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Trials

MEETING ABSTRACTS Open Access

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P-1
Abstract omitted

P-2
Some practical considerations in the design of multi-arm multi-stage designs

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Trials 2019, **20(Suppl 1):**P-2

Introduction: In the design of cancer clinical trials, one is often concerned with a number of options in the event that several treatments are of interest.
Methods: We explore in this work the distinct possibilities when four treatments are available, one acting as control and three as potentially efficacious alternatives. This design may be embedded within the context of multi-arm multi-stage (MAMS) trials where one may select a two- or three-stage design.
Potential Results: We explore the application of such designs, including trade-offs between potential gains in the number of patients with additional stages contrasted with patients "lost" due to practical considerations such as patients randomised in dropped arms while waiting for interim analyses and inspection by an Independent Data and Safety Committee. In addition, in cancer studies one may focus on the primary end-point using a time-to-event analysis or a binary outcome by looking at the probability of (potentially progression-free) survival at a specific, clinically meaningful, time point. The effect of such choices is extensively investigated.
Potential Relevance & Impact: We conclude with a discussion of the available software for MAMS designs and their advantages and disadvantages in terms of accuracy.

P-3
The UK plasma based Molecular profiling of Advanced breast cancer to inform Therapeutic CHoices (plasmaMATCH) Trial: A multiple parallel-cohort, phase IIa platform trial aiming to provide proof of principle efficacy for designated targeted therapies in patient subgroups identified through ctDNA screening (CRUK/15/010)

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Trials 2019, **20(Suppl 1):**P-3

Introduction: plasmaMATCH is a novel platform trial which assesses the potential of circulating tumour DNA (ctDNA) screening to direct targeted therapies in advanced breast cancer (ABC) patients. The trial recruited ahead of target and will report initial results within 3years of first patient first visit demonstrating efficiency of this design.
Methods: plasmaMATCH is an open-label, multi-centre phase IIa platform trial, consisting of a ctDNA screening component and five parallel treatment cohorts. Patients with an actionable mutation identified at ctDNA screening are invited to enter Cohorts A-D to receive a targeted treatment matched to the mutation identified (A: ESR1–extended-dose fulvestrant; B: HER2–neratinib+/-fulvestrant; C&D: AKT1 (or PTEN for Cohort D) –AZD5363+/-fulvestrant). Cohort E was added

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was a multicentre randomised controlled trial run in neonatal units in the UK and Ireland, investigating two speeds of increasing milk feeding in 2804 infants with gestational age at birth <32 weeks and/or birth weight <1500g. Primary outcome was the proportion of infants surviving without moderate or severe neurodevelopmental disability at 24 months of age, assessed via parent-completed questionnaire.
Methods: Questionnaires were posted 17 days before participants reached 24 months of age corrected for prematurity. Lack of parental response triggered two postal reminders and one by phone, with two weeks between each.
Measures introduced to improve response included contacting parents prior to the questionnaire being posted; offering online questionnaire completion; a second reminder being accompanied by a phone call and text message; promotion by Bliss (third sector stakeholder); sending posters to sites for display in outpatient clinics; and ultimately an incentive voucher (described elsewhere). Outcome data were also sourced from routine clinical follow-up appointments at sites for infants whose parents did not complete the questionnaire.
Results: Response rate prior to all interventions was 51.0%; at data lock in April 2018 it was 76.5% (p<0.01). The largest increases (6%) following a single intervention were seen after introducing pre-questionnaire phone calls (p=0.07) and online completion (p=0.04).
Recruiting sites supplied additional data from 351 routine clinical follow-up appointments. Primary outcome could be determined for 88.5% of the cohort.
Discussion: Multiple methods of contact, especially phone contact prior to dispatch of questionnaire and availability of the questionnaire online, may improve response rate to postal questionnaires among parents of very preterm infants. Over time, promotion by sites and on social media may also play a role. Missing data can be supplemented by information from routine sources.

