EVERPET-WG

Best evidence for management of peritoneal metastases

Cytoreductive surgery (CRS) with hyperthermic intraoperative peritoneal chemotherapy (HIPEC) with systemic chemotherapy versus cytoreductive surgery with systemic chemotherapy versus systemic chemotherapy in people with peritoneal metastases from colorectal, ovarian or gastric origin:

Systematic review, network meta-analysis, and individual participant data meta-analyses (IPD) of effectiveness and cost-effectiveness

Protocol

Conducted by the
EVidencE Review of PEritoneal Tumours (EVERPET) Working Group

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EVERPET-IPD research team

Project Management Group

Kurinchi Gurusamy
Division of Surgery and Interventional Science
University College London
Email: k.gurusamy@ucl.ac.uk
Tel: +44 (0)20 7794 0500 Ext: 33943
Claire Vale
MRC Clinical Trials Unit at UCL
Email: claire.vale@ucl.ac.uk
Tel: +44 (0)20 7670 4723
Rajesh Bhanot (patient representative)
Email: will be disclosed on a need to know basis
Research associate (to be appointed)

Research Steering Group

Kurinchi Gurusamy
Claire Vale
Brian Davidson
University College London
Email: b.davidson@ucl.ac.uk
Sarah O'Dwyer
The Christie NHS Foundation Trust
Email: Sarah.O'Dwyer@christie.nhs.uk
Omer Aziz
The Christie NHS Foundation Trust
Email: Omer.Aziz@christie.nhs.uk
Mark Saunders
The Christie NHS Foundation Trust
Email: Mark.Saunders@christie.nhs.uk
Tim Mould
University College London NHS Foundation Trust
Email: t.mould@nhs.net
Muntzer Mughal
University College London NHS Foundation Trust
Email: muntzer.mughal@nhs.net
Elena Pizzo

Centre of Applied Health Research
University College London
Email: e.pizzo@ucl.ac.uk
Dr Vic Verwaal
University of Southern DenmarkEmail: Victor.Jilbert.Verwaal@rsyd.dk

Two additional patient representatives

Meta-analysis Group

Kurinchi Gurusamy
Claire Vale
Research associate (to be appointed)

Collaborating Trialists

To be completed once additional confirmation is obtained

Contents

Background and rationale

What is the problem being addressed?

Approximately 7 million people worldwide and 160,000 people in UK develop colorectal, ovarian, or gastric cancer each year [1], of whom 8% to 50% develop peritoneal metastases. The peritoneum is one of the commonest sites of metastases from these cancers [2-8], and is often the only site of metastases [7-9]. In general, people with peritoneal metastases have poorer prognosis than those with other metastases (liver or lung) [10], with median reported survival ranging from 6 to 24 months depending on from the primary cancers and treatment received [11-13].

Treatment of peritoneal metastases

The current standard of care of people with peritoneal metastases from these cancers is systemic chemotherapy alone or in combination with either cytoreductive surgery (CRS) or palliative surgery [7, 8, 12-15]. CRS + hyperthermic intraoperative peritoneal chemotherapy (HIPEC) is an alternative treatment for these patients. The main principle of CRS+HIPEC is to remove all visible (macroscopic) peritoneal metastases followed by HIPEC to treat any remaining microscopic peritoneal metastases [16]. HIPEC involves peritoneal circulation of chemotherapy drugs (usually mitomycin C, 5-Fluorouracil, and oxaliplatin, or cisplatin) [17] heated to temperatures of 42° C, at which the chemotherapy drugs are potentiated [18]. Until only a decade ago, less than 5% of patients with peritoneal metastases underwent CRS+HIPEC, however this has progressively increased to about 10% of patients by 2012 [8, 9, 14]. CRS+HIPEC has been commissioned by NHS England for patients with peritoneal metastases from appendiceal tumours and colorectal adenocarcinoma.

Why is this research important to patients and health and care services?

Although CRS+HIPEC has the potential to improve the survival and health-related quality of life (HRQoL) in people with peritoneal metastases [14, 19, 20], there have been concerns raised about its safety. Reports have shown a 30-day mortality after CRS+HIPEC of 1-3% [6], and a major complication rate of 32% [6, 21], albeit that local audit data from high volume centres suggest that mortality and morbidity rates are somewhat less than in these reports (local audit data). The average costs of CRS+HIPEC per patient varies from about 20,000 USD to 80,000 USD [22-28]. Because of these reasons, this research is important to address the significant uncertainty about the benefits of an intervention that carries significant risk of harm to patients and costs to the NHS.

