RAFT Study: Keyword Definitions

1. Definitions

Table 1. Example 2x2 Factorial Trial

		Drug B	
		High-dose	**Low-dose**
Drug A	**Active**	Active A + High Dose B	Active A + Low Dose B
	Placebo	Placebo A + High Dose B	Placebo A + Low Dose B

N.B: Low-dose drug B is current standard of care and is taken to be the control condition for factor B

Table 2. Key terms

Term	**Definition**
Factorial trial	In factorial trials, two or more interventions are assessed simultaneously (e.g. active drug A vs. placebo drug A, and high-dose drug B vs. low-dose drug B).
Factor	Each overall intervention group to be compared is a factor (e.g. active drug A and placebo drug A together comprise one factor; high-dose drug B and low-dose drug B together make up the other factor).
Level within factors	The specific interventions within a factor are the 'levels' (e.g. active drug A and placebo drug A are the two levels of this factor).
Interaction	Interactions occur when the effect of one treatment depends on whether participants also receive the other treatment (e.g. drug A may be less effective when used alongside high-dose drug B than when used with low-dose drug B).
Comparison	Which treatment groups will be compared against each other. For example the effect of treatment A may be estimated by comparing all participants randomised to active drug A (groups active A + high-dose B, and active A + low-dose B) with all participants randomised to placebo drug A (groups placebo A + high-dose B, and placebo A + low-dose B). Similarly, the effect of high-dose B may be estimated by comparing all participants randomised to high-dose B with those randomised to low-dose B. Another possible comparison is the effect of the combined treatment active A + high-dose B versus placebo A + low-dose B (double-control).
Full factorial design	All factors and levels are combined so the design comprises all possible combination of factor levels, and all participants are eligible to be randomised for each factor.
Partial factorial design	Some participants are not eligible to be randomised for certain factors. For example, some participants may have contraindications to Drug A; those who do will only be randomised between high-dose vs. low-dose drug B (receiving placebo A automatically), and those who do not will be

	randomised both between high-dose vs. low-dose drug B, and between active vs. placebo drug A.
Estimand	A precise description of the treatment effect we wish to estimate, including specification of the treatment conditions, population of interest, endpoint, population-level summary measure, and handling of intercurrent events. Factorial trials additionally need to specify how alternate factors are to be handled in the estimand, as well as how intercurrent events affecting alternate factors are to be handled.
Factorial analysis	Also called an "at the margins" analysis. All participants allocated to active drug A (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 (double-control)), and vice versa for treatment B
Multi-arm analysis	Also called an "inside the table" analysis. The combinations of levels for each factor are compared: active A + low-dose B, placebo A + high-dose B, and active A + high-dose B are each compared against placebo A + low-dose B (double-control)).

2. Example

The SEAFOOD Polyp Prevention Trial was a 2x2 factorial trial assessing eicosapentaenoic acid (EPA) and aspirin to prevent colorectal adenomas in participants with sporadic colorectal neoplasia (1) (Table 2).

Table 3. SEAFOOD Polyp Prevention Trial

		Aspirin	
		Yes	**No**
EPA	**Yes**	EPA+aspirin	EPA alone
	No	Aspirin alone	Double-placebo

The trial had two factors (EPA, aspirin) and each factor had two levels (EPA or EPA placebo for the EPA factor; aspirin or aspirin placebo for the aspirin factor). Because all factors and levels were combined, and all participants were eligible for each factor, this trial utilised a full factorial design (i.e. participants were randomised to one of the four groups made up of the different levels: EPA alone, aspirin alone, EPA+aspirin, or double-placebo). To preserve blinding, placebo treatments were used and all participants were provided with two sets of tablets; for brevity, "EPA alone" means participants were active EPA + placebo aspirin, etc.

There were two main comparisons: All EPA vs. all not EPA (EPA alone and EPA+aspirin vs. aspirin alone and double-placebo), and all aspirin vs. all not aspirin (aspirin alone and EPA+aspirin vs. EPA alone and double-placebo).

Comparisons were undertaken using a factorial ("at the margins") analysis, where all participants allocated to EPA were compared to all those who were not, and similarly for aspirin.

There was no evidence of an interaction effect of EPA and aspirin on the primary outcome: the effect of EPA appeared to be the same both when used on its own and when used in conjunction with aspirin (and similarly for the effect of aspirin).

3. Reference

(1) Hull MA, Sprange K, Hepburn T, *et al*. Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFOod Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2×2 factorial rial. Lancet 2018;392:2583–94.doi:10.1016/S0140-6736(18)31775-6