Reporting of factorial randomized trials: extension of the CONSORT 2010 Statement

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Abstract

Importance

Transparent reporting of randomized trials is essential to facilitate critical appraisal and interpretation of results. Factorial trials, in which two or more interventions are assessed in the same set of participants, have unique methodological considerations. However, reporting of factorial trials is suboptimal.

Objective

To develop a consensus-based extension to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement for factorial trials.

Design

Using the Enhancing the Quality and Transparency of Health Research (EQUATOR) methodological framework, the CONSORT extension for factorial trials was developed by (1): generating a list of reporting recommendations for factorial trials using a scoping review of methodological articles identified using a MEDLINE search (inception to May 2019) and supplemented with relevant articles from the personal collections of the authors; (2) a three-round Delphi survey between January and June 2022 to identify additional items and assess the importance of each item, completed by 104 panelists from 14 countries; and (3) a hybrid consensus meeting attended by 15 panelists to finalize the selection and wording of items for the checklist.

Findings

This CONSORT extension for factorial trials modifies 16 of the '37' items in the CONSORT 2010 checklist and adds one new item. The rationale for the importance of each item is provided. Key recommendations are: (1) the reason for using a factorial design should be reported, including whether an interaction is hypothesized; (2) the treatment groups that form the main comparisons

should be clearly identified; and (3) for each main comparison, the estimated interaction effect and its precision should be reported.

Conclusions and Relevance

This extension of the CONSORT 2010 Statement provides guidance on the reporting of factorial randomized trials and should facilitate greater understanding of and transparency in their reporting.

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Background

In a factorial trial, two or more interventions are assessed in a single study by allocating participants to multiple factors.[1-14] In a 2x2 trial with factors A and B, participants are allocated to intervention A or its comparator, and also to intervention B or its comparator, meaning participants are assigned to one of four treatment groups: A alone, B alone, A + B, or neither A nor B (Table 1).

Factorial designs are used to address different research questions (i.e., *estimands*, Box 1). They can be used to evaluate more than one intervention in a single trial without increasing the sample size ("two-in-one" trials), to evaluate whether interventions interact, or to identify the best combination of interventions.[8, 13, 15, 16] These disparate aims require different methodology, including sample size calculations and analysis strategies. Factorial trials also have additional methodological complexities compared with other trial designs, including choice of which treatment groups to include in main comparisons, how potential interactions should be handled during analysis, and non-concurrent enrolment of participants.[1, 2, 4, 6, 10-13, 17]

Here, an extension of the Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist for the reporting of factorial trials is presented.[18, 19] A glossary of key terms is provided in Box 1.

Methods

This CONSORT extension development occurred in parallel with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) extension for factorial trials.[20] First, we performed a scoping review using a MEDLINE search from inception to May 2019 to create an initial list of reporting recommendations applicable to factorial trials. Second, we performed a three-round Delphi survey (January–June 2022; n=104 panellists from 14 countries) to identify additional items and assess the importance of each item. Third, an expert consensus meeting (6–7 September 2022, n=15 panellists) was held to establish the final checklist. Item wording was finalised after the meeting through iterative discussions.

Results

The checklist for the reporting of factorial randomized trials includes 16 modified items and one new item (Table 2). Reporting items for abstracts of factorial randomized trials are provided in Table 3.[21, 22]

The scoping review identified 31 recommendations pertinent to reporting factorial trials, which were evaluated in the Delphi survey. Thirty-two recommendations met the criteria to be evaluated at the consensus meeting (one recommendation was added in round two of the Delphi survey).

Given the variation in terminology used to describe factorial trials, items in this statement have been written to replace the original CONSORT items. Users are advised to refer to definitions of key terms in Box 1. This article contains brief explanations of the modified items in the CONSORT factorial extension.