Review of existing evidence

There have been several overviews, systematic reviews, and health technology assessments (HTA) investigating this area. Sixteen systematic reviews of comparative studies have been undertaken, comparing CRS+HIPEC to other treatment modalities in peritoneal metastases from colorectal, ovarian, or gastric cancer [6, 17, 20, 29-41]. Ten of these included at least one RCT, but the conclusions were largely based on non-randomised studies [6, 17, 20, 29, 31-33, 35, 39, 41]. Although most of these systematic reviews concluded that CRS+HIPEC can improve survival in people with peritoneal metastases, all had limitations and deficiencies. Firstly, all are at high risk of bias according to ROBIS (risk of bias in systematic reviews) tool [42] with concern about bias across all domains. Secondly, the systematic reviews included only a single RCT [13] and/or based their evidence predominantly on non-randomised studies, without any adjustment for baseline differences in disease-related or patient-related prognostic characteristics [6, 17, 20, 29, 31-33, 35, 39, 41]. Finally, meta-analyses could only include a small proportion of the results from the studies because of the way these results had been reported (e.g. proportion survived versus median survival) [17, 20, 29, 35, 37]. Therefore, there is still considerable uncertainty about the benefits of CRS+HIPEC and which patient groups will benefit from it.

There have been two formal HTAs on this issue [26, 43]. The HTA reviewing patients with peritoneal disease from colorectal cancer concluded that there was moderate quality evidence that CRS+HIPEC prolonged survival based on a single RCT, but the costs were high [26]. The HTA on ovarian cancer (which did not include any RCTs) concluded there was no clear benefit of CRS+HIPEC for ovarian peritoneal metastases [43].

Justification for IPD

Through the collection and reanalysis of IPD from all relevant randomised controlled trials, we aim to overcome the limitations of the existing evidence and provide the highest quality evidence synthesis of the benefits and harms of CRS + HIPEC in patients with peritoneal metastases to inform clinical practice and future research. Importantly, the main advantages of using IPD over aggregate data in this setting are the following.

1. Overcome lack of reporting of key survival outcomes: The key survival outcomes have not been reported in a format that can be meta-analysed. This can be overcome with IPD.
2. Harmonise definitions of performance indicators and outcome: Use of IPD can ensure that the definitions of the prognostic and confounding factors, and outcomes are harmonised.
3. Improve the quality of the analysis: IPD is commonly reported to improve the quality of analyses [44, 45].
4. Investigate whether any patient-related or disease-related characteristics impact on the treatment effect at the individual level

Justification for changes in objectives

Justification for network meta-analysis and immediate cost-effectiveness analysis

The final results of the PRODIGE 7 trial , which showed that CRS with systemic chemotherapy provided equivalent results as CRS + HIPEC with systemic chemotherapy and resulted in fewer complications [46] are about to be published. The controversies and widespread implications of the PRODIGE 7 results [47-50] have already led to some governments withdrawing CRS + HIPEC for treatment of patients and colorectal peritoneal metastases and low or high PCI approving the treatment for only those with medium PCI [47]. Some clinical experts have concluded that HIPEC does not add value to CRS with systemic chemotherapy [49]. Other clinical experts noted that one of the most important questions in light of the PRODIGE 7 trial seems to be whether HIPEC adds value to CRS [48]. Yet another clinical expert stated: “the global ripples emanating from the preliminary results of PRODIGE 7 are palpable” [50]. The clinical co-applicant of the grant, Prof Sarah O’Dwyer (Lead Clinician for the Peritoneal Tumour Service at The Christie NHS Foundation Trust) emphasised the need for an immediate cost-effectiveness analysis to ensure that the NHS can make an informed decision about HIPEC.

Impact of COVID-19 on collection of IPD

By early 2020, three major trialists in the field had indicated willingness to provide data and investigators of many other smaller trialists had shown interest in participation. We were engaging with one major trialist to complete the approvals for data release. However, COVID-19 has brought this to a halt. We agreed in the Oversight Committee in March 2020 to suspend the study for 6 months. Given the ongoing crisis with COVID-19, we do not foresee that the COVID-19 situation will be resolved before the end of 2021 (with the advent of a vaccine) and to publicise the IPD in major conferences. Therefore, the cost-effectiveness analysis required immediately will not be available much later if based on IPD.

We will also need to set up a data transfer agreements between the trialists and UCL to transfer the data, but we may also need to get the Institute Review Board (IRB) approval in some centres resolved first because of the tougher regulations to transfer data (we got ethics from UCL, but it seems that it has become tougher to obtain IPD).

Justification for collection and analysis of aggregate data

Due to the COVID-related delays outlined above relating to completion of trials to time, and difficulties in securing access to IPD, it is unlikely that a full meta-analysis of IPD, as was our initial intent, is achievable. With the consent of the TSC, we will now aim to complete a meta-analysis using reported or other aggregate data from all completed trials. Inevitably, there will be some limitations to this approach and some of the original project aims would only be possible with IPD. Furthermore, as fewer than anticipated trials have reached completion, power to reliably detect and determine treatment effects overall and in particular, the impact of patient or treatment characteristics on the treatment effect will be hampered, whether IPD or aggregate data are analysed. Nevertheless, we aim to provide the most up-to-date and rigorous summary of the effects of adding HIPEC to CRS in this patient population to date, on which to base decisions regarding future clinical practice and research.

