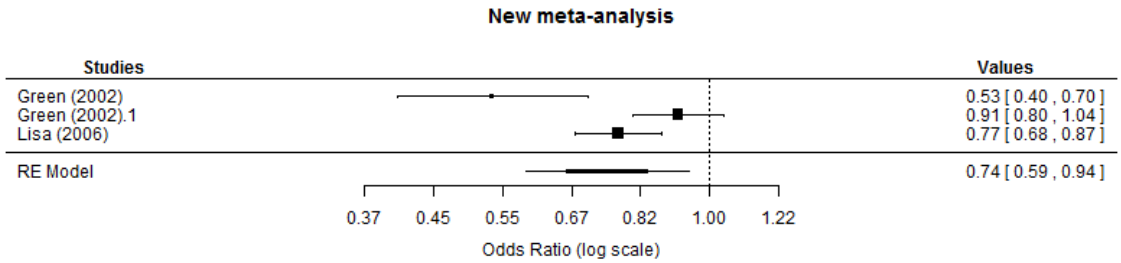
Main Summary

```
Random-Effects Model (k = 3; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.0351 (SE =
0.0460)
tau (square root of estimated tau^2 value):      0.1874
I^2 (total heterogeneity / total variability):   84.12%
H^2 (total variability / sampling variability):  6.30

Test for Heterogeneity:
Q(df = 2) = 12.5956, p-val = 0.0018

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
-0.2963   0.1205  -2.4588   0.0139  -0.5324  -0.0601        *

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

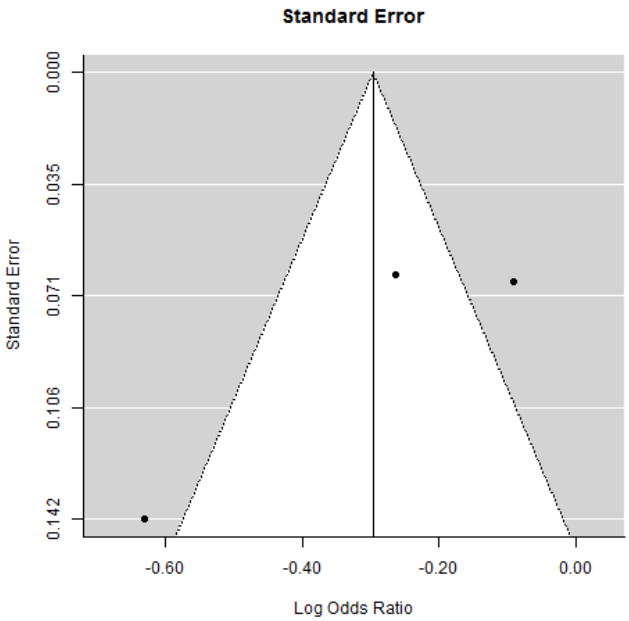
Fit Statistics

