The statistical methods used to analyse each of the datasets were:
1.Repeated analysis of covariance (ANCOVA) at each follow-up time point.
2.Generalised estimating equations, and
3.Mixed effects.
The performance measures used to compare the methods were convergence, power, type I error, and coverage. Stata IC 14 software and the University of Oxford Advanced Research Computing (ARC) facility are being used to conduct this work.
Timing of Potential Results: It is anticipated that this study will be completed during the summer of 2019.
Potential Relevance & Impact: The results will provide evidence to inform the choice of longitudinal analysis methods in randomised trials. This could allow trialists to select the methods that will provide the highest statistical power for the anticipated pattern of treatment effect and could result in reducing the required sample size whilst maintaining adequate statistical power.

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Allowance for learning and clustering effects in the design and analysis of multicentre randomised trials: current practice and experiences

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Introduction: Patient outcomes can depend on the treating centre, or health professional, delivering the intervention. Differences in treatment delivery can be more prominent in trials investigating a complex intervention, such as surgery. Considering any potential difference in delivery at trial outset will ensure that any adjustments, as appropriate, can be made. The objective of this work was to establish current practice for the allowance of learning and clustering effects in the design and analysis of randomised multicentre trials.
Methods: A ten question survey was developed by the study team comprising open and closed questions that drew upon quotes from existing guidelines, references to relevant publications, and example trial scenarios. All registered UK Clinical Research Collaborative registered Clinical Trials Units were invited to participate.
Results: Completed surveys were obtained from 44 of 50 registered Units. Adjusting for learning by design through defining a minimum level of expertise for treatment provider was common (89%), although one third of units also had experience of expertise based designs. Managing clustering by design through stratification by centre was universally most common across the various trial types presented, and by treatment provider less so. Analysis of learning was rarely performed for the main analysis (n=1), although many units reported approaches to complement such analyses, such as sensitivity analyses. The majority of responders had indicated experience in adjusting during analysis for clustering, by centre or treatment provider, although approaches to doing so varied. Responders provided insight behind the approaches used within their unit and reasons for, or against, alternative approaches.
Discussion: This survey identifies widespread awareness of the potential methodological challenges associated with the design and analysis of multicentre trials, although approaches used and opinions on these vary.

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An Independent Patient Data Meta Analysis to compare adjuvant therapies in patients suffering with Pancreatic Cancer

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Introduction: Pancreatic Cancer is a disease with particularly poor prognosis with approximately 5% of patients surviving 5 years or more. Only 20% of patients are eligible for surgery and adjuvant therapy, but for those who do, prognosis improves with reported 5 year survival rates of 30% or more. A number of trials have explored the use of radiotherapy and chemotherapy although the best approach is still a matter of much discussion.
Methods: An independent patient data meta analysis of randomised controlled trials was performed using 3553 patients from 10 randomised controlled trials. Data are analysed using a Hierarchical Bayesian Network Meta Analysis incorporating frailty terms for patient nationality, modelling the baseline hazard function using a Piecewise Exponential Model and adjusting for trials with more than two therapies evaluated. Sub groups analysis are performed on consistent prognostic factors.
Results: An established network allows for comparisons of radiotherapy vs Chemotherapy Vs Observation only using direct and indirect evidence. Furthermore, networks allow direct and indirect comparisons of various types of chemotherapy. Subgroup analysis shows that the effect of therapy does depend on reported prognostic factors.
Discussion: IPD meta analysis improves the knowledge base of the effect of adjuvant therapies for resectable pancreatic cancer and identifies consistent prognostic factors which can help direct treatment decisions.

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Joint Modelling for longitudinal measures of marker CA19-9 and survival data in patients with pancreatic cancer

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Introduction: Diagnosis of pancreatic cancer is increasing worldwide but its prognosis remain extremely poor even after resection. The ESPAC-4 trial showed that the adjuvant combination of gemcitabine and capecitabine improves overall survival compared to gemcitabine alone after resection for pancreatic ductal adenocarcinoma. CA19-9 concentration is a post-operatively established prognostic marker but little is known of its role in providing predictions of survival probabilities over time.
Methods: The relationship between longitudinal and time-to-event data was explored on 431 patients from the ESPAC-4 trial by means of joint modelling technique. A Cox proportional hazard regression was used for modelling survival data while linear mixed model was applied for CA19-9 follow-up measurements, incorporating random intercept and slope components.
Results: Joint modelling describes the evolution of the CA19-9 marker in time and provides an estimate of its association with time to death. Results show that CA19-9 decrease after surgery, reaching a plateau for the following months. However, the marker concentration spikes again with proximity to death.
Discussion: Joint modelling analysis improves the understanding of the latent association between CA19-9 marker and survival outcome,