Aims and objectives

The overarching aim of this project is to answer the following research question:
Does CRS+HIPEC improve survival and/or quality of life compared to SoC in people with peritoneal metastases (from colorectal, ovarian, or gastric cancers) who can withstand major surgery and is it cost-effective in the NHS setting?

Primary objectives

To compare the relative benefits and harms of CRS+HIPEC versus CRS versus palliative treatment in people with peritoneal metastases from colorectal, ovarian, or gastric cancers eligible to undergo CRS+HIPEC by a systematic review and component network meta-analysis supplemented by IPD meta-analysis, when possible.

Secondary objectives

To compare the cost-effectiveness of CRS+HIPEC versus CRS versus palliative treatment from an NHS and PSS (personal social services) perspective using a model-based cost-utility analysis.

General Methods

Eligibility criteria

Type of studies

All RCTs regardless of the publication status, year of publication, and language of publication will be included.

Setting

Secondary or tertiary care with expertise to perform CRS+HIPEC

Type of participants

Inclusion criteria

People with synchronous or metachronous peritoneal metastases from colorectal cancer, ovarian cancer, or gastric cancer, eligible to undergo CRS+HIPEC regardless of the involvement of other organs and whether the primary cancer was resected completely (i.e. R0 resection). We will also include people with appendiceal adenocarcinomas under colorectal cancer as they behave in a similar way to colorectal adenocarcinomas.

Exclusion criteria

Studies on pseudomyxoma peritonei (PMP) will be excluded.

Intervention and control

We will include trials comparing the following interventions against one another.

1. CRS+HIPEC + systemic chemotherapy
2. CRS + systemic chemotherapy
3. Systemic chemotherapy based on platin-based regimens
4. Systemic chemotherapy based on older regimens such as 5-fluorouracil (for colorectal cancer)

Control

Outcomes

Primary outcomes

1. Overall survival, defined as time from randomisation until death by any cause.
2. HRQoL using any validated measure
3. Serious adverse events or Clavien-Dindo grade III or above [51, 52]

Secondary outcomes

4. Time to disease progression: defined as time from randomisation to death in people who died of treatment or disease-related causes, time from randomisation to recurrence in people in whom complete CRS was achieved, and time from randomisation to disease progression as defined by RECIST (Response Evaluation Criteria in Solid Tumors) criteria of 20% increase in size of the tumour or appearance of new lesions [53], or similar criteria used by authors
5. Non-serious adverse events or Clavien-Dindo grade I or II [51, 52]
6. Patient reported outcome measures

Search strategy

Electronic searches

We will search MEDLINE, EMBASE, Cochrane library, and the Science Citation Index for published trials as well as ClinicalTrials.gov, and WHO ICTRP trial registers for ongoing or unreported studies. The search strategies, which combine the Cochrane sensitivity maximising RCT filter [54] with a combination of subject headings and free text terms relating to the interventions and diseases of interest, are provided in Appendix 1. Searches will be updated periodically until October 2019.

Other resources

We will also search the references of all identified studies for additional studies eligible for inclusion. We will also contact the American Society of Peritoneal Surface Malignancies, the Canadian HIPEC Collaborative Group (CHICG), The Peritoneal Surface Oncology Group International (PSOGI), and the study authors who agree to participate in this project for further studies.

Data collection

Selection of studies

Two review authors will independently screen the titles and abstracts of all records retrieved and make the final selection based on full text (after translation if required, i.e. there will be no language restrictions). We will document the process to enable completion of the PRISMA flow-chart. We will resolve discrepancies through discussion and arbitration.

Data collection

At the study level, we will record the contact details of the study author and the study contact, information required to assess the risk of bias, details of the treatment centres (name and the average number of CRS+HIPEC performed per year).

At the participant level, we will collect the following details:

1. Centre at which treated
2. Patient demographics: age, gender, comorbidities, performance index
3. Cancer details (including severity)
4. Intervention details
5. Control details
6. Follow-up details
7. Outcome data
8. Resource utilisation data
    a. Operating time
    b. Quantity of blood and blood products transfused
    c. Length of hospital stay (including readmissions)
    d. Length of intensive care unit stay
    e. Chemotherapy regimen used in HIPEC and in control group if applicable
    f. Proportion in whom surgery was performed and the nature of surgery in the control group

g. Additional surgery and other palliative treatments

These data will be sought for all patients randomised into each trial. Up to date follow-up will be requested in order to report on longer-term outcomes: the existing ethical approval for the studies usually cover collection of data.

