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ASSESSMENT OF METHODOLOGICAL QUALITY IN RANDOMIZED CARDIOVASCULAR CLINICAL TRIALS

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I. Introduction

As in all clinical fields, clinical trials are essential in cardiology in order to provide the information needed to answer questions that arise in clinical practice. However, inappropriate design and conduct of clinical trials will result in distorted information that will affect medical decision-making and, in extreme cases, may lead to patients not receiving the most appropriate treatment.As RCTs constitute the foundational background of modern medical practice, the increasing prevalence of cardiovascular disease around the world requires high quality of clinical research and translation of its findings into new therapeutic and diagnostic strategies. Unfortunately, although there was a significant increase in the quantity of scientific literature concerning cardiovascular disease published in recent years, it was indicated that this has not resulted in guideline recommendations with more certainty and supporting evidence. The American College of Cardiology and the American Heart Association (ACC/AHA) clinical practice guidelines are still based on a lower quality of evidence and expert opinions, indicating the lack of high-quality studies with relevant data. Also the RoB has not been assessed in these studies. Several tools exist that support researchers to plan and conduct high-quality research and make trial results completely and transparently available. Guidelines for clinical trial protocols (e.g., SPIRIT) facilitate trial planning in all important details. Reporting guidelines (e.g., CONSORT for RCTs) have the aim of decreasing the risk of non-reporting bias, i.e., facilitating that clinical trial methods are described as they were conducted, and trial results are fully published. Mandatory RCT registration by the International Committee of Medical Journal Editors (ICMJE) has been put forward with detailed registration before commencing the RCTs enabling more transparent and complete reporting and the European Medicines Agency and WHO also support clinical trial registration. Methodological flaws in the design, conduct, analysis, and reporting of RCTs can cause the true intervention effect to be underestimated or overestimated. This is why these systemic errors (defined as the RoB) are assessed when systematic reviews are conducted, or evidence-based guidelines are developed. Concerns arising due to the high RoB in trials included in evidence syntheses lead to the downgrading of evidence level and consequently will decrease our certainty in the pooled results. However, the extent to which we can draw final conclusions based on RCTs strongly depends on how rigorous study methodology is; methodological inaccuracies during trial planning and conduct will subsequently reduce the reliability of results and their usability in medical practice. Biased results can finally lead to the underestimation or overestimation of the true intervention effect. The RoB reflects the degree to which the results of a trial should be believed. To reduce the possibility of RoB in RCT's, the Cochrane Collaboration introduced a tool designed to appraise RoB, involving six domains related to the internal validity of a trial: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" potential threats to validity. The RoB assessment enables the assessment of flaws in the trial design, conduct, and analysis that may affect study results.

Risk of bias in randomized clinical trial

The reliability of results of the cardiovascular RCTs depends on the extent to which potential sources of bias have been avoided. In epidemiology "bias" represents a systematic error. The bias translates in a deviation from the truth, which will consequently be incorporated in the results of a study. One of the main characteristics of bias is that it can lead to underestimation or overestimation of the true intervention effect.Cochrane's risk of bias (RoB) tool contains six domain (including seven items): selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other sources of bias.

Selection bias

Selection bias refers to systematic differences between baseline characteristics of the groups that are compared. Successful randomization prevents selection bias in allocating interventions to participants. A rule for allocating interventions to participants must be specified, based on some chance (random) process, which is called sequence generation. One suitable method for assigning interventions would be to use a simple random sequence, and to conceal the upcoming allocations from those involved in enrolment into the trial.

Performance bias

Performance bias refers to systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest. After enrolment into the study, blinding (or masking) of study participants and personnel may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes. Effective blinding can also ensure that the compared groups receive a similar amount of attention, treatment, and diagnostic investigations.

Detection bias

Detection bias refers to systematic differences between groups in how outcomes are determined. Blinding (or masking) of outcome assessors may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement.

Attrition bias

Attrition bias refers to systematic differences between groups in withdrawals from a study. Withdrawal from the study lead to incomplete outcome data. Attrition refers to situations in which outcome data are not available.

Reporting bias

Reporting bias refers to systematic differences between reported and unreported findings. Within a published report those analyses with statistically significant differences between interventions groups are more likely to be reported than non-significant differences. This sort of bias is usually known as outcome reporting bias or selective reporting bias.

Other biases

In addition, there are other sources of bias that are relevant only in certain circumstances. These

relate mainly to particular trial designs (e.g. recruitment bias in cluster-randomized trials or bias due to the lack of an adequate washout period in RCTs with a cross-over design); and there may be sources of bias that are only found in a particular clinical setting.