CONSORT checklist extension for factorial randomized trials

Item 1a. CONSORT 2010: Identification as a randomized trial in the title

Extension for factorial trials: Identification as a factorial randomized trial in the title

Notifying readers of the factorial design alerts them to potential implications of the design for analysis and interpretation.[2, 4, 5, 8, 23, 24]

Item 2a. CONSORT 2010: Scientific background and explanation of rationale

Extension for factorial trials: Rationale for using a factorial design, including whether an interaction is hypothesised

Different research hypotheses require different methodology. By clarifying the rationale for using the factorial design, as well as whether an interaction is hypothesised, readers are signposted

towards the key objectives and alerted to the assumptions and methodological features required.[1, 4-6, 24]

Item 2b. CONSORT 2010: Specific objectives or hypotheses

Extension for factorial trials: A statement of which treatment groups form the main comparisons

In factorial trials, interventions can be compared in different ways. In a 2x2 factorial trial with factors A and B, the treatment effect for intervention A vs. its comparator can be estimated by comparing: (i) participants allocated to A vs. not A; (ii) those allocated to A alone vs. neither A nor B; or (iii) those allocated to A + B vs. B alone. These alternative comparisons can target different *estimands* and are underpinned by different assumptions (Box 2).[4, 6, 11]

Item 3a. CONSORT 2010: Description of trial design (such as parallel, factorial) including allocation ratio

Extension for factorial trials: Description of the type of factorial trial (such as a full or partial, number of factors and levels within each factor)

Most factorial trials use a "full" factorial design, whereby all participants are eligible to be randomized to all combinations of factors and factor-levels.[9, 25, 26] Other designs include "fractional" factorial designs (where some combinations of factors are omitted) and "partial" factorial designs (where some participants are only eligible to be randomized to certain factors), which require alternative methodology.[1, 27]

Item 4a. CONSORT 2010: Eligibility criteria for participants

Extension for factorial trials: Eligibility criteria for each factor, noting any differences, if applicable

Differences in eligibility criteria across factors can have implications for the design and analysis, and can increase the risk of bias if not handled properly. For instance, participants who are not eligible for randomization to a specific factor should not be included in the comparison for that factor, as their inclusion means the analysis is no longer based on a randomized comparison, which can lead to confounding bias.[1, 27]

Item 7a. CONSORT 2010: How sample size was determined

Extension for factorial trials: How sample size was determined for each main comparison, including whether an interaction was assumed in the calculation

Sample size calculations for factorial designs are more complicated than in standard parallel group designs. In some factorial trials, the planned main comparisons may require different sample sizes if they are expected to produce different effect sizes, or if the choice of primary outcome varies for each factor.[6, 28] If an interaction is hypothesised, the sample size may need to be increased.[1, 2, 6, 24]

Item 7b. CONSORT 2010: When applicable, explanation of any interim analyses and stopping guidelines

Extension for factorial trials: When applicable, explanation of any interim analyses and stopping guidelines, noting any differences across main comparisons and reasons for differences

The plan for interim analyses and subsequent stopping guidelines may be different for each factor.[27] If one factor is stopped before the other, there may be implications for randomization, choice of comparator, or analysis.[1, 27, 29]

Item 8b. CONSORT 2010: Type of randomisation; details of any restriction (such as blocking and block size)

Extension for factorial trials: If applicable, whether participants were allocated to factors at different time-points

Participants may be randomized to factors at different time-points, for example, for factor A at diagnosis of disease, then for factor B once treatment A is complete. The time-point of randomization for each factor may inform key design features, such as the baseline period, duration of follow-up, and likelihood of treatments interacting.[2]

Item 12a. CONSORT 2010: Statistical methods used to compare groups for primary and secondary outcomes

Extension for factorial trials: Statistical methods used for each main comparison for primary and secondary outcomes, including:

- Whether the target treatment effect for each main comparison pertains to the effect in the presence or absence of other factors;

The statistical methods alone are not always sufficient to allow readers to understand the exact treatment effect being estimated.[30-32] In factorial trials, the treatment groups used for comparison are not always the same as those in which there is interest in estimating the treatment effect.[11, 33] For example, many factorial trials use a factorial analysis to compare “all A” vs. “all not A” for reasons of efficiency, even though interest really lies in the effect of A alone vs. control (the effect of A in the absence of B), or alternatively, the effect of A + B vs. B alone (the effect of A in the presence of B) if treatment B has been demonstrated to be effective.[11] A clear description of the target treatment effect, including whether it pertains to the effect in the presence or absence of other

factors, allows readers to understand the exact question being addressed.[11, 30, 31, 34] The target treatment effect is called the *estimand* and should be specified for each comparison (Box 2).[11, 34]

- Approach to analysis, such as factorial or multi-arm;

Different statistical methods can be used to analyse a factorial trial depending on the estimand of interest. In a factorial (or "at-the-margins") analysis, all participants allocated to factor A (A alone, and A + B) are compared with all those not allocated to A (B alone, and double-control).[2, 4, 6, 11, 35, 36] Alternatively, in a multi-arm (or "inside-the-table") analysis, the trial is analyzed as if a multi-arm design had been used.[2, 4-6, 10-12, 17, 23, 35, 36] The two approaches offer different benefits and require different assumptions (see Box 2).