The proposed data format and coding conventions for these data will be developed as part of the project to obtain the EVERPET-IPD data dictionary. Transfer guide will be developed as part of the project. Although the aim of the conventions is to facilitate data transfer, they are not essential. Data will be accepted in the format most convenient for the individual trial investigator or data centre, however, **all personal identifiers (e.g. names) are to be removed before sharing**. Data should be transferred by encrypted email or source ftp site. Further details are included in the data transfer guide.

Data checking and management

Once trial investigators have agreed to provide the IPD, they will be asked to sign a data transfer agreement that covers the transfer, use and storage of that data. By signing up to the agreement, investigators also declare that they have complied with all laws and regulations relating to the conduct of their studies and the collection of data as part of those studies.

On receipt, data will be cleaned and checked for accuracy, consistency and validity. This will include checks for missing data, randomisation integrity, follow-up and censoring. We will query any anomalies with the study contact to ensure that the data are represented accurately, and send a summary of the final dataset from each trial to the study contacts for verification.

Once checked and verified, we will store the trial data securely. Access to the data will be restricted to the Project Management Group, who are all trained in data protection and personal data confidentiality and who will act as custodians of the data under the terms of the data transfer agreement, which will be developed as part of this project. In line with that agreement, data will be deposited in the EVERPET-IPD repository.

Assessment of risk of bias in included studies

We will use the Cochrane risk of bias tool to assess the risk of bias in RCTs [54]. If the RoB 2.0 [55] is validated, we will use the RoB 2.0 for assessment of risk of bias.

Meta-analysis of clinical effectiveness

Measures of treatment effect and data synthesis

We will use risk ratio for binary outcomes (proportion of people with serious and non-serious adverse events), mean difference (if same scales are reported in the studies) or standardised mean difference (if different scales are reported in the studies) for continuous outcomes (HRQoL), rate ratios for count outcomes (number of serious and non-serious adverse events), and hazard ratio for time-to-event outcomes (overall all-cause mortality and time to progression) with their respective 95% confidence intervals.

We will perform a two-step IPD, i.e. calculate the adjusted effect estimate from each included study and then perform a random-effects model meta-analysis using DerSimonian and Laird method [56] for binary outcomes and inverse variance method for other types of outcomes. The reason for choosing the two-step IPD over one-step IPD is the way the confounding factors are reported in the studies, for example, comorbidities can be reported as different types of performance indices and the extent of peritoneal disease can be reported in different ways [57, 58]. However, if we agree on an approximation to convert different performance indices into a single measure and convert the different measures of extent of peritoneal involvement into a single measure, we will perform a single-step meta-analysis to check the robustness of the two-step meta-analysis. We will test our assumptions in approximations (of the different performance indices into a single measure and different measures of extent of peritoneal involvement into a single measure) by sensitivity analyses. We will use multilevel modelling to take the clustering of data in the studies into account for the one-step IPD meta-analysis, as the unit of analysis will be the individual participant.

Dealing with missing data

We will perform an intention-to-treat analysis whenever possible [59]. If data on the classification of the treatment as intervention or control is missing, and cannot be ascertained though discussion with trialists, we will exclude such participants. If outcome data are missing, we will use multiple imputation method if the data are likely to be missing at random or best-case and worst-case scenarios analysis if it is felt that the outcome data are not missing at random.

Assessment and investigation of heterogeneity

We will assess the clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. Clinical heterogeneity could be due to the type of participants included in the studies (performance index, stage of cancer, extent of peritoneal involvement, other organ involvement), different interventions (complete CRS or not, chemotherapy agents used), different controls (chemotherapy alone or CRS or both), whether complete CRS was achieved (if the control group was CRS), or different follow-up methods (routine imaging versus clinical examination). Different study designs and risk of bias may contribute to methodological heterogeneity. We will calculate and report the between-trial standard deviation and I^2 as measures of heterogeneity.

If we identify substantial clinical, methodological, or statistical heterogeneity, we will explore and address it in subgroup analyses and/or metaregression using participant level covariates on the sources of clinical heterogeneity mentioned above except for routine imaging which will be a trial-level covariate. All sources of methodological heterogeneity will be trial-level covariates.

Sensitivity analysis

We will perform the following sensitivity analyses to assess the impact of:

- data not missing at random
- non-participation in the IPD
- methods (two-step versus single-step) and model (fixed-effect versus random-effects model) used for meta-analysis

- using ‘time from diagnosis’ rather than ‘time from randomisation’ for defining ‘time to disease progression’
- risk of bias.

Network meta-analysis

We will perform a component network meta-analysis of aggregate data to compare the different components of the interventions, namely, HIPEC, CRS, and systemic chemotherapy whenever possible.

