designed to provide one-sided alpha equal to 2.5%, and 90% power. If, due to lack of adherence to the standard drug, the constancy assumption fails and the active-control therapy is 10% less effective than planned, the probability of a false non-inferiority finding rises from 2.5% to 16%. If the active control therapy is 10% more effective than planned (for example, if adherence were higher than planned), power falls from 90% to 52%. By revising the NI margin according to the pre-specified meta-regression model, and maintaining the pre-specified MCID, both alpha and power can be corrected to planned levels without modification to the planned sample size. If the allowable effectiveness of the experimental therapy is permitted to vary depending on the estimated active-control effect, alpha and power can be partially corrected by updating the margin, and fully corrected by updating both the margin and the sample size.

Conclusion

If prior placebo-controlled trials provide evidence of an association between population characteristics and the effectiveness of an active-control therapy, non-inferiority margins can be adjusted based on observed population features, effectively maintaining pre-specified levels of Type-I error and power.

O6

A revised tool for assessing risk of bias in randomized trials (RoB 2.0)

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Background

The Cochrane risk of bias tool for randomized trials seeks to determine whether the findings of a randomized trial can be believed. First released in 2008, and revised slightly in 2011, it is the most widely used risk of bias tool in both Cochrane and non-Cochrane reviews on the effects of interventions. However, evaluations of the tool have highlighted some problems. Objective: To introduce a revised tool to assess risk of bias in randomized trials (RoB 2.0), which builds on the established Cochrane risk-of-bias tool as well as the thinking behind the recently developed tool for non-randomized studies (ROBINS-I).

Methods

Over the last year, we assembled collaborators from across the world to develop RoB 2.0. We held an initial development meeting in August 2015 where the main structure of the tool was agreed. Working groups were formed and tasked with developing signalling questions, criteria for reaching a judgment and full guidance. Working groups' contributions were collated and the draft version of the new tool was extensively piloted by individuals with varying degrees of experience, at a three-day event held in Bristol in February 2016 and remotely. The piloting feedback was considered at a second development meeting in April 2016, where refinements to the tool and to the written guidance that accompanies it were made. The working groups were further tasked with developing algorithms for reaching a domain-level judgment and creating worked examples. Further pre-release piloting took place in September 2016.

Results

Key changes in RoB 2.0 compared with the 2011 version of the tool are: – simplification of issues into fewer (mandatory) bias domains; – clearer focus on risk of bias in a specific result from the randomized trial; – introduction of signalling questions - which are reasonably factual in nature - to facilitate risk-of-bias judgements; – algorithms to reach risk of bias judgements; – clarification of differences between the review team's interest on the effect of assignment to intervention (the intention-to-treat effect) versus the effect of starting and adhering to intervention: issues of blinding, implementation and adherence differ importantly between these; – clarification that selective reporting should be assessed only when a result is available (whereas selective non-reporting should be assessed at meta-level); – separate templates for parallel group trials, cluster-randomized trials and cross-over trials.

Conclusions

We believe the new tool will offer considerable advantages over the existing tool. Once programmed into software, we expect the tool will be easier to use than the first version. Some issues remain to be resolved, however, such as how many results should be assessed for each study, and how best to integrate the assessment into the data extraction process. This presentation will provide an introduction to the tool. Further details of RoB 2.0 will be available from riskofbias.info.

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O7

Simulation of various strategies for optimal selection of randomization methods in multicenter clinical trials

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The random allocation and masking of participants to treatment are procedures in a study design essential to minimizing bias and the success of a clinical trial. The essence of the randomization process is to ensure an equal probability for each participant to be assigned to active or control treatment groups, which naturally leads to three properties of the randomization procedure: balance in sample size and constitution between treatment and control groups, unpredictability in the allocation of a participant to a certain group, and simplicity for an investigator to implement without compromising the randomization principle. With recent advances in biomedical and statistical methodologies, the area of clinical trial design is evolving rapidly with varying opinions on an optimal randomization method. Randomization methods have now expanded into more advanced approaches beyond the classical assignment to treatment groups (e.g. covariate adjustment in the randomization procedure, changing probability of assignment as in adaptive designs). Thus, the traditional randomization method faces new challenges, both theoretically and pragmatically. With increasingly complex trial designs, it becomes more challenging to determining the most appropriate randomization method. To help select an optimal randomization method, we performed numerical simulations to assess various randomization strategies in a centralized randomization system for multicenter clinical trials, by considering varying values for several design parameters including trial sample size, covariate strata, clinical sites, treatment arms, and allocation schema. For each scenario of simple, permuted block, stratified permuted block, and adaptive randomization strategies, imbalance and predictability were estimated through numerical simulations (repeated 10,000 times). Simulation results are tabulated in a series of tables serving as a useful reference for choosing an appropriate randomization method given a particular trial design. The goal of this study is to provide data support for identifying an optimal randomization method, accounting for the trade-off between precision of randomization balance and simplicity of implementation since more complex methods may lead to a greater likelihood of randomization schedule or allocation algorithm errors during implementation and human errors during the trial.

O8

Should consort do more to improve the quality of missing data reporting in trials?