II. Aims

We aimed to describe the reliability of cardiovascular diseases evidence using a representative sample of cardiovascular RCTs published in 2017 and 2012.

Specific objectives:

To examine the reliability of published cardiovascular clinical trials using RoB tool.
To define specific trial characteristics which increase the likelihood of unclear/high RoB.
To reveal any potential differences in methodological issues between cardiovascular RCTs funded by the industry or the academy.
To investigate tendencies over time to answer whether there was an improvement in measures of methodological quality and reporting in RCTS between 2012 and 2017.
To assess how well cardiovascular RCTs were able to estimate the true intervention effect in 2017 as compared to 2012.

III. Methods

3.1. Methodological Quality and Risk of Bias Assessment of Cardiovascular Disease Research: Analysis of Randomized Controlled Trials Published in 2017

Selection of studies

We used the Cochrane CENTRAL Register of Controlled Trials to search for RCTs published in 2017 using subject headings and keywords related to adults (aged ≥ 18 years) and CVDs (such as, atherosclerosis, arrhythmia, cardiomyopathy, heart failure, hypertension, ischemic heart disease, heart attack, angina, sudden death, cardiac arrest, hypercholesterolemia, high blood pressure, CVD, ejection fraction, echocardiography, pericarditis, coronary artery disease, angioplasty, and angiography. The search and the screening of identified studies for eligibility were conducted by the first author. Our search yielded a total of 2,556 studies. Following deduplication, 2,419 studies underwent further analysis. Cochrane CENTRAL was the priority search source as it is the most comprehensive resource available of RCTs, containing publications from MEDLINE and EMBASE, as well as hand-search results, and gray literature. Results of the search were randomly ordered in Excel, by the following method: after exporting the search result as an Excel file from Cochrane CENTRAL, we assigned a random number between 0 and 1 to each record using Excel's random number generator, then reordered them from the smallest to the highest number. As a next step, we screened studies consecutively for eligibility, and the first 250 (10%) RCTs matching our prespecified inclusion criteria were selected. Trials were eligible for inclusion if they were published in the year 2017, were written in English, the described results of an RCT in the field of cardiovascular medicine, and included participants aged ≥ 18 years. Decision on the inclusion of a study was made after a careful consideration of the methodology in the full text.

Data Extraction

For data extraction, we used a data extraction sheet already tested and described in a previous study, data extracting guide available here: https://doi.org/10.1016/j.jpeds.2017.09.014. The following data were extracted: journal type (e.g., specialty cardiovascular, or general medical), the publication details and characteristics of the published trials (such as study design, intervention, trial conduct, study sample, sample size, presence of a data monitoring committee, research outcomes, and conclusions). Further, we collected information about trial registration. Data extraction was completed by two reviewers: the first reviewer extracted the data and then, the second reviewer double-checked the sample. Conflicts were resolved through discussion and by reaching a consensus. Trial registration and protocol availability were investigated by retrieving information from the publications and via additional Internet searches (in Google and Google scholar). For the internet searches, we used the trial register number, the investigators' names, and keywords describing the intervention or the condition.

Assessment of Methodological Quality and Reporting

We used the Cochrane RoB assessment tool to evaluate the methodological quality of included RCTs. This tool assesses seven domains as mentıoned above ın details. We used the Cochrane RoB tool to assess RoB for the primary outcome. When the primary outcome was not clearly

defined, we presumed it was the outcome either (1) described under aims/objectives of the study, (2) the outcome used to determine the sample size, or (3) the first outcome reported in the publication. One researcher performed a RoB assessment, while a second researcher was assigned to ensure the correctness of the assessments for each study. Following Cochrane procedures, we classified each domain as low, unclear, or high risk. Then, the overall RoB was determined as follows: low when all domains were assessed as low RoB; unclear when at least 1 domain was assessed as unclear, and no domains were assessed as high RoB; and high if any domain was assessed as high RoB.

3.2. Change over Five Years in Important Measures of Methodological Quality and Reporting in Randomized Cardiovascular Clinical Trials

Sample selection and data extraction

We conducted two searches to identify RCTs published in either 2012 or 2017. As mentioned above in details we used same methodology to identify our studies. Our search resulted in 2566 trials. We included the first 250 (about 10%) eligible RCTs for both year 2012 and 2017. We used a data extraction tool that was developed for assessing the methodological quality of RCTs in child health research.

IV. Results

4.1Methodological Quality and Risk of Bias Assessment of Cardiovascular Disease Research: Analysis of Randomized Controlled Trials Published in 2017

Study Design and Reporting Characteristics of the Study Sample

Out of the 2,419 studies identified via search, we included the first 250 randomly selected trials, which met our search inclusion criteria as shown in Figure 1. The publication and trial characteristics of our sample are shown in Table 1.