We will conduct NMA on all outcomes with multiple treatment comparisons. We will obtain a network plot to understand the network geometry and ensure that the trials are connected by interventions using Stata/SE 15.1. We will ensure that similar types of participants are included in the trials included in the network. If it was felt that the types of participants included in the trials were different across comparisons, we will only not include the trials in the network meta-analysis. We will report only the direct pairwise meta-analysis for comparisons not connected to the network.

When we get the individual participant data, we will include the subset of trial participants who were similar across the different comparisons. Therefore, it is possible that the trials and participants that we include in the network meta-analysis may differ based on the aggregate data and individual participant data.

We will summarise the population and methodological characteristics of the trials included in the NMA in a table based on pairwise comparisons. We will conduct a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3 as per guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents using aggregate data (in the first instance) and appropriate likelihood, and link functions [60]. We will calculate the additive main effects, 2-way interaction, and the full interaction models based on component network meta-analysis [61], i.e. when there were combination of treatments or different components for treatments, we will calculate the effect of each component or combinations of treatment, synergistic or antagonistic interactions between the component or combinations of treatments, and treat each combination of component of treatment as a different treatment. We will use the model fit to guide the selection of the model to be reported. We will use systemic chemotherapy as the reference group.

For binary outcomes, we will calculate the odds ratio (OR) with 95% credible interval (CrI). For continuous outcomes, we will calculate the mean difference (MD) (if trials used same scale) or standardised mean difference (SMD) (if trials used different scales) with 95% Crl. For count outcomes, we will calculate the rate ratio (RaR) with 95% Crl. For time-to-event data, we will calculate hazard ratio (HR) with 95% Crl.

We will perform a fixed-effect model and random-effects model for the network meta-analysis, and report the more conservative model (treatment effect is smaller compared to the other model, i.e. usually using the random-effects model in the absence of ‘small-study’ bias). The codes we use for analysis will account for the correlation between the effect sizes from studies with more than two groups [60].

We will use a hierarchical Bayesian model using ‘vague’ priors and three different sets of initial values (to ensure convergence of values), employing codes provided by NICE DSU. We will use technical details similar to those of the PI's previous network meta-analyses (i. e. normal distribution with large variance (10,000) for treatment effect priors (vague priors) centred at no effect, uniform distribution uniformly (limits: 0 to 5, but adjusted according to the summary values for continuous outcomes) for the between-trial standard deviation in random-effects model assuming same between-trial variability across treatment comparisons). We will use a 'burn-in' of 30,000 iterations, check for convergence (of effect estimates and between-study heterogeneity) visually, and run the models for another 30,000 iterations to obtain effect estimates. If we do not obtain convergence, we will increase the number of simulations for the 'burn-in', use 'thin' or 'overrelax' options, or a combination of these approaches. If we still do not obtain convergence, we will use alternate priors and initial values [62]. We will estimate the probability that each intervention ranks at one of the possible positions using the NICE DSU codes. We will obtain the surface under the cumulative ranking curve (SUCRA) (cumulative probability) and rankogram [63, 64].

Direct comparison

We will perform the direct comparisons, i.e. pairwise meta-analysis of head-to-head evaluations using the same codes and the same technical details.

Additional sensitivity analysis in network meta-analysis

We will perform a sensitivity analysis taking the baseline into account using metaregression models provided in the DSU guidance.

Additional sensitivity analysis in direct comparisons (for mortality)

Panoramic meta-analysis is an approach that was first proposed for overviews of systematic reviews, where the effect of an intervention has been assessed across multiple disease types or settings. IN such scenarios, it is common for decision-making in one disease to take into account evidence from other settings. In this evaluation of HIPEC in addition to standard care (cytoreductive surgery +/- chemotherapy), we aim to look at three primary cancer types: ovarian, gastric and colorectal. Even among the individual cancer types, the effect of the intervention could vary according to whether complete cytoreduction is likely to be achieved or whether the intervention is used for recurrent cancer. Therefore, we aim to perform a panoramic meta-analysis to formally combine data across the three cancer settings using meta-regression approach (Hemming et al. Pooling systematic reviews of systematic reviews: a Bayesian panoramic meta-analysis. Statist. Med. 2012, 31 201–216) which through the assumption of partial exchangeability, produce slightly more precise estimates of treatment efficacy compared with the independent analysis. The meta-regression approach with partial exchangeability was chosen as the assumption of complete exchangeability of treatment effects across the different types of cancers (and in the case of the ovarian cancer, participants with primary or recurrent ovarian cancer) in likely to be wrong as indicated in the major differences in the treatment effects between different cancer types. In the meta-regression approach, we will include systemic chemotherapy in both arms as a factor and explore interaction of systemic chemotherapy with the treatment effect (of HIPEC).