P-182

Conditional versus Non-Conditional Incentives to Maximise Return of Postal Questionnaires in Clinical Trials: A Randomised Study Within a Trial

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Trials 2019, **20(Suppl 1):**P-182

Background: High levels of retention in clinical trials is essential to gain robust evidence to guide care. Many approaches have been used to improve participant retention, but few have been evaluated. The addition of a monetary incentive has been shown to increase retention, but it is not known whether the point at which an incentive is given matters. We aimed to determine whether there was a difference in follow-up trial questionnaires returned when a monetary incentive given to trial participants at recruitment (non-conditional), and when patients were informed at recruitment that the incentive would be given only once a questionnaire had been returned (conditional).
Method: This was a sub-study within the Antivirals for influenza-Like Illness, An rCt of Clinical and Cost effectiveness in primary CarE Trial. Sites were matched according to previous recruitment or practice list size. Practice pairs were randomised to giving either a non-conditional or conditional incentive. Analyses were conducted according to randomised group irrespective of compliance. Statistical significance was assessed at the two-sided 5% level. The primary analysis was regression adjusted for practice pair with various sensitivity analyses.
Results: Only 28 out of the 42 sites recruited at least one participant (range 1 to 56) with 10 practice pairs recruiting one or more participants at both constituent sites. There was no evidence of a difference in the proportion of questionnaires returned, time taken to return questionnaires, nor proportion of pages completed, by intervention group (all p>0.05). Findings of the sensitivity analyses yielded similar findings. The conditional incentive cost approximately £23 less per diary returned.
Discussion: There was no evidence of a difference in questionnaire returns, nor the time to questionnaire return or completeness. There was low precision, given the small number of sites which recruited, and variability between sites in recruitment performance. The conditional approach cost less.

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Pen and Social Incentive Letter Retention Study within a Trial (SWAT) - An embedded, factorial design randomised controlled trial to investigate whether the inclusion of a pen and/or social incentive text cover letter included with the 12-month postal questionnaire improved response rates

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Trials 2019, **20(Suppl 1):**P-183

Introduction: Poor return of questionnaires in randomised controlled trials (RCTs) affects retention rates. This can introduce bias and thus affect generalisability and validity, with an associated reduction in statistical power. The objective of this study within a trial (SWAT) was to assess whether a pen and/or social incentive text cover letter sent with the 12-month questionnaire increased postal questionnaire response rates for participants in an RCT. We aimed to compare the inclusion of a pen in questionnaires with no pen; and the use of a social incentive text cover letter compared with no cover letter.
Methods: A 2x2 factorial SWAT within the 'Occupational therapist home assessment and modification for prevention of falls trial (OTIS)' host trial. Participants due their 12-month follow-up questionnaire were randomised to be sent a pen; a social incentive text cover letter; both; or neither. Primary outcome was the proportion of participants in each group who completed and returned the questionnaire. Secondary outcomes were time to return and completeness of the questionnaire, number of reminder letters sent and the cost effectiveness. To date 624 participants have been randomised.
Timing of Potential Results: By the time of the conference we will present findings on questionnaire response rates, time to return and completeness of the questionnaire, number of reminders and cost effectiveness. Odds ratios will be calculated and reported, along with confidence intervals and p values. Adjusted hazard ratio results will be presented for time to return the questionnaire, and the need for a reminder.
Potential Relevance and Impact: Our SWAT will add to evidence for improving retention rates in RCTs. Findings of the pen SWAT will be combined with results of other SWATs in a meta-analysis to detect small but cost-effective differences. Evidence for the social incentive cover letter will need to be replicated in further SWATs.

P-184

Factors that affect attrition in RCTs for the treatment of depression

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Trials 2019, **20(Suppl 1):**P-184

Introduction: Attrition is a common feature in clinical trials; higher attrition rate can affect the statistical power of an RCT and can undermine the external validity of the study. Therefore, it is important to evaluate and understand the factors that could affect attrition so that informed decisions can be made when planning a trial. We undertook a systematic review and meta-analysis of randomised studies treating depression to determine attrition, and predictors of attrition in these RCTs.
Methods:A comprehensive search was undertaken to identify RCTs of interventions to treat depression. Firstly, Cochrane reviews with "depression" in the title, abstract or keywords were identified and were eligible if were published in or after 2005; their scope matched our review's eligibility criteria; and their inclusion criteria did not

require another co-morbidity to be present (e.g. Bipolar disorder). We then screened both included and excluded trials from these reviews to identify eligible trials.
As well as estimating attrition rates overall, we hypothesised these may depend on year of the study, blinding, burden of the outcome measures, follow-up schedules, intervention burden, target sample size, recruitment setting, number of arms, type of intervention, type of control and participant characteristics.
Results: Many studies did not report their target sample size, number screened or drop out details. The average attrition rate was 22% but ranged from 0% to over 70%. Our results suggest that trials that had combinations of intervention types (i.e. behavioural and drugs) had lower attrition rate than trials with interventions that were purely drugs or behavioural therapy.
Discussion: Although a review cannot identify and quantify the true relationship between trial design and attrition, this review provides some insight into what levels of attrition may be expected in a future trial. It also highlights the lack of reporting of key factors.