TABLE 1. Publication and trial characteristics (N = 250).

Study characteristics	**N (%)**
The geographical location of the corresponding author	
Asia	65 (26.0%)
North America	69 (27.6%)
Europe (Excluding United Kingdom)	93 (37.2%)
South America	13 (5.2%)
Australia	2 (0.8%)
United Kingdom	8 (3.2%)
Type of journal **Specialty cardiovascular journal**	**100 (40.0%)**
General cardiovascular journal	46 (18.4%)
Specialty medical journal	49 (19.6%)
General medical journal	41 (16.4%)
Non-medical journal	14 (5.6%)
Study design	
Parallel	231 (92.4%)
Crossover	15 (6.0%)

Factorial	4 (1.6%)
Study type	
Efficacy/Superiority	237 (94.8%)
Equivalence	3 (1.2%)
Non-inferiority	4 (1.6%)
None of the above	6 (2.4%)
Intervention	

Drug	**139 (55.6%)**
Prevention or screening	20 (8.0%)
Device	23 (9.2%)
Other	68 (27.2%)
Placebo-controlled	
Yes	68 (27.2%)
No	182 (72.8%)
Number of centers	
Multicenter	157 (62.8%)
Single center	93 (37.2%)
Data Monitoring Committee	
Yes	105 (42.0%)
No	94 (37.6%)
Unclear	51 (20.4%)
Funding source	
Academic or Research institute	94 (37.6%)
Pharmaceutical	48 (19.2%)
Government	24 (9.6%)
Industry for device	10 (4.0%)
No external funding	4 (1.6%)
Private	50 (20.0%)
Unclear	21 (8.4%)
Primary outcome explicitly specified	
Yes	157 (62.8%)
No	93 (37.2%)
Intervention favored	
Treatment	139 (55.6%)
Control	9 (3.6%)
None	104 (41.6%)
Sample size calculation reported	
Yes	151 (60.4%)
No	99 (39.6%)
Was there at least one statistically significant outcome?	
Yes	215 (86.0%)
No	35 (14.0%)
Was the primary outcome statistically significant?	
Yes	173 (69.2%)
No	77 (30.8%)
Overall authors conclusion	
Positive	170 (68.0%)
Negative	34 (13.6%)
Neutral	46 (18.4%)
Adverse events	
Reported	170 (68.0%)
Non-reported	82 (32.8%)
Trial registered	
Yes	209(83.6%)

Most of the included trials had a parallel design (92.4%) and were efficacy trials (94.8%). Overall, 20.8% were placebo-controlled trials. An important part of the results of the trial was published in specialty cardiovascular journals (40.0%). In 139 studies (55.6%), the main goal was to evaluate the effects of pharmacological interventions. All geographic areas were represented; the majority of authors were from Europe (37.4%) and North America (26.0%). The funding source was specified in 91.6% of the included trials: most of the trials were funded by an academic grant or a research institute (37.6%), while industrial and pharmaceuticals funding were reported in 23.2% of the trials.
When analyzing the main results of trials, we observed that at least one statistically significant result was reported in 86.0% of the studies; in these studies, the primary outcome was reported to be statistically significant in 69.2% of the cases. The treatment was favored in 55.6% and control in 3.6%. At least one adverse event was reported in 68% of the trials. A data monitoring committee was reported in 42% and sample size calculation in 60.4%. A total of 83.6% of the studies were registered in one of the clinical trials registries out of the 77.5% were registered in clinicaltrials.gov.

Risk of Bias Assessment

Table 2 shows the RoB assessment results. Overall, 29.2% of the studies were deemed as low RoB, while the remaining studies were at either unclear (39.6%) or high risk (31.2%). We rated the domains sequence generation, allocation concealment, and selective reporting to be the domains most often at high RoB (13.2, 9.6, and 10.4%, respectively). We investigated whether the RoB was associated with the following variables: type of the intervention (drug vs. non-drug); single or multiple study centers; sample size; the presence of a Data Monitoring Committee; statistical significance of the primary outcome and trial registration (Table 3).

TABLE 2. Risk of bias (RoB) assessments by domain (n=250).

Domain	**Risk of bias assessment N (%)**		
	High	**Unclear**	**Low**
Sequence generation	33 (13.2%)	68 (27.2%)	149 (59.6%)
Allocation concealment	24 (9.6%)	51 (20.4%)	175 (70.0%)
Blinding: participant and personnel	11 (4.4%)	112 (44.8%)	127 (50.8%)
Blinding: outcome assessor	11 (4.4%)	33 (13.2%)	206 (82.4%)
Incomplete outcome data	8 (3.2%)	57 (22.8%)	185 (74.0%)
Selective reporting	26 (10.4%)	67 (26.8%)	157 (62.8%)
Other bias	36 (14.4%)	106 (42.4%)	108 (42.8%)
Overall RoB	78 (31.2%)	99 (39.6%)	73 (29.2%)

TABLE 3. Multivariable regression analyses for all included trials, and trials with and without stated funding from the industry*.