```
ML
logLik:    0.368944
deviance:  8.569461
AIC:       3.262112
BIC:       1.459337
AICc:     15.262112
```

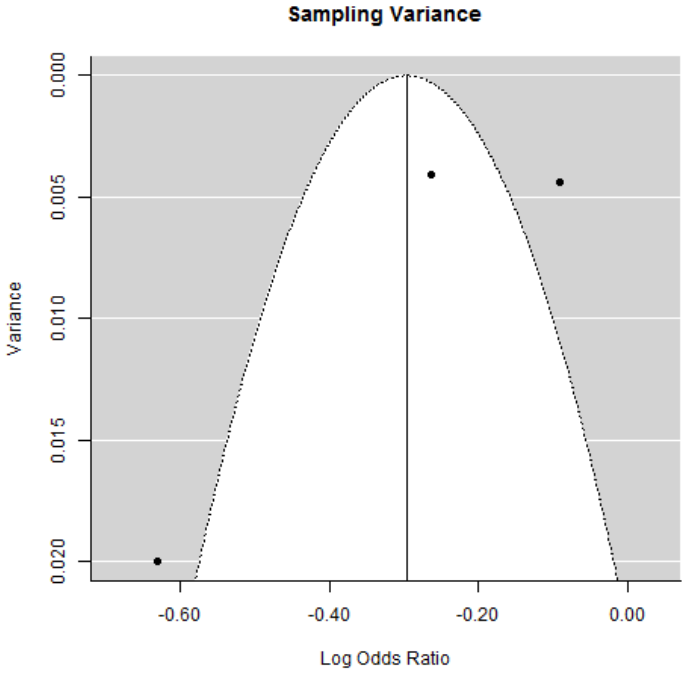
Forest plot



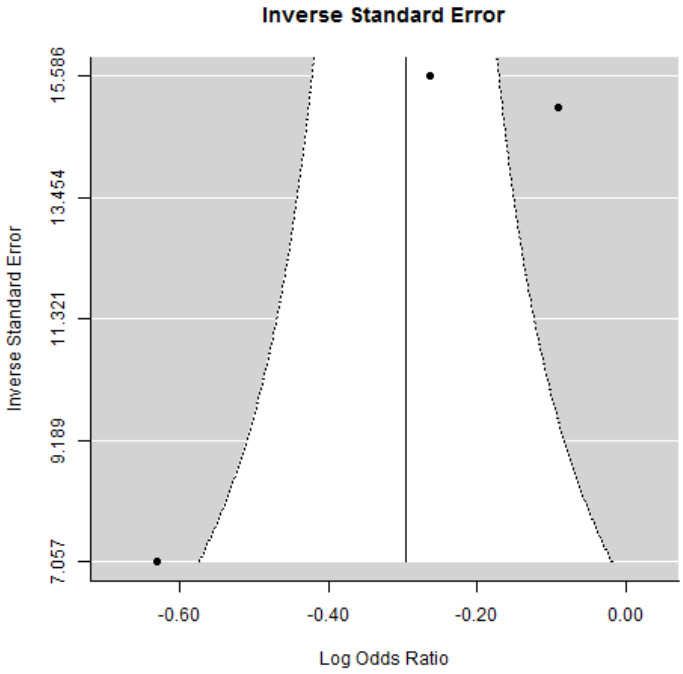
Funnel plot (Standard Error)



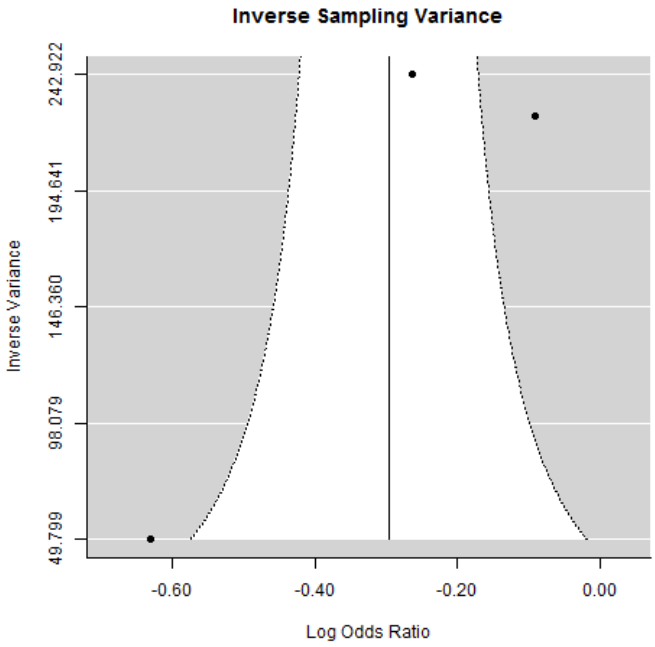
Funnel plot (Sampling Variance)



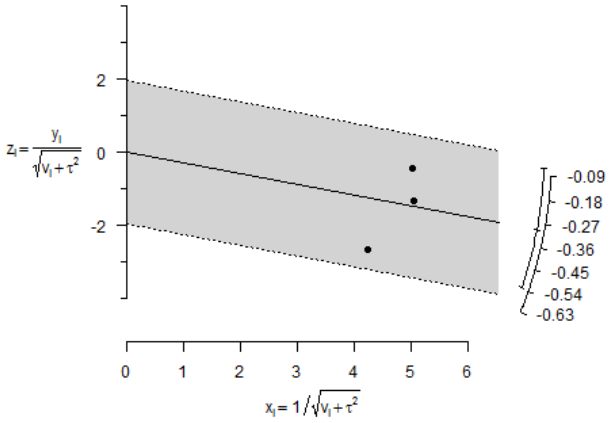
Funnel plot (Inverse Standard Error)



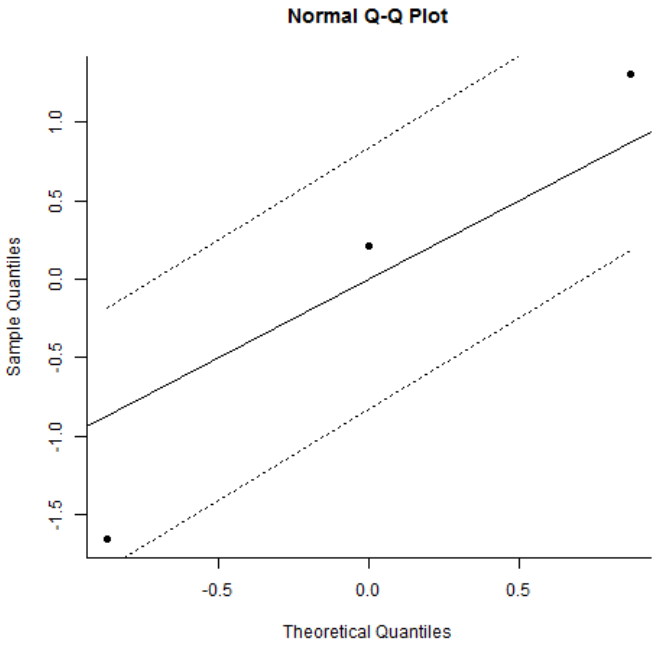
Funnel plot (Inverse Sampling Variance)



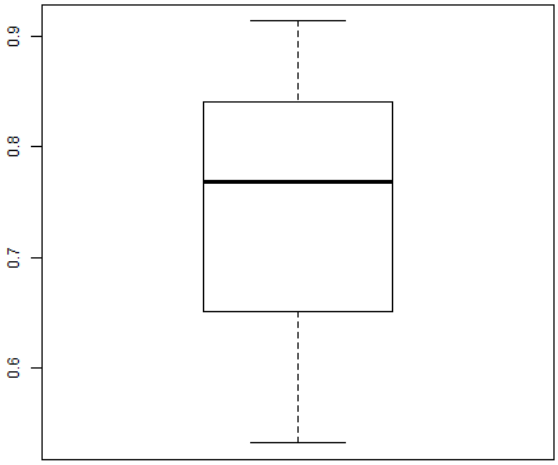
Radial (Galbraith) Plot



Normal QQ Plot (for selected statistical model)



Boxplot of effect size estimates



Meta-analysis

Stillbirth CCS vs non-exposed CCS

Main Summary