P-185

Methods to improve follow up procedures in a sexual health study [safetxt]

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Trials 2019, **20(Suppl 1):**P-185

Introduction: Almost half of trials fail to achieve their follow up target. Follow up in young people and on sensitive topics is particularly challenging, with less than 50% return rate of postal STI samples sent to young people in previous trials. Effective evidence-based strategies to increase follow up rates were used.
safetxt, a study of a sexual health intervention, recruited 6252 participants aged 16-24 from 52 UK sexual health sites. Participants were required to return two postal questionnaires and an STI test kit at 12 months. We used evidence-based strategies to increase follow up rates through contact by post, telephone, text message and email.
In May 2018, follow up return rates were 88.7% for the four week questionnaire, 74.7% for the one year questionnaire and 67.75% for the test kit. We aimed to further increase follow up rates.
Methods: Retaining participants that regularly changed address and phone number was challenging, but contact was achieved through various approaches. Sites were encouraged to emphasise the importance of follow up to participants at the time of consent and provided participants with pocket cards with a reminder of follow up dates. Mail outs were developed to improve communication with participants and simplify return methods.
Additional evidence based methods were implemented, including the use of postage stamps on return envelopes and a cash prize draw for returned test kits.
Results: By April 2019, follow up rates of the four week questionnaire were maintained. At one year, follow up rates were 76.8% for the questionnaire and 71.7% for the test kit.
Follow up rates for the one-year questionnaire and test kits returns have continued to increase since introducing strategies from May 2018.
Discussion: Even when evidence based methods are already being used, developing new approaches and employing additional evidence based strategies improved follow up rates.

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Assessing attrition in Randomised Control Trials, the identification of attrition risk factors and the challenges of poor reporting: A comparison of reports from 2013 and 2018

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Trials 2019, **20(Suppl 1):**P-186

Background: Addressing attrition in clinical trial design is an important priority. Despite availability of statistical methods for missing data, prevention is preferred. The development of effective retention interventions needs to be based on improved understanding of attrition risk factors. We aimed to identify attrition risk factors.
Methods: Two-arm, parallel, RCTs reported in JAMA, NEJM, BMJ and The Lancet during 2013 and the first quarter of 2018 were identified using MEDLINE(Ovid). The number of randomised participants without observed primary outcome data were dual extracted. Associations with intervention type, primary outcome characteristics and trial setting were assessed using univariate analysis.
Results: 141/159 (89%) of 2013 trials had missing data equating to 5.4% [1.5, 10.7] of randomised participants per trial. This was lower in 2018 with 38/46 (83%) reporting a median 2.6% [0.3-15.4]. In 2013, increased attrition was associated with outpatient data collection, studies within chronic conditions, smaller trials (recruitment target and number randomised), shorter recruitment and longer follow up. Data collection by clinicians and recruitment in acute settings was associated with lower levels of attrition. The 2018 cohort generally supported these observations although in some areas the numbers were too small for comparison. Data extraction was challenging and the CONSORT often did not provide an effective trial summary: A fifth of all diagrams were in the supplementary material; 19% did not report the numbers analysed for the primary outcome and for a further 6% this did not match the results; Imputed data was not clearly reported in 27%.
Discussion: Levels of missing data were lower than anticipated, but this still equated to wasting an average of one month of participant recruitment. Poor reporting may underestimate the extent of missing data. Improvements to the CONSORT are recommended, in particular explicit reporting of imputed primary outcome data.

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Generating collaborative relationships for a successful trial follow-up

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Trials 2019, **20(Suppl 1):**P-187

Introduction: Collection of developmental follow-up outcomes is critical to demonstrate long-term effects of interventions in neonatal trials.
The Benefits of Oxygen Saturation Targeting (BOOSTII) trial enrolled 1135 infants born less than 28 weeks gestation, to investigate the