- How the approach was chosen, such as pre-specified or based on estimated interaction;

Using a test of interaction to guide the choice of analysis can introduce bias even when there is no interaction, and is not recommended.[17] Clarification of whether the final analysis approach was pre-specified based on prior knowledge or an assumption of no interaction or chosen based on the size of the estimated interaction helps alert readers to any risk of bias associated with the analysis approach.

- Method(s) used to evaluate statistical interaction(s)

It is recommended practice to evaluate the presence of statistical interactions, either because analyses rely on the assumption that treatments do not interact, or because the interaction is itself of direct interest.[2, 4-6, 10, 11, 24] The presence of an interaction may depend on the scale of analysis (for example, an interaction may be present on the risk difference scale, but not the risk ratio scale), and so careful consideration should be given to choice of scale. Reporting details of how interaction(s) were evaluated, and on what scale, enables readers to understand the appropriateness of method(s).

- If factorial approach used, whether factors were adjusted for each other;

Factorial analyses can be adjusted for whether participants were allocated to the other factor(s) by including a term for this in the statistical model.[2, 6, 11, 28] This can increase statistical power, and in some cases failure to adjust for the other factors can introduce bias for certain estimands.[11]

- If applicable, how non-concurrent recruitment to factors was handled

Non-concurrent recruitment, in which certain participants are not randomized for some factors (e.g., if the trial used a partial factorial design or recruitment to one factor is paused or terminated), can induce bias if not handled correctly during analysis (see item 4a).[1, 27]

Item 13a. CONSORT 2010: For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome

Extension for factorial trials: For each main comparison, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome

For factorial trials, especially those beyond a 2x2 designs, it can be difficult for readers to identify the relevant participant flow, as this information may differ across main comparisons. Presenting this information for each main comparison increases clarity and understanding.[2, 4-6, 8, 10, 35]

Item 14a. CONSORT 2010: Dates defining the periods of recruitment and follow-up

Extension for factorial trials: Dates defining the periods of recruitment and follow-up for each factor, noting any differences, with reasons

If periods of recruitment are different across factors, then participants enrolled after one factor has stopped recruitment will only be eligible to be randomized for the ongoing factor(s), posing similar statistical issues as in a partial factorial design (see CONSORT item 4a).[27]

Item 17a. CONSORT 2010: For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)

Extension for factorial trials: For each primary and secondary outcome, results for each main comparison, the estimated effect size and its precision (such as 95% confidence interval)

For each primary outcome, the estimated interaction effect and its precision

If done, estimated interaction effects and precision for secondary outcomes

For factorial trials predicated on the assumption of no interaction (two-in-one trials) or those in which the interaction is of main interest, evaluation of interactions is essential to interpretation.[2, 4-6, 10, 11, 24] The size of the estimated interaction effect should be presented along with a measure of precision, such as the 95% confidence interval.[2, 5, 6] For trials in which evaluation of interaction(s) is not deemed essential, this decision should be justified.

Item 18b. CONSORT 2010: New item (Additional data summaries)

New item for factorial trials: Participant flow, losses and exclusions, and outcome data (including primary and secondary outcomes, harms, and adherence) presented by treatment groups

Outcomes and other post-randomisation data such as adherence, harms, and participant flow may be affected when treatments interact.[26] Presentation of such data by treatment group (e.g., groups A alone, B alone, A + B, and double-control in a 2x2 trial), in addition to presentation by main comparisons, allows readers to assess to what extent such data may be unduly influenced by interactions due to the factorial design.[3-6, 8, 10]

Discussion

This extension to the CONSORT 2010 Statement provides guidance for reporting factorial trials. The extension checklist represents the minimum essential requirements for reporting of factorial trials - for some trials there will be additional items that are important to report. For instance, if primary or secondary outcomes differ by factor, this should be reported. Similarly, if multiple testing is deemed to be an issue, authors should report how this was handled, or explain why it was not a concern.