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Background
Transparent reporting of missing data is crucial to the critical appraisal of trial results. This is particularly important in palliative care trials where large amounts of missing data and truncated data due to death occur. Although the CONSORT 2010 statement recommends the impact of missing data on the validity of intention-to-treat analyses be reported, it does not provide specific guidance on how to report: methods to handle missing data, assumptions about the missing data mechanism and missing data sensitivity analyses. Several other groups have provided further missing data reporting recommendations that include such criteria. Whether trials report missing data according to the recommendations by CONSORT and other groups however is not known.
Objectives
Assess (i) the quality of reporting and handling missing data in palliative care trials against current guidance, (ii) any differences in the complete reporting of criteria specified by the CONSORT 2010 statement compared to those not specified by CONSORT, (iii) the association between the quality of missing data reporting and journal impact factor and CONSORT endorsement status, to explore how implementation of reporting guidance may be optimised.
Methods
Systematic review of palliative care randomised controlled trials. An information specialist searched CENTRAL, MEDLINE, and EMBASE (2009–2014) with no language restrictions. A random sample of identified trials were screened, selected and had data extracted by two independent reviewers.
Results
108 trials (15,560 participants) were included. In general missing data reporting was incomplete and not handled in accordance with current guidance. Reporting criteria specified by the CONSORT statement were better reported than those not specified by CONSORT (proportion of trials reporting CONSORT criteria: account for all participants who enter the study 69%, data completeness 94%, reason for missing data 71%). However item-level (15%) and secondary outcome (9%) missing data were poorly reported, so the proportion of missing data stated is likely to be an underestimate. Provided reasons for missing data were unclear for 54% of participants. 48% of trials clearly reported their method to handle missing data, of the trials with missing data (n = 93): 60% used complete case analysis alone and 16% reported a missing data sensitivity analysis. Only one trial used a recommended method to handle truncated data due to death. As the journal impact factor doubled the odds of reporting the flow of participants (odds ratio (OR) 1.54, 95% CI 1.20, 1.97), data completeness (OR 1.39, 95% CI 1.15, 1.69), comparison of baseline characteristics of those with and without missing data (OR 1.50, 95% CI 1.20, 1.87), and method of handling missing data (OR 1.40, 95% CI 1.13, 1.73) were statistically significantly increased. There was insufficient evidence that the criteria specified by CONSORT were more likely to be reported in journals that endorsed the CONSORT statement.
Conclusion
The rigorous methods, evolving nature, and wide recognition of the CONSORT statement make it ideally placed to facilitate better reporting of missing data. Further development and implementation of the CONSORT missing data reporting guidance is likely to improve the quality of reporting. Specific suggestions for CONSORT will be discussed.

O9

Using outcomes to analyze patients rather than patients to analyze outcomes: partial credit, pragmatism, and benefit: risk evaluation

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Trials 2017, **18(Suppl 1):**O9

In the future, clinical trials will have an increased emphasis on pragmatism, providing a practical description of the effects of new treatments in realistic clinical settings. Accomplishing pragmatism requires better summaries of the totality of the evidence that allow for informed benefit:risk decision-making and in a way that clinical trials consumers, patients, physicians, insurers find transparent. The current approach to the analysis of clinical trials is to analyze efficacy and safety separately and then combine these analyses into a benefit:risk assessment. Many assume that this will effectively describe the impact on patients. But this approach is suboptimal for evaluating the totality of effects on patients. We describe a broad vision for the future of clinical trials consistent with increased pragmatism. Greater focus on using outcomes to analyze patients rather than patients to analyze outcomes particularly in late-phase/stage clinical trials is an important part of this vision. We discuss partial credit, a strategy for design and analysis of clinical trials based on benefit:risk assessment that has greater pragmatism than standard methods. The strategy involves utilizing composite benefit:risk endpoints with a goal of understanding how to analyze one patient before trying to figure out how to analyze many. With a desire to measure and weigh outcomes that are most important from the patient's perspective, we engage patients as a resource to inform analyses. We discuss partial credit within the context of antibiotic clinical trials.

O10

Regression discontinuity for replication of randomized controlled trial results: an application to the mycotic ulcer treatment trials

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Background
Regression discontinuity (RD) is a quasi-experimental method that utilizes threshold rules for determining treatment assignment to estimate causal effects when randomization is not available. Examples of clinical threshold rules include CD4 count for determining antiretroviral therapy eligibility in HIV-infected individuals or blood pressure determining eligibility for hypertension treatment. However, the validity of RD has not been established via direct comparison to effects estimated via the gold standard randomized controlled trial (RCT). Here, two concurrent RCTs allow us to directly compare an effect size from an RCT to that of RD. We utilize a continuous enrollment criterion in the RCTs to test if regression discontinuity achieves similar results to the intention-to-treat (ITT) effect from the trial itself.
Methods
The Mycotic Ulcer Treatment Trials (MUTT-I & MUTT-II) were two contemporaneous randomized controlled trials with identical outcome assessments designed to compare strategies for the treatment of fungal corneal ulcers. MUTT-I, which enrolled patients with better best spectacle-corrected visual acuity (BSCVA) (<20/400), compared topical voriconazole to topical natamycin. MUTT-II enrolled patients with worse BSCVA (20/400) and compared adding oral voriconazole versus placebo to topical voriconazole. We estimated the RD effect of natamycin versus voriconazole on 1) 3-month BSCVA and 2) odds of perforation and/or requiring a therapeutic penetrating keratoplasty (TPK), and compared these results to those estimated in the trial. We utilized enrollment visual acuity as a clinical decision rule to replicate the results of MUTT-I, using the natamycin arm from MUTT-I and the placebo arm of MUTT-II, and 20/400 as the threshold for receiving natamycin (<20/400) or voriconazole (20/400), representing an RD design. The RD model included terms for being above or below the threshold and a term for baseline visual acuity above and below the threshold.
Results
In the MUTT-I RCT, patients randomized to natamycin had a nearly 2-line improvement in BSCVA at 3 months (logMAR −0.18, 95%CI −0.30 to −0.05) and reduced odds of perforation and/or TPK (OR = 0.42, 95%CI 0.22 to 0.80) compared to voriconazole. In the RD model,