```
Random-Effects Model (k = 4; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.1662)
tau (square root of estimated tau^2 value):      0
I^2 (total heterogeneity / total variability):   0.00%
H^2 (total variability / sampling variability):  1.00

Test for Heterogeneity:
Q(df = 3) = 1.8960, p-val = 0.5943

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
0.4846   0.1988   2.4373   0.0148   0.0949   0.8742        *

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

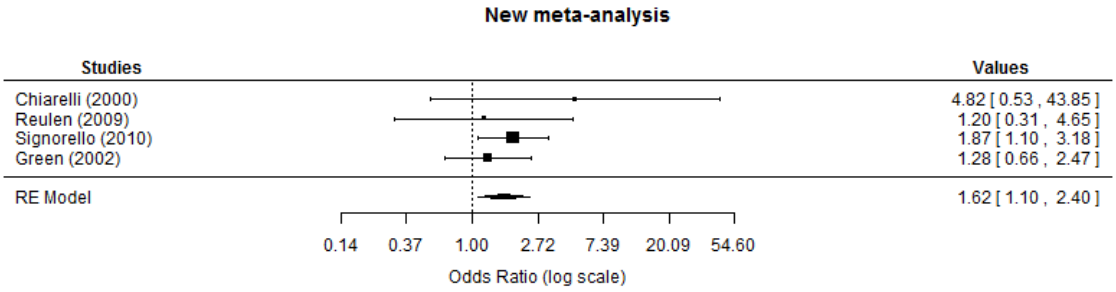
Fit Statistics

```
ML
logLik:   -1.979876
deviance:  1.895957
AIC:       7.959753
BIC:       6.732341
AICc:     19.959753
```