In order to evaluate the impact of the missing studies (studies which were registered but never reported the results), we will perform sensitivity analyses. All the trials that we have identified are relatively small trials. There is anecdotal evidence that even the largest trials in this area have difficulty in being published if the results are negative, noting the time interval between presentation in conferences and full publication of results in the area. Therefore, the traditional methods of adjusting for small-study bias such as trim-and-fill method, Copas method, or the regression approach (Rücker et al. Detecting and adjusting for small-study effects in meta-analysis. Biom J. 2011 Mar;53(2):351-68) may not be applicable. As the main reasons for lack of publication in this situation is because of delays due to COVID-19 (where missing at random can be a reasonable assumption) or because of the negative results (i.e., results not favouring HIPEC), we will perform a sensitivity analysis where the missing studies are using the treatment effect observed in the studies reporting the data (missing at random assumption) and null effect (missing because of negative results). For the baseline control group proportion (required for calculating the standard error of the assumed estimate), we will use the control group proportion in the studies that reported the outcome.

Use of frequentist methods

If network meta-analysis is not feasible, we will perform the direct comparison analyses using frequentist approach as more systematic reviewers are familiar with the frequentist approach.

Cost-effectiveness analysis

Model

We will perform a model-based cost-utility analysis estimating mean costs and quality-adjusted life years (QALYs) per patient. We will compare CRS+HIPEC versus SoC in each of the three cancers by three separate cost-effectiveness analyses. The time horizon will be life-time time horizon. We will calculate the costs from the NHS and personal social services (PSS) perspective. We will discount the costs and utilities at the rate of 3.5% per annum [65].

We will create a decision tree model (one for each cancer) along the lines of the model that we used to compare two types of surgeries in pancreatic cancer [66]. Briefly, a patient with peritoneal metastases from one of the three cancers (colorectal cancer, ovarian cancer, or gastric cancer) and eligible for CRS+HIPEC can either undergo CRS+HIPEC or SoC. A proportion of patients undergoing CRS+HIPEC will have complete CRS (i.e. all macroscopic tumour is removed). A proportion of patients in whom CRS+HIPEC will develop complications (whether complete CRS was achieved or not), a proportion of whom may die within 90 days. Those who are alive at 90 days may die subsequently (a Markov model will be used to model this). The decision tree pathways in the people who had SoC will be identical: some will have complete CRS, some will have complications, some will die within 90 days, and some will die after 90 days.

Most of the information required for populating the decision tree (including resource utilisation data) will be obtained from the systematic review and IPD meta-analysis. For information not available from the systematic review and IPD meta-analysis, we will perform literature searches of NHS Economic Evaluation Database (NHS EED), the Health Economic Evaluations Database (HEED), MEDLINE, and EMBASE (for MEDLINE and EMBASE, we will combine the search strategy from Table 5 with sensitivity maximising 'economics' filter developed as a part of The Hedges Project of the Health Information Research Unit of McMaster University). We will also review the Cost-Effectiveness Analysis Registry (CEA) at Tufts University for information on quality of life. Currently, there is no HRG (Healthcare Resource Group) code available for CRS+HIPEC and SoC (which will vary according to the nature of the treatment). We will obtain resource utilisation data as part of the systematic review and IPD (please see above) and convert these to costs on the basis of NHS National Tariff, NHS National Schedule of Reference costs, British National Formulary, and/or local estimates as required.

We will assume that the people who die in each period will do so at a constant rate during the period and check whether this assumption is true using the IPD. If this assumption is not true, then we will use more complex models to mirror the survival curves based on the IPD. When no data are available from the IPD or published sources, a range of values will be used in the model. We will tabulate the inputs used in the decision tree model and the source of these inputs in the project report.

Measuring cost-effectiveness

We will measure cost-effectiveness using net monetary benefits (NMBs). For each treatment, we will calculate the NMB as the mean QALYs per patient accruing to that treatment multiplied by decision-makers' maximum willingness to pay for a QALY (also referred to as the cost-effectiveness threshold), minus the mean cost per patient for the treatment. In the UK, the lower and upper limit of the maximum willingness to pay for a QALY are £20,000 and £30,000 respectively [65]. NMBs will be calculated using the base case parameter values to obtain the deterministic results, which do not depend on chance. The option with the highest NMB represents best value for money. The NMB for CRS+HIPEC minus the NMB for SoC is the incremental NMB. If the incremental NMB is positive then CRS+HIPEC represents better value for money; if it is negative, the SoC represents better value for money.