	All trials (N = 250)		**Industry-funded trials (N = 106)**		**Non-industry funded trials (N = 119)**	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Drug trial (vs. non-drug trial)	0.53 (0.29 – 0.97)	0.04	0.49 (0.18 – 1.27)	0.15	0.50 (0.20 – 1.20)	0.12
Multicentre (vs. single center)	0.39 (0.18 – 0.80)	0.01	0.13 (0.02 – 0.61)	0.02	0.80 (0.32 – 2.00)	0.64
Sample size (>500 vs. smaller)	0.67 (0.34 – 1.31)	0.24	0.60 (0.23 – 1.56)	0.29	1.72 (0.52 – 6.86)	0.40
Data Monitoring Committee (yes vs. no)	0.59 (0.32 – 1.09)	0.09	0.36 (0.13 – 0.96)	0.045	0.91 (0.37 – 2.27)	0.84
Primary outcome statistically significant (vs. not)	0.92 (0.48 – 1.74)	0.80	0.52 (0.81 – 1.11)	0.49	1.36 (0.54 – 3.38)	0.51
Trial registration reported (vs. not reported)	0.06 (0.003 – 0.31)	<0.01	0.19 (0.01 – 1.28)	0.15	1.13 (0.01 – 0.75)	0.06

*Funding was not reported in N = 25 studies

TABLE 4. Risk of bias assessments by domain in studies funded by the industry or non-industry (N = 250).

RoB domain	**Funding source (industrial vs. non-industrial)**				
	Industrial	**N (%)**	**Non-industrial**	**N (%)**	**P value**
Random sequence generation	Low	66 (62.3)	Low	71(59.7)	0.4533
	Unclear	32 (30.2)	Unclear	33 (27.7)	
	High	8 (7.5)	High	15 (12.6)	
Allocation concealment	Low	90 (84.9)	Low	76 (63.9)	0.0014*
	Unclear	13 (12.3)	Unclear	32 (26.9)	
	High	3 (2.8)	High	11 (9.2)	
Blinding participant and personnel	Low	70 (66.0)	Low	51 (42.9)	0.0001*
	Unclear	35 (33.0)	Unclear	61 (51.3)	
	High	1 (0.94)	High	7 (5.9)	
Blinding outcome assessor	Low	95 (89.6)	Low	95 (79.8)	0.1198
	Unclear	8 (7.5)	Unclear	19 (16.0)	
	High	3 (2.8)	High	5 (4.2)	
Incomplete outcome data	Low	86 (81.1)	Low	91 (76.5)	0.1734
	Unclear	14 (13.2)	Unclear	25 (21.0)	
	High	6 (5.7)	High	3 (2.5)	
Selective reporting	Low	80 (75.5)	Low	86 (72.3)	0.8598
	Unclear	23 (21.7)	Unclear	29 (24.4)	
	High	3 (2.8)	High	4 (3.4)	
Other bias	Low	55 (51.9)	Low	47 (39.5)	0.1659
	Unclear	41 (38.7)	Unclear	56 (47.1)	
	High	10 (9.4)	High	16 (13.4)	
Overall RoB	Low	42 (39.6)	Low	30 (25.2)	0.0587
	Unclear	41 (38.7)	Unclear	53 (44.5)	
	High	23 (21.7)	High	36 (30.3)	
Statistical analysis was made by regression analysis. *Statistically significant results ($p < 0.001$).					

Of these variables, trial registration influenced overall RoB to the greatest extent (odds ratio [OR] 0.06, 95% CI 0.03–0.31). Drug trials were more likely to have a low RoB than non-drug trials (OR 0.53, 95% CI 0.29–0.97), and multicenter trials more likely than single center trials (OR 0.39, 95% CI 0.18–0.80).When we investigated individual RoB intems separately: drug trials (OR 0.39, 95% CI 0.22–0.66) and registered trials (OR 0.39, 95% CI 0.18–0.83) were more likely to have low RoB for random sequence generation.Drug trials (OR 0.51, 95% CI 0.28–0.93), registered trials (OR0.49, 95% CI 0.26–0.91), and multicenter trials (OR 0.49, 95% CI 0.26–0.91) were more likely to have low RoB for allocation concealment, while trials with a statistically significant result were more likely to have unclear or high RoB (OR 2.59, 95% CI1.34–5.31).Registered trials (OR 0.18, 95% CI 0.06–0.43), trials larger than 500 participants (OR0.47, 95% CI 0.24–0.92), and trials with a Data Monitoring Committee (OR 0.50, 95% CI 0.28–0.87) had more often low RoB for the blinding of participants and personnel while the blinding of outcome assessors was more often low RoB in multicenter trials (OR 0.42, 95% CI 0.19–0.89) and registered trials (OR 0.27, 95% CI 0.12–0.63).