This extension was developed in conjunction with the SPIRIT extension for factorial trials. Together, these guidelines provide a framework for cohesive reporting from the trial protocol to publication of results. The latest version of this and other CONSORT statements can be found online (https://www.consort-statement.org/).

Limitations

This study has several limitations. First, this extension was developed for studies in which results for each factor would be published simultaneously in the same article. This may not always be feasible, for instance due to the early stopping of one factor, or because each factor requires different durations of follow-up. In this case, we recommend that each publication follows the checklist as far as possible, though recognizing that the information for some items might differ. For example, each article could report how the sample size was determined for the relevant comparison, rather than the sample size calculations for each comparison (though each calculation would need to clarify whether an interaction was assumed).

Second, although we followed the EQUATOR guidelines to develop this guideline, Delphi respondents were self-selecting, and consensus meeting panellists were purposively identified based on their expertise. Therefore, while results represent the views of a large, multinational group of experts and end users, the views of individuals not well represented by the Delphi survey or

consensus meeting panellists may differ. However, the systematic and evidence-based approach used to develop this guideline, including a rigorous scoping review, should help to mitigate the potential effects of these limitations.

Conclusion

This extension of the CONSORT 2010 Statement provides specific guidance for the reporting of factorial randomized trials to facilitate greater transparency and completeness in the reporting of these trials.

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References

1. Green S, Liu PY and O'Sullivan J. Factorial design considerations. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2002; 20: 3424-3430. 2002/08/15.
2. Kahan BC, Tsui M, Jairath V, et al. Reporting of randomized factorial trials was frequently inadequate. *J Clin Epidemiol* 2020; 117: 52-59. 2019/10/05. DOI: 10.1016/j.jclinepi.2019.09.018.
3. Lubsen J and Pocock SJ. Factorial trials in cardiology: pros and cons. *Eur Heart J* 1994; 15: 585-588. 1994/05/01. DOI: 10.1093/oxfordjournals.eurheartj.a060552.
4. McAlister FA, Straus SE, Sackett DL, et al. Analysis and reporting of factorial trials: a systematic review. *JAMA* 2003; 289: 2545-2553. 2003/05/22. DOI: 10.1001/jama.289.19.2545.
5. Montgomery AA, Astin MP and Peters TJ. Reporting of factorial trials of complex interventions in community settings: a systematic review. *Trials* 2011; 12: 179. 2011/07/21. DOI: 10.1186/1745-6215-12-179.
6. Montgomery AA, Peters TJ and Little P. Design, analysis and presentation of factorial randomised controlled trials. *BMC Med Res Methodol* 2003; 3: 26. 2003/11/25. DOI: 10.1186/1471-2288-3-26.
7. Byth K and Gebski V. Factorial designs: a graphical aid for choosing study designs accounting for interaction. *Clinical trials (London, England)* 2004; 1: 315-325. 2005/11/11.
8. Dakin H and Gray A. Economic evaluation of factorial randomised controlled trials: challenges, methods and recommendations. *Statistics in medicine* 2017; 36: 2814-2830. 2017/05/05. DOI: 10.1002/sim.7322.
9. Dakin HA, Gray AM, MacLennan GS, et al. Partial factorial trials: comparing methods for statistical analysis and economic evaluation. *Trials* 2018; 19: 442. 2018/08/18. DOI: 10.1186/s13063-018-2818-x.
10. Freidlin B and Korn EL. Two-by-Two Factorial Cancer Treatment Trials: Is Sufficient Attention Being Paid to Possible Interactions? *Journal of the National Cancer Institute* 2017; 109 2017/09/28. DOI: 10.1093/jnci/djx146.
11. Kahan BC, Morris TP, Goulao B, et al. Estimands for factorial trials. *Statistics in medicine* 2022; 41: 4299-4310. 20220625. DOI: 10.1002/sim.9510.
12. Korn EL and Freidlin B. Non-factorial analyses of two-by-two factorial trial designs. *Clinical trials (London, England)* 2016 2016/07/22. DOI: 10.1177/1740774516659472.
13. McClure LA, Coffey CS and Howard G. Monitoring futility in a two-by-two factorial design: the SPS3 experience. *Clinical trials (London, England)* 2013; 10: 250-256. 2013/02/05. DOI: 10.1177/1740774512474374.
14. Lin DY, Gong J, Gallo P, et al. Simultaneous inference on treatment effects in survival studies with factorial designs. *Biometrics* 2016; 72: 1078-1085. 20160317. DOI: 10.1111/biom.12507.
15. Bria E, Di Maio M, Nistico C, et al. Factorial design for randomized clinical trials. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2006; 17: 1607-1608. 2006/06/13. DOI: 10.1093/annonc/mdl106.
16. Byar DP. Some statistical considerations for design of cancer prevention trials. *Preventive medicine* 1989; 18: 688-699. 1989/09/01.
17. Kahan BC. Bias in randomised factorial trials. *Statistics in medicine* 2013; 32: 4540-4549. 2013/06/05. DOI: 10.1002/sim.5869.
18. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340: c869. 20100323. DOI: 10.1136/bmj.c869.
19. Schulz KF, Altman DG and Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340: c332. DOI: 10.1136/bmj.c332.
20. Hall SS, Juszczak E, Birchenall M, et al. Development of extensions to SPIRIT and CONSORT guidelines: the Reporting Factorial Trials (RAFT) Study. *OSF (https://osfio/e3n5r/files/osfstorage/643e568f5d9aba24f7adc222)* 2023.