A probabilistic sensitivity analysis (PSA) will also be undertaken [65]. The PSA involves Monte Carlo simulation and takes variability of all selected inputs into account simultaneously. Distributions will be assigned to parameters to reflect the uncertainty with each parameter value. A random value from the corresponding distribution for each parameter will be selected (by the computer). This will generate an estimate of the mean cost and mean QALYs and the NMB associated with each treatment. This will be repeated 5000 times and the results for each simulation will be noted. The mean costs, QALYs and NMB for each treatment will be calculated from the 5000 simulations; these are probabilistic results because they depend on chance. The NMB will also calculated for each of the 5000 simulations and the proportion of times each treatment had the highest NMB will be calculated for a range of values for the maximum willingness to pay for a QALY. These will be summarised graphically using cost-effectiveness acceptability curves. We will derive the 95% confidence intervals around the base case values using the 2.5 and 97.5 percentiles calculated from the PSA. We will also perform a value of information analysis and calculate the expected value of perfect information and the expected value of partially perfect information.

For the deterministic univariate sensitivity analysis, each variable in the cost-effectiveness model will be varied one at a time. The results of the sensitivity analysis will be represented in the tornado diagram which reflects the variation in the NMB within the range of the lowest and highest value used for a parameter with all else equal. If the variation in the NMB includes 0, then there is uncertainty in the cost-effectiveness due to the variation of the parameter.

We will also perform various subgroup analyses and sensitivity analyses guided by the results of the systematic reviews and IPD meta-analyses but will include subgroup analysis of different types of control (i.e., CRS alone or systemic chemotherapy alone or both) as a minimum. We will also perform a sensitivity analysis using information from 'real-life' prospective data from Christie NHS foundation trust (and from other NHS specialist centres if such information is available).

Project management

The overall project will be managed by the principal applicant, Prof Kurinchi Gurusamy (KG). The day-to-day management, research co-ordination, data collection, and data cleaning will be performed by a research associate (RA) appointed as part of this grant. Methodological support will be provided by KG and Dr Claire Vale (CV). The health economics supervision will be provided by Prof Steve Morris. The clinical co-applicants will help with recruitment of trialists through their professional connections with those trialists. The Research Management Group (RMG) comprising of the KG, CV, a patient representative, and the newly appointed RA will be established to ensure that the project is progressing as planned, and to take any remedial actions to ensure that the project milestones are met. The RMG will meet either via teleconferences or with face to face meetings monthly. The RMG will report on progress every 6 months to the research steering group (RSG) made up of all co-applicants and key collaborators. The RMG and RSG will ensure smooth running of the project and adherence to key milestones.

Dissemination and reporting plan

The authorship of the systematic review manuscript will comprise the Project Management Group, International Advisory Group, representatives from the included trials and patient representatives. Author names will be listed "for the EVERPET-IPD Working Group". We aim to present the findings at appropriate international meetings and publish the review, irrespective of the findings, in a peer-reviewed journal. A manuscript will be drafted, circulated to the Working Group for comment prior to being submitted for publication.

Project / research timetable

The timetable for key activities of the project have been revised as follows.

Proposed Timetable	
Spring 2019	Finalise and register protocol
Summer / Autumn 2019	Appoint Research Associate Finalise and establish data use agreements
Winter 2019	Set up secure database Initiate collaboration and data collection
Spring 2020 to Spring 2021 (April 2021)	Aggregate data meta-analysis completed
Summer/Autumn 2021 (October 2021)	Cost-effectiveness analysis based on aggregate data
Winter 2022	IPD data if available and cost-effectiveness analysis updated based on aggregate data

Appendix 1: Search Strategies

Medline

1. Hyperthermia, Induced/
2. ((hyperthermic or heated) adj3 (intraperitoneal or intra-peritoneal) adj3 (chemotherapy or chemotherapies)).ti,ab.
3. (intraperitoneal adj3 chemohyperthermia).ti,ab.
4. (HIPEC or IPHC or HIIC).ti,ab.
5. 1 or 2 or 3 or 4
6. Cytoreduction Surgical Procedures/
7. ((cytoreductive or cytoreduction or debulking) adj3 (surgery or surgeries or surgical or procedure or procedures)).ti,ab.
8. 6 or 7
9. 5 or 8
10. exp Colorectal Neoplasms/
11. exp Ovarian Neoplasms/
12. Stomach Neoplasms/
13. ((colorectal or bowel or colon or colonic or rectum or rectal or ovary or ovaries or ovarian or gastric or stomach) adj3 (cancer or cancers or carcinoma or carcinomas or tumour or tumours or tumor or tumors or neoplasm or neoplasms)).ti,ab.
14. 10 or 11 or 12 or 13
15. 9 and 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.
19. placebo.ab.
20. drug therapy.fs.
21. randomly.ab.
22. trial.ab.
23. groups.ab.
24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. exp animals/ not humans.sh.
26. 24 not 25
27. 15 and 26
28. (cost: or cost benefit analys: or health care costs).mp.
29. 15 and 28
30. 27 or 29

Embase

1. hyperthermic intraperitoneal chemotherapy/
2. ((hyperthermic or heated) adj3 (intraperitoneal or intra-peritoneal) adj3 (chemotherapy or chemotherapies)).ti,ab.
3. (intraperitoneal adj3 chemohyperthermia).ti,ab.
4. (HIPEC or IPHC or HIIC).ti,ab.