There were no factors that increased the likelihood of low RoB for incomplete outcome data; however, trials with statistically significant results decreased the likelihood of low RoB for incomplete outcome data (OR 2.40, 95% CI 1.18–5.21).Larger trials with more than 500 participants were more likely to have low RoB for selective reporting (OR 0.44, 95% CI 0.19–0.95).Registered trials (OR0.23, 95% CI 0.08–0.56) and multicenter trials (OR 0.31, 95% CI0.16–0.59) were more likely to have low RoB for other biases.

Risk of Bias According to a Funding Source

When funding source was added as an additional independent variable to the multivariable regression model, funding did not seem to influence the likelihood of overall low RoB (industry funding: OR 0.76, 95% CI 0.40–1.45).

In the sub-group of industry-funded trials, multicenter trial and Data Monitoring Committee were factors that increased the likelihood of overall low RoB. None of the investigated factors influenced the overall RoB within the sub-group of trials with non- industry funding (Table 3). Compared with non-industry funded studies more industry funded studies were rated as low RoB (84.9 vs. 63.9%) and less were rated as unclear (12.3 vs. 26.9%) or high RoB (2.8 vs. 9.2%) for allocation concealment ($p < 0.001$) (Table 4). More industry funded studies were rated low (66.0 vs.42.9%) and fewer were rated as unclear (33.0vs 51.3%) or high risk (0.94vs 5.9%) for the blinding of participants and personnel ($p<0.001$).

4.2 Change over Five Years in Important Measures of Methodological Quality and Reporting in Randomized Cardiovascular Clinical Trials

Descriptive Analysis

The main characteristics of included cardiovascular RCTs are shown in Table 5. Data from 2017 have been previously partly reported. Values from 2012, some data on additional measures of methodological quality and reporting for both years and statistical comparisons were novel.

TABLE 5. Characteristics of cardiovascular trials from 2012(n=250) and 2017(n=250)

Characteristics	**2012, n (%)**	**2017, n (%)**	**p Value**
Type of Journal			<0.001
Specialty cardiovascular journal	96 (38.4%)	100 (40.0%)	
General cardiovascular journal	41 (16.4%)	46 (18.4%)	
Specialty medical journal	26 (10.4%)	49 (19.6%)	
General medical journal	50 (20.0%)	41 (16.4%)	
Other	37 (14.8%)	14 (5.6%)	
Continent of corresponding author			<0.05
Africa	3 (1.2%)	0 (0.0%)	
Asia	57 (22.8%)	65 (26.0%)	
Australia	10 (4.0%)	2 (0.8%)	
Europe (excluding UK)	70 (28.0%)	93 (37.2%)	
North America	89 (35.6%)	69 (27.6%)	
South America	8 (3.2%)	13 (5.2%)	
United Kingdom	13 (5.2%)	8 (3.2%)	
Total	250 (100%)	250 (100%)	
Study type			0.093
Efficacy/Superiority	244 (97.6%)	237 (94.8%)	
Equivalence	2 (0.8%)	3 (1.2%)	
Non-inferiority	4 (1.6%)	4 (1.6%)	

None of the above	0 (0.0%)	6 (2.4%)	
Study design			<0.01
Cluster	7 (2.8%)	0 (0.0%)	
Parallel	201 (80.4%)	231 (92.4%)	
Crossover	34 (13.6%)	15 (6.0%)	
Factorial	5 (2.0%)	4 (1.6%)	
Other	3 (1.2%)	0 (0.0%)	
Intervention type			<0.001
Alternative therapeutic	24 (9.6%)	32 (12.8%)	
Behavioral	0 (0.0%)	2 (0.8%)	
Cell therapy	0 (0.0%)	1 (0.4%)	
Communication,	4 (1.6%)	13 (5.2%)	
Device	17 (6.8%)	23 (9.2%)	
Diet, nutrition	26 (10.4%)	10 (4.0%)	
Drug	117 (46.8%)	139 (55.6%)	
Prevention or screening	43 (17.2%)	20 (8.0%)	
Rehabilitation or psychosocial	18 (7.2%)	6 (2.4%)	
Surgery or radiotherapy	1 (0.4%)	3 (1.2%)	
Other	0 (0.0%)	1 (0.4%)	
Type of control			0.628
Active intervention	153 (61.2%)	160 (64.0%)	
No intervention	10 (4.0%)	21 (8.4%)	
Placebo	86 (34.4%)	68 (27.2%)	
Other	1 (0.4%)	1 (0.4%)	
Was the study multicenter?			0.063
Yes	117 (46.8%)	157 (62.8%)	
No	131 (52.4%)	93 (37.2%)	