21. Hopewell S, Clarke M, Moher D, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008; 371: 281-283. DOI: 10.1016/s0140-6736(07)61835-2.
22. Hopewell S, Clarke M, Moher D, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 2008; 5: e20. DOI: 10.1371/journal.pmed.0050020.
23. Juszczak E, Altman DG, Hopewell S, et al. Reporting of Multi-Arm Parallel-Group Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA* 2019; 321: 1610-1620. 2019/04/24. DOI: 10.1001/jama.2019.3087.
24. Mdege ND, Brabyn S, Hewitt C, et al. The 2 x 2 cluster randomized controlled factorial trial design is mainly used for efficiency and to explore intervention interactions: a systematic review. *J Clin Epidemiol* 2014; 67: 1083-1092. 2014/07/27. DOI: 10.1016/j.jclinepi.2014.06.004.
25. Allore HG and Murphy TE. An examination of effect estimation in factorial and standardly-tailored designs. *Clinical trials (London, England)* 2008; 5: 121-130. 2008/04/01. DOI: 10.1177/1740774508089278.
26. Baker TB, Smith SS, Bolt DM, et al. Implementing Clinical Research Using Factorial Designs: A Primer. *Behavior therapy* 2017; 48: 567-580. 2017/06/05. DOI: 10.1016/j.beth.2016.12.005.
27. White IR, Choodari-Oskooei B, Sydes MR, et al. Combining factorial and multi-arm multi-stage platform designs to evaluate multiple interventions efficiently. *Clinical trials (London, England)* 2022; 19: 432-441. 20220517. DOI: 10.1177/17407745221093577.
28. Curran D, Sylvester RJ and Hoctin Boes G. Sample size estimation in phase III cancer clinical trials. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 1999; 25: 244-250. 1999/05/25. DOI: 10.1053/ejso.1998.0635.
29. Slud EV. Analysis of factorial survival experiments. *Biometrics* 1994; 50: 25-38.
30. Cro S, Kahan BC, Rehal S, et al. Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands. *BMJ* 2022; 378: e070146. 20220823. DOI: 10.1136/bmj-2022-070146.
31. Kahan BC, Morris TP, White IR, et al. Estimands in published protocols of randomised trials: urgent improvement needed. *Trials* 2021; 22: 686. DOI: 10.1186/s13063-021-05644-4.
32. Mitroiu M, Teerenstra S, Oude Rengerink K, et al. Estimation of treatment effects in short-term depression studies. An evaluation based on the ICH E9(R1) estimands framework. *Pharmaceutical Statistics*; n/a. DOI: https://doi.org/10.1002/pst.2214.
33. Tian Z, Esserman D, Tong G, et al. Sample size calculation in hierarchical 2×2 factorial trials with unequal cluster sizes. *Statistics in medicine* 2022; 41: 645-664. DOI: https://doi.org/10.1002/sim.9284.
34. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf.
35. Pocock SJ, Clayton TC and Stone GW. Challenging Issues in Clinical Trial Design: Part 4 of a 4-Part Series on Statistics for Clinical Trials. *Journal of the American College of Cardiology* 2015; 66: 2886-2898. 2016/01/01. DOI: 10.1016/j.jacc.2015.10.051.
36. Leifer ES, Troendle JF, Kolecki A, et al. Joint testing of overall and simple effects for the two-by-two factorial trial design. *Clinical Trials* 2021; 18: 521-528. DOI: 10.1177/17407745211014493.