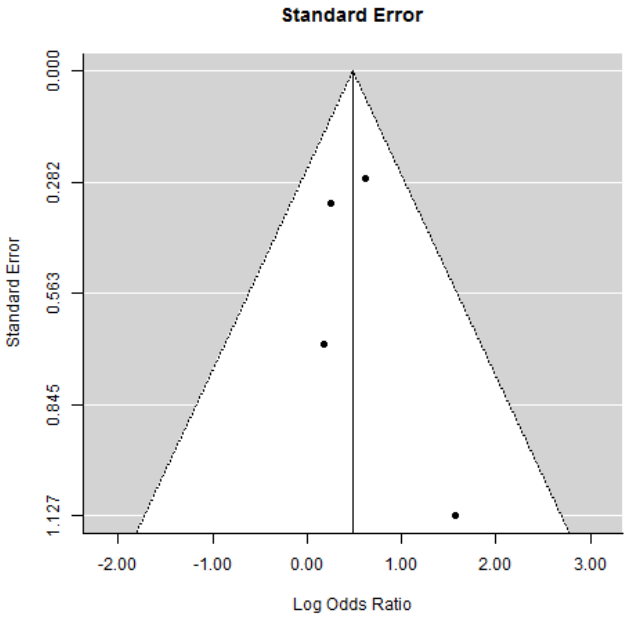
Confidence Intervals

```
estimate  ci.lb   ci.ub
tau^2    0.0000 0.0000  4.7612
tau      0.0000 0.0000  2.1820
I^2(%)   0.0000 0.0000 95.9005
H^2      1.0000 1.0000 24.3929
```

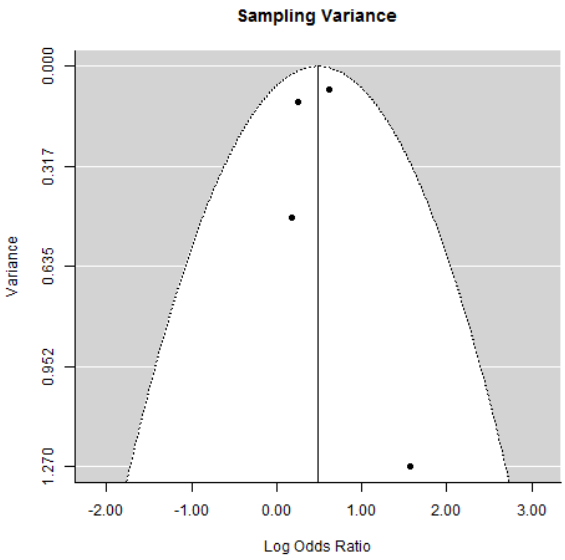
Forest plot



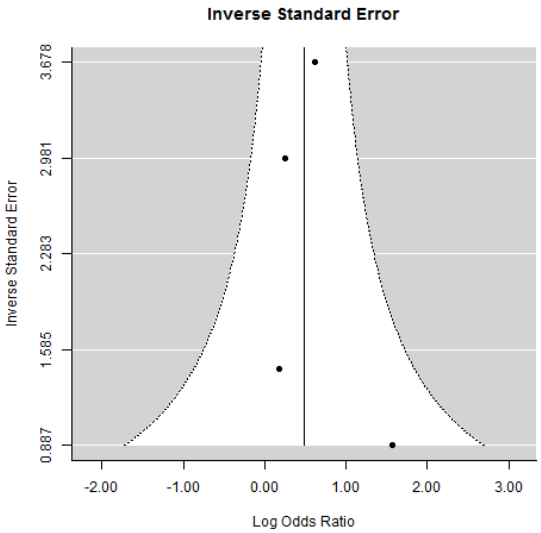
Funnel plot (Standard Error)



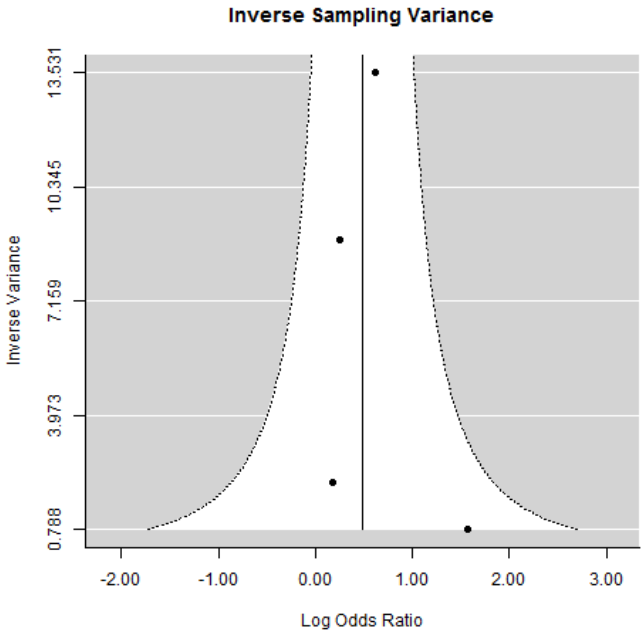
Funnel plot (Sampling Variance)