Unclear	2 (0.8%)	0 (0.0%)	
Was the study multinational?			<0.05
Yes	45 (18.0%)	69 (27.6%)	
No	205 (82.0%)	181 (72.4%)	
Where were participants recruited from?			<0.001
Developing country	3 (1.2%)	21 (8.4%)	
Transitional country	8 (3.2%)	13 (5.2%)	
Established market economy	239 (95.6%)	216 (86.4%)	
Who funded the study?			<0.001
Academic or Research institute	113 (45.2%)	94 (37.6%)	
Government	44 (17.6%)	24 (9.6%)	
Industry for device	4 (1.6%)	10 (4.0%)	
No external funding	3 (1.2%)	4 (1.6%)	
Pharmaceutical	36 (14.4%)	48 (19.2%)	
Private	13 (5.2%)	50 (20.0%)	
Unclear	37 (14.8%)	21 (8.4%)	
How was the study population selected?			0.775
Inpatients	144 (57.6%)	133 (53.2%)	
Outpatients	98 (39.2%)	116 (46.4%)	
Unclear	7 (2.8%)	1 (0.4%)	
Primary diagnostic category in the study			0.971
Circulatory system	250 (100%)	244 (97.6%)	
Congenital malformations	0 (0.0%)	1 (0.4%)	
Factors influencing health status	0 (0.0%)	2 (0.8%)	
Metabolic disease	0 (0.0%)	2 (0.8%)	
Unclear	0 (0.0%)	1 (0.4%)	

TABLE6. Changes in important measures of methodological quality and reporting

Study Characteristics	**2012, *n* (%)**	**2017, *n* (%)**	***P Value***
Funding source			0.002
Specified	243 (97.2%)	229 (91.6%)	
Not specified	7 (2.8%)	21 (8.4%)	
Consent obtained			0.895
Reported	250 (100%)	248 (99.2%)	
Not reported	0 (0.0%)	2 (0.8%)	
Number of patients approached to participate in the study			0.854
Reported	2 (0.2%)	12 (4.8%)	
Not reported	248 (99.8%)	238 (95.2%)	
Number of patients consented to participate in the study			0.534
Reported	2 (0.2%)	12 (4.8%)	
Not reported	248 (99.8%)	238 (95.2%)	
Number of participants randomized			0.972
Reported	2 (0.2%)	2 (99.8%)	
Not reported	248 (99.8%)	248 (2.0%)	
Number of participants analyzed			0.887
Reported	2 (0.2%)	1 (0.4%)	
Not reported	248 (99.8%)	249 (99.6%)	
Sample size calculation			<0.01
Reported	124 (49.6%)	151 (60.4%)	
Not reported	126 (50.4%)	99 (39.6%)	
Data Monitoring Committee			<0.001
Yes	86 (34.4%)	105 (42.0%)	
No	39 (15.6%)	94 (37.6%)	

Unclear	125 (50.0%)	51 (20.4%)	
Analysis described as intention to treat			0.120
Yes	232 (92.8%)	222 (88.8%)	
No	18 (7.2%)	28 (11.2%)	
Primary outcome specified in trial registry			0.823
Yes	135 (54.0%)	157 (62.8%)	
No	115 (46.0%)	93 (37.2%)	
Primary outcome was objective			0.652
Objective	247 (98.8%)	248 (99.2%)	
Subjective	3 (1.2%)	2 (0.8%)	
Type of primary outcome			0.124
Behavioural	20 (8.0%)	6 (2.4%)	
Biomarker	40 (16.0%)	21 (8.4%)	
Physiological	172 (68.8%)	206 (82.4%)	
Psychological	5 (2.0%)	5 (2.0%)	
Techniques/Training	8 (3.2%)	6 (2.4%)	
Quality of life	3 (1.2%)	1 (0.4%)	
Other	2 (0.8%)	3 (1.2%)	
At least one statistically significant outcome			0.899
Yes	213 (85.2%)	215 (86.0%)	
No	37 (14.8%)	35 (14.0%)	
Significant statistical primary outcome			<0.01
Yes	197 (78.8%)	173 (69.2%)	
No	53 (21.2%)	77 (30.8%)	
The author's overall conclusion			<0.01
Negative	32 (12.8%)	34 (13.6%)	
Neutral	18 (7.2%)	46 (18.4%)	