Box 1 – Glossary of terms

Factorial trial: When two or more interventions are assessed in the same participants within a single study.

Factor: Each intervention and its comparator(s) together comprise a factor (e.g. Active-A and Placebo-A together comprise one factor; High Dose-B and Low Dose-B together make up the other factor).

Level within factors: The specific interventions within a factor are the levels (e.g. Active-A and Placebo-A are the two levels of factor A).

Treatment group: The unique combinations of factors and levels to which participants can be randomized (e.g. Active-A + High Dose-B comprises one treatment group; Active A + Low Dose-B another; etc).

Full factorial design: All factors and levels are combined so the design comprises all possible combinations of factor levels, and all participants are eligible to be randomized for each factor.

Partial factorial design: Some participants are not randomized to certain factors. For example, a subset of participants will only be randomized between active-A vs. control-A, and will receive control-B automatically.

Fractional factorial design: Some combinations of factors are omitted. For example, in a trial with three factors (A, B, and C), participants may be randomized to 4 of the 8 possible combinations.

Comparison: Which treatment groups will be compared against each other. For example, the effect of intervention A may be estimated by comparing all participants randomized to Active-A (treatment groups Active-A + High Dose-B, and Active-A + Low Dose-B) with all participants randomized to Placebo-A (treatment groups Placebo-A + High Dose-B, and Placebo-A + Low Dose-B).

Main comparison(s): The comparison(s) that will primarily be used to draw conclusions about effectiveness of each intervention.

Estimand: A description of the treatment effect to be estimated from the trial, including specification of the treatment conditions, population, endpoint, summary measure, and strategies to handle intercurrent events. Factorial trials should additionally specify how the other factors are to be handled in the estimand (for instance, whether interest lies in the effect of Active-A + Low Dose-B vs. Placebo-A + Low Dose-B, or else Active-A + High Dose-B vs. Placebo-A + High Dose-B).

Factorial analysis: Also called an “at the margins” analysis. All participants allocated to active-A (treatment groups Active-A + High Dose-B, and Active-A + Low-Dose-B) are compared against all those allocated to Placebo-A (Placebo-A + High Dose-B, and Placebo-A + Low Dose-B), and similarly for the factor B comparison.

Multi-arm analysis: Also called an “inside the table” analysis. The treatment groups (1) Active-A + Low Dose-B, (2) Placebo-A + High Dose-B, and (3) Active-A + High Dose-B, are each compared against (4) Placebo-A + Low Dose-B (double-control).

Interaction: Interactions occur when the effect of one treatment depends on whether participants also receive the other treatment (e.g. Active-A may be less effective when used alongside High Dose-B than when used with Low Dose-B). Interactions may occur for biological or social reasons (for instance, if receipt of one treatment affects the mechanism of action for the other). Interactions may also occur due to choice of analysis scale (for instance, Active-A may be equally effective with High Dose-B as with Low Dose-B when measured on the risk ratio scale, but less effective on the risk difference scale). Trials interested in evaluating whether treatments interact are typically interested in biological/social interactions, while trials which use analyses which require an assumption of no interaction are affected by any type of interaction.

Box 2 – Estimands in factorial trials

Estimands for factorial trials:

- An *estimand* describes a research question a trial sets out to address (Box 1).
- Different estimands may be specified for factorial trials depending on the aims.
- An estimand for the effect of treatment A could be defined based on a comparison of treatment A vs. not A if no one received treatment B, or as the effect of A vs. not A if everyone received treatment B.
- The former may be more common for "two-in-one" factorial trials as it provides the effect of treatment A that would be seen in a parallel group design where treatment B isn't used. However, either effect may be of interest.
- Alternatively, an estimand for treatment A could also be defined based on the effect of A vs. not A averaged across those who do and those who do not receive treatment B[a]. Because this estimand does not typically reflect how treatments are used in practice, other choices are usually more relevant for "two-in-one" trials.