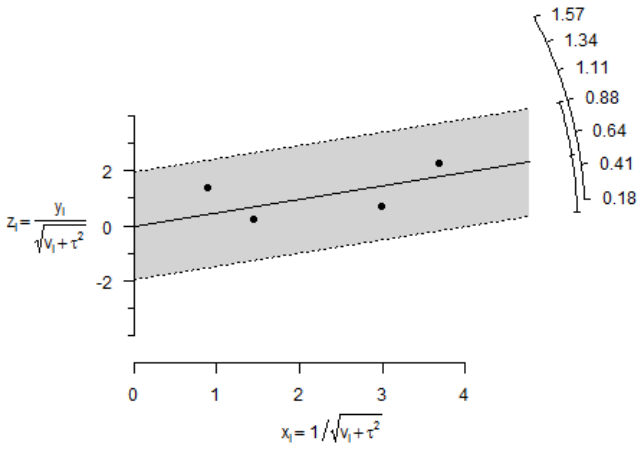
Funnel plot (Inverse Standard Error)



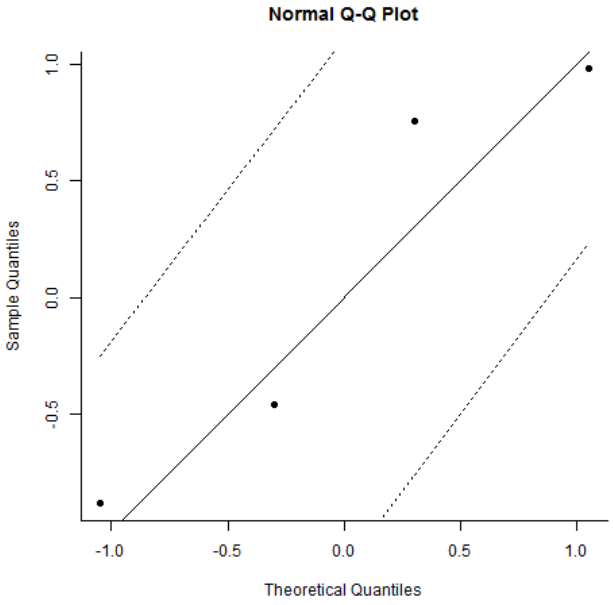
Funnel plot (Inverse Sampling Variance)



Radial (Galbraith) Plot



Normal QQ Plot (for selected statistical model)



Boxplot of effect size estimates

Meta-analysis

Miscarriage CCS vs non-exposed CCS

Main Summary

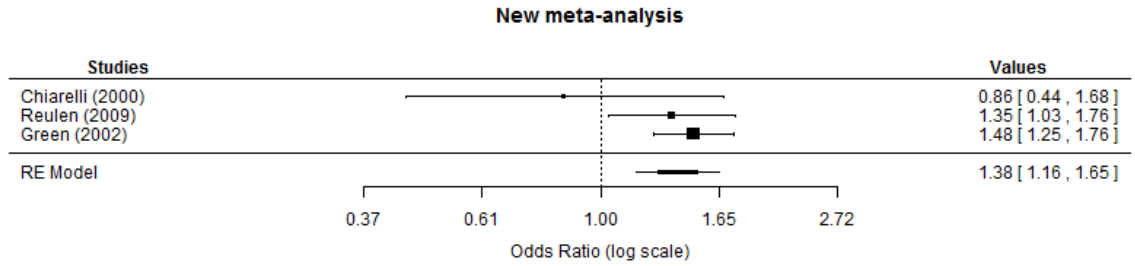
```
Random-Effects Model (k = 3; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.0060 (SE =
0.0285)
tau (square root of estimated tau^2 value):      0.0771
I^2 (total heterogeneity / total variability):   21.10%
H^2 (total variability / sampling variability):  1.27

Test for Heterogeneity:
Q(df = 2) = 2.5349, p-val = 0.2816

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
0.3251   0.0901   3.6074   0.0003   0.1485   0.5018      ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Fit Statistics

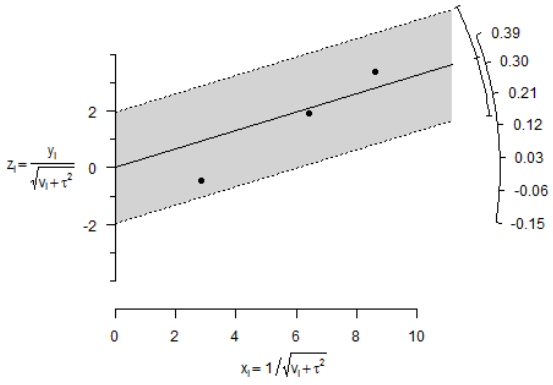
```
ML
```