Positive	193 (77.2%)	170 (68.0%)	
Insufficient evidence (intermediate)	7 (2.8%)	(0.0%)	
Planning to collect adverse effects/events or side effects			<0.001
Reported	185 (74.0%)	121 (48.4%)	
Not reported	65 (26.0%)	129 (51.6%)	
Harms reported			<0.001
Yes	130 (52.0%)	170 (68.0%)	
No	120 (48.0%)	80 (32.0%)	
Blinding performed			0.087
Yes	126 (50.4%)	145 (58.0%)	
No	124 (49.6%)	105 (42.0%)	
Trial registered			0.238
Yes	135 (54.0%)	192 (76.8%)	
No	115 (46.0%)	58 (23.24%)	
Primary register			0.031
clinicaltrials.gov	124 (68.9%)	164 (78.4%)	
Other	56 (31.1%)	45 (21.6%)	
Primary outcome stated the same in trial registry and in the publication			<0.001
Yes	132 (52.8%)	183 (73.2%)	
No	76 (30.4%)	26 (10.4%)	
N/A	42 (16.8%)	41 (16.4%)	

We observed significant differences in the country of origin defined based on the first author's affiliation between 2012 and 2017. In our 2017 sample, more publications were published in specialty medical journals (19.6% compared to 10.4%; the logistic regression result on the Type of Journal variable was: $p < 0.001$). In 2017 we included more RCTs with parallel design (92.4% compared to 80.4%; $p < 0.01$), and among the interventions there were more drug trials (55.6% compared to 46.8%) and surgical interventions (1.2% compared to 0.4%), ($p < 0.001$). In the 2017 sample, we had a larger number of multinational trials (27.6% compared to 18%), ($p < 0.05$) where developing (8.4% compared to 1.2%) and transitional economy countries (5.2% compared to 3.2%) were more often concerned ($p < 0.001$). In 2017 included trials were more often funded by pharmaceutical companies or industry ($p < 0.001$). Table 6 shows changes in important measures of methodological quality and reporting.

Change in Important Measures of Methodological Quality and Reporting

As compared to 2012, we observed an improvement in 2017 in the reporting of the presence of a data monitoring committee (42.0% compared to 34.4%; $p < 0.001$). As com- pared to 2012, there was a positive change in registering trials in trial registries in 2017 and, among clinical trial registries, the clinicaltrials.gov database had increased popularity (registration rate in clinicaltrials.gov was: 78.4% compared to 68.9%; $p = 0.03$). Also, significantly more RCTs reported sample size calculation (60.4% compared to 49.6%; $p< 0.01$) in 2017 as compared to 2012. Although fewer RCTs specified plan to collect adverse effects in 2017 (48.4% compared to 74%; $p < 0.001$), they reported harms more often in 2017 (68% compared to 52%; $p < 0.001$). When we investigated the reporting of results, we observed that the number of RCTs with statistically significant results of the primary outcome was lower in the 2017 sample (69.2% compared to 78.8%; $p <0.01$). Further, there were more publications with neutral conclusions in 2017 (18.4% compared to 7.2%; $p < 0.01$). There were no statistically significant differences between 2012 and 2017 in the number of intentions to treat analyses, in the type of outcomes (as most outcomes were objective), or specific types of primary outcomes.

Change in Risk of Bias

We provided a RoB assessment by each domain for trials published in 2012 and 2017 year (Table 7). Compared with 2012, more 2017 RCTs were rated low (70.4% compared to 38.8%) and fewer were rated unclear (20.4% compared to 50%; $p < 0.001$) risk for allocation concealment. Fewer 2017 RCTs were rated low (50.8% compared to 65.6%; $p< 0.001$) risk for blinding of participants and personnel, for blinding of outcome assessors (82.4% compared to 90.8%; $p < 0.001$), and selective outcome reporting (62.8% compared to 80.0%; $p < 0.001$). A similar proportion of 2017 RCTs were rated low risk for random sequence generation (59.6% compared to 56.0%), and for incomplete outcome data (74% compared to 73.6%;) compared to 2012. In 2017, more RCTs were rated low (42.8% compared to 33.6%) risk for other RoB ($p < 0.01$). More trials were rated low (29.2% compared to 21.2%) for overall RoB in 2017 compared to 2012 ($p < 0.01$). In 2017, multicenter trials (OR 0.39, 95% CI 0.18 to 0.80), drug trials (OR 0.53, 95%CI 0.29 to 0.97), and registered trials (OR 0.06, 95% CI 0.003 to 0.31) were also more likely to have a low overall RoB. In 2012, there was not yet a significant difference between multicenter or single-center trials (OR 0.52, 95% CI 0.24 to 1.22), drug trials, and non- drug trials (OR 0.82, 95% CI 0.44 to 1.56). Trial registration was not yet shown to have positive effects on RoB in 2012 either (OR 0.85, 95% CI 0.38 to 1.84).