Implications for statistical analysis[b]

- The estimand (i.e. research question) should determine the method of statistical analysis.
- "Two-in-one" trials typically use a factorial ("at-the-margins") analysis as this realises the efficiency gained by using a factorial design. For the comparison for treatment A, this does so by average across the two strata of those allocated to receive B and not receive B, even though this typically isn't the estimand of interest. Therefore, a factorial analysis can only be used to estimate the "effect of treatment A if no one receives B" if treatments A and B do not interact.
- A multi-arm ("inside-the-table") analysis could also be used to estimate the effect of treatment A if no one receives B, and is unbiased regardless of whether treatments A and B interact. However, it does not realise the efficiency gained through using a factorial design, and so it less frequently used for "two-in-one trials".

[a] This averaging could correspond to the study proportions allocated to B and not B, or to some other proportions defined by the investigators. The exact method of averaging therefore needs to be made explicit.

[b] A factorial analysis can be used to estimate either (i) the effect of A if no one got B; or (ii) the effect of A if everyone got B; or (iii) the effect of A, averaged over those who receive and do not receive B according to the study proportions. The first two of these require the assumption of no interaction, however the analysis for (iii) does not. A multi-arm analysis can be used to estimate either (i) above (by comparing A alone vs. double-control), or (ii) (by comparing A + B vs. B alone). These do not require the assumption of no interaction. If interest lies in the effect of A averaged over those who do and do not receive B according to proportions other than the study proportions, this could be estimated by first estimating the effect of A separately in both stratum (those who receive, and do not receive B), then taking a weighted average of these according to the desired proportions. This analysis does not require the assumption of no interaction. For a full overview, see reference 11.

Table 1 – Example of a 2x2 factorial randomized trial. In a "full" factorial trial all participants are eligible to be randomized between each of the four treatment groups; in a "partial" factorial trial, a subset of participants would only be randomized between High Dose-B and Low Dose-B, and automatically assigned to Placebo-A without randomization. In a "factorial" analysis, all participants allocated to intervention A (Active-A + Low Dose-B, and Active-A + High Dose-B) are compared against those not allocated to A (Placebo-A + Low Dose-B, and Placebo-A + High Dose-B), and similarly for the comparison for intervention B. In a "multi-arm" analysis, each of the treatment group is compared against control (e.g. Active-A + High Dose-B, Active-A + Low Dose-B, and Placebo-A + High Dose-B are all compared against Placebo-A + Low Dose-B).

		Treatment B [1]	
		High-dose[2]	**Low-dose**[2]
Treatment A [1]	**Active**[2]	Active-A + High Dose-B[3]	Active-A + Low Dose-B[3]
	Placebo[2]	Placebo-A + High Dose-B[3]	Placebo-A + Low Dose-B[3]

[1] A and B are FACTORS

[2] Active-A and Placebo-A are LEVELS within factor A; High Dose-B and Low Dose-B are LEVELS within factor B. Note Low Dose-B is taken as the control condition for factor B.

[3] Active-A + High Dose-B, Active-A + Low Dose-B, etc are the four TREATMENT GROUPS

Table 2 – CONSORT checklist of information to include when reporting factorial randomized trials[a,b]

Section/Topic	Item No.	CONSORT 2010 Statement Checklist Item	Extension for Factorial trials
Title and abstract			
Title	1a	Identification as a randomized trial in the title	Identification as a factorial randomized trial in the title
Abstract	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	See separate factorial checklist for abstracts
Introduction			
Background	2a	Scientific background and explanation of rationale	Scientific background and rationale for using a factorial design, including whether an interaction is hypothesised
Objectives	2b	Specific objectives or hypotheses	Specific objectives or hypotheses and a statement of which treatment groups form the main comparisons[b]
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Description of the type of factorial trial (such as full or partial, number of factors, levels within each factor[b]), and allocation ratio
Change from protocol	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	Eligibility criteria for each factor, noting any differences, if applicable
Setting and location	4b	Settings and locations where the data were collected	-
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	-
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	-
Changes to outcomes	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	How sample size was determined for each main comparison, including whether an interaction was assumed in the calculation
Interim analyses and stopping guidelines	7b	When applicable, explanation of any interim analyses and stopping guidelines	When applicable, explanation of any interim analyses and stopping guidelines, noting any differences across main comparisons and reasons for differences
Randomisation			