```
logLik:     1.1864867

deviance:   3.1372145

AIC:        1.6270266

BIC:       -0.1757488

AICc:      13.6270266
```

Forest plot



Radial (Galbraith) Plot



Appendix 12 – Risk of bias scores

Risk of Bias

Green (2002)	Chiarelli (2000)
Selection • truly representative of a childhood cancer survivor **selection of control group** • drawn from the same community **Ascertainment of exposure** • secure record • self-report **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *siblings* **Outcome** • record linkage or other (please specify) • self-report **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement [Info] *in main study* • good quality score *3,1,2*	**Selection** • somewhat representative **selection of control group** • drawn from the same community **Ascertainment of exposure** • secure record • interview **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *different treatment type* **Outcome** • self-report **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement • poor quality *score -3,1,1*

Haggar (2014)	Green (2010)
Selection • somewhat representative **selection of control group** • drawn from a different source [Info] *non exposed population* **Ascertainment of exposure** • secure record **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for age of cases • study controls for other reason (please specify) [Info] *non-cancer* **Outcome** • record linkage or other (please specify) **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement	**Selection** • somewhat representative [Info] *restricted in terms of limited cohort as NWTSG cohort only.* **selection of control group** • drawn from the same community **Ascertainment of exposure** • secure record • self-report **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *radiotherapy vs non- radiotherapy unilateral Wilms survivors* **Outcome** • record linkage or other (please specify) • self-report **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement
• good quality score *3,2,2*	• good quality score *3,1,2*

Lie Fong (2010)	Winther (2008)
Selection • somewhat representative [Info] *one centre data therefore cannot be generalised to population* **selection of control group** • drawn from a different source [Info] *registry* **Ascertainment of exposure** • secure record **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *pregnancy outcome* **Outcome** • record linkage or other (please specify) **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement	**Selection** • truly representative of a childhood cancer survivor **selection of control group** • drawn from a different source [Info] *nationwide registry comparison* **Ascertainment of exposure** • secure record **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *non-cancer match* **Outcome** • record linkage or other (please specify) **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement
• good quality *score 4,1,2*	• good quality score *3,1,2*

Mueller (2009)	Signorello (2006)
Selection • somewhat representative [Info] *limited geographically* **selection of control group** • drawn from a different source **Ascertainment of exposure** • secure record **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) **Outcome** • record linkage or other (please specify) **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement	**Selection** • truly representative of a childhood cancer survivor **selection of control group** • drawn from the same community **Ascertainment of exposure** • secure record • self-report **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *siblings that had a pregnancy* **Outcome** • record linkage or other (please specify) • self-report **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement
• good quality score *3,1,2*	• good quality *score 4,1,2*

Reulen (2017)	Reulen (2009)
Selection • truly representative of a childhood cancer survivor **selection of control group** • drawn from a different source **Ascertainment of exposure** • interview • self-report **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *gen pop from HES registry* **Outcome** • record linkage or other (please specify) • self-report **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement	**Selection** • truly representative of a childhood cancer survivor **selection of control group** • drawn from the same community **Ascertainment of exposure** • secure record • self-report **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *radiotherapy vs chemo* **Outcome** • record linkage or other (please specify) • self-report **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement
• good quality score *3,1,2*	• good quality score *4,1,2*

Signorello (2010)
Selection • truly representative of a childhood cancer survivor **selection of control group** • drawn from the same community **Ascertainment of exposure** • secure record • self-report **demonstration that outcome was not present at start of study** • yes **Comparability** • study controls for other reason (please specify) [Info] *RT VS CHEMO* **Outcome** • record linkage or other (please specify) • self-report **was follow up after diagnosis long enough** • yes **Adequacy of follow up** • no statement
• good quality score *4,1,2*

Appendix 13 – Algorithm for risk for stillbirth