5. 1 or 2 or 3 or 4
6. cytoreductive surgery/
7. ((cytoreductive or cytoreduction or debulking) adj3 (surgery or surgeries or surgical or procedure or procedures)).ti,ab.
8. 6 or 7
9. 5 or 8
10. exp colon cancer/
11. exp rectum cancer/
12. exp ovary cancer/
13. exp stomach cancer/
14. ((colorectal or bowel or colon or colonic or rectum or rectal or ovary or ovaries or ovarian or gastric or stomach) adj3 (cancer or cancers or carcinoma or carcinomas or tumour or tumours or tumor or tumors or neoplasm or neoplasms)).ti,ab.
15. 10 or 11 or 12 or 13 or 14
16. 9 and 15
17. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/
18. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af.
19. 17 or 18
20. 16 and 19
21. (cost or costs).tw.
22. 16 and 21
23. 20 or 22

Cochrane

#1 MeSH descriptor: [Hyperthermia, Induced] this term only
#2 ((hyperthermic or heated) near/3 (intraperitoneal or intra-peritoneal) near/3 (chemotherapy or chemotherapies))
#3 (intraperitoneal near/3 chemohyperthermia)
#4 (HIPEC or IPHC or HIIC)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Cytoreduction Surgical Procedures] this term only
#7 ((cytoreductive or cytoreduction or debulking) near/3 (surgery or surgeries or surgical or procedure or procedures))
#8 #6 or #7
#9 #5 or #8
#10 MeSH descriptor: [Colorectal Neoplasms] explode all trees
#11 MeSH descriptor: [Ovarian Neoplasms] explode all trees
#12 MeSH descriptor: [Stomach Neoplasms] this term only
#13 ((colorectal or bowel or colon or colonic or rectum or rectal or ovary or ovaries or ovarian or gastric or stomach) near/3 (cancer or cancers or carcinoma or carcinomas or tumour or tumours or tumor or tumors or neoplasm or neoplasms))
#14 #10 or #11 or #12 or #13

#15	#9 and #14

Science Citation Index

# 1	TS=((hyperthermic or heated) near/3 (intraperitoneal or intra-peritoneal) near/3 (chemotherapy or chemotherapies))
# 2	TS=(intraperitoneal near/3 chemohyperthermia)
# 3	TS=(HIPEC or IPHC or HIIC)
# 4	#3 OR #2 OR #1
# 5	TS=((cytoreductive or cytoreduction or debulking) near/3 (surgery or surger-ies or surgical or procedure or procedures))
# 6	#5 or #4
# 7	TS=((colorectal or bowel or colon or colonic or rectum or rectal or ovary or ovaries or ovarian or gastric or stomach) near/3 (cancer or cancers or carci-noma or carcinomas or tumour or tumours or tumor or tumors or neoplasm or neoplasms))
#8	TS=(random* or placebo* or blind* or meta-analysis or cost or costs)
#9	#8 AND #7 AND #6

WHO trials register

Condition: colorectal OR bowel OR colon OR colonic OR rectum OR rectal OR ovary OR ovaries OR ovarian OR gastric OR stomach
Intervention: HIPEC OR hyperthermic intraperitoneal chemotherapy OR IPHC OR intraperitoneal chemohyperthermia OR HIIC OR heated intraoperative intraperitoneal chemotherapy OR cytoreductive surgery OR CRS

ClinicalTrials.gov

Condition: colorectal OR bowel OR colon OR colonic OR rectum OR rectal OR ovary OR ovaries OR ovarian OR gastric OR stomach
Study Type: Interventional Studies (Clinical Trials)
Intervention/treatment: HIPEC OR hyperthermic intraperitoneal chemotherapy OR IPHC OR intraperitoneal chemohyperthermia OR HIIC OR heated intraoperative intraperitoneal chemotherapy OR cytoreductive surgery OR CRS
Interventional studies, phase 2,3,4
Interventional Studies | colorectal OR bowel OR colon OR colonic OR rectum OR rectal OR ovary OR ovaries OR ovarian OR gastric OR stomach | HIPEC OR hyperthermic intraperitoneal chemotherapy OR IPHC OR intraperitoneal chemohyperthermia OR HIIC OR heated intraoperative intraperitoneal chemotherapy OR cytoreductive surgery OR CRS | Phase 2, 3, 4

Cost-Effectiveness Analysis (CEA) Registry

The following terms were searched:
Hyperthermic
Cytoreduction
Cytoreductive

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