Sequence generation	8a	Method used to generate the random allocation sequence	-
Sequence generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Type of randomisation; details of any restriction (such as blocking and block size); and if applicable, whether participants were allocated to factors at different time-points
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	-
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes)	-
Similarity of interventions	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Statistical methods used for each main comparison for primary and secondary outcomes, including: • Whether the target treatment effect for each main comparison pertains to the effect in the presence or absence of other factors; • Approach to analysis, such as factorial or multi-arm; • How the approach was chosen, such as pre-specified or based on estimated interaction; • If factorial approach used, whether factors were adjusted for each other; • If applicable, how non-concurrent recruitment to factors was handled • Method(s) used to evaluate statistical interaction(s)
Additional analyses	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	For each main comparison, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome

Losses and exclusions	13b	For each group, losses and exclusions after randomisation, together with reasons	For each main comparison, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Dates defining the periods of recruitment and follow-up for each factor, noting any differences, with reasons
Trial end	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	A table showing baseline demographic and clinical characteristics for each main comparison
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each main comparison, the number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	For each primary and secondary outcome, results for each main comparison, the estimated effect size and its precision (such as 95% confidence interval) For each primary outcome, the estimated interaction effect and its precision If done, the estimated interaction effects and precision for secondary outcomes
Binary outcomes	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18a	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Additional data summaries[c]	18b		Participant flow, losses and exclusions, baseline data and outcome data (including primary and secondary outcomes, harms, and adherence) presented by treatment groups[b]
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	All important harms or unintended effects for each main comparison
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-

Generalisability	21	Generalisability (external validity, applicability) of the trial findings	-
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			
Registration	23	Registration number and name of trial registry	-
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	-

[a] It is strongly recommended that this checklist is read in conjunction with the CONSORT 2010 checklist https://www.equator-network.org/reporting-guidelines/consort/ and Statement Explanation and Elaboration paper[18] for important clarification on the items.

[b] *Factor*: Each overall intervention group to be compared is a factor (e.g. in a 2x2 trial with factors A and B, active A and control A together comprise one factor; active B and control B together comprise another factor). *Levels*: The specific interventions within a factor are the levels (e.g. active A and control A are the two levels of factor A). *Treatment groups*: These are the unique combinations of factors and levels (e.g. in a 2x2 trial with factors A and B there will be four treatment groups: active A + control B, active A + active B, etc). *Main comparison*: Which treatment groups will be compared against each other to draw main conclusions about the effectiveness of each intervention.

[c] New item

Table 3 – Items to include when reporting a randomized factorial trial in a journal or conference abstract

Item	CONSORT for Abstracts Checklist Item	Extension for Factorial trials
Title	Identification of the study as randomized	Identification of the study as a factorial randomized trial
Authors *	Contact details for the corresponding author	-
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	Description of the trial design (e.g., parallel, cluster, non-inferiority) and number of factors (e.g., 2x2)
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	Eligibility criteria for each factor, noting any differences if applicable, and the settings where the data were collected
Interventions	Interventions intended for each group	-
Objective	Specific objective or hypothesis	-
Outcome	Clearly defined primary outcome for this report	-
Randomization	How participants were allocated to interventions	-
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	-
Results		
Numbers randomized	Number of participants randomized to each group	Number of participants randomized for each main comparison
Recruitment	Trial status	-
Numbers analyzed	Number of participants analyzed in each group	Number of participants analyzed for each main comparison
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	For the primary outcome, results for each main comparison, the estimated effect size and its precision, and estimated interaction effect and its precision
Harms	Important adverse events or side effects	Important adverse events or side effects for each main comparison
Conclusions	General interpretation of the results	-
Trial registration	Registration number and name of trial register	-
Funding	Source of funding	-

**this item is specific to conference abstracts*

Author Contributions

Dr Kahan and Dr Hall had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Kahan, Hall, Beller, Chan, Elbourne, Juszczak, Montgomery

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Kahan

Critical revision of the manuscript for important intellectual content: All authors

Administrative, technical, or material support: Kahan, Hall, Birchenall

Conflict of Interest Disclosures

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