TABLE 7. Risk of bias assessments by domain in 2012 (n = 250) and in 2017 (n = 250)

	N (%) in 2012	**RoB Domains**	**N (%) in 2017**
Random sequence generation			0.381
Low	140 (56.0%)	149 (59.6%)	
Unclear	95 (38.0%)	68 (27.2%)	
High	15 (6.0%)	33 (13.2%)	
Allocation concealment			<0.001
Low	97 (38.8%)	175 (70.0%)	
Unclear	125 (50.0%)	51 (20.4%)	
High	28 (11.2%)	24 (9.6%)	
Blinding participants and personnel			<0.001
Low	164 (65.6%)	127 (50.8%)	
Unclear	73 (29.2%)	112 (44.8%)	

High	13 (5.2%)	11 (4.4%)	
Blinding outcome assessors			<0.001
Low	227 (90.8%)	206 (82.4%)	
Unclear	19 (7.6%)	33 (13.2%)	
High	4 (1.6%)	11 (4.4%)	
Incomplete outcome data			0.469
Low	184 (73.6%)	185 (74.0%)	
Unclear	60 (24.0%)	57 (22.8%)	
High	6 (2.4%)	8 (3.2%)	
Selective outcome reporting			<0.001
Low	200 (80.0%)	157 (62.8%)	
Unclear	48 (19.2.0%)	67 (26.8%)	
High	2 (0.8%)	26 (10.4%)	
Other bias			<0.01
Low	84 (33.6%)	108 (42.8%)	
Unclear	131 (52.4%)	106 (42.4%)	
High	35 (14.0%)	36 (14.4%)	
Overall bias			<0.01
Low	53 (21.2%)	73 (29.2%)	
Unclear	142 (56.8%)	99 (39.6%)	
High	55 (22.0%)	78 (31.2%)	

Novel findings and practical applications

1. Our results underline the need of further improvement in the process of planning and performing a clinical trial in the field of CVD research.
2. Trial registration was associated with a larger likelihood of low RoB, therefore mandatory trial registration should be endorsed and enforced by ethic committees, funders, and journal editors.
3. Favorable trial features associated with the lower RoB were multicenter trials, larger trials with more than 500 participants, and trials with a Data Monitoring Committee.Trials funded by the academy were more often at a high RoB for the allocation concealment and the blinding of participants and personnel than those funded by the industry, indicating, that studies without industry involvement need to pay greater attention to following certain methodological recommendations. The same is applicable for cardiovascular research trials investigating the effects of a non-drug interventions.
4. Our study identified several features of clinical trial planning and conducting that need further improvement in the field of cardiovascular research, including a lower number of RCTs with a low RoB for blinding of participants and personnel and blinding of outcome assessors in 2017 as compared to 2012. Improvements in study design, conduct, and reporting will decrease research waste and support the realization of evidence-based decisions in the field of cardiology.
5. As compared to 2012, in 2017 there were significant changes in important measures of methodological quality and reporting, including an improvement in the reporting of the presence of a data monitoring committee, and a positive tendency of registering trials in trial registries. Also, we observed that significantly more RCTs reported sample size calculations in 2017 as compared to 2012.

List of publications

Articles related to the thesis

Baasan O, *Freihat O, Nagy DU and Lohner S. Methodological Quality and Risk of Bias Assessment of Cardiovascular Disease Research: Analysis of Randomized Controlled Trials Published in 2017. Front. Cardiovasc. Med. 2022; 9:830070. doi: 10.3389/fcvm.2022.830070 (IF2022:* ***3.6)***

Baasan O, *Freihat O, Nagy D, Lohner S. Change over Five Years in Important Measures of Methodological Quality and Reporting in Randomized Cardiovascular Clinical Trials. J. Cardiovasc. Dev. Dis. 2024; 11, 2. https://doi.org/10.3390/ jcdd11010002 (IF2022****: 2.4)***

Additional articles

Sándor-Bajusz KA, Kraut A, ***Baasan O,*** *Márovics G, Berényi K, Lohner S. Publication of clinical trials on medicinal products: follow-up on trials authorized in Hungary. Trials. 2022 Apr 21;23(1):330. doi: 10.1186/s13063-022-06268-y. PMID: 35449017; PMCID: PMC9022244. (IF2022:* ***2.5)***

Abstracts and oral presentations

Odgerel Baasan 1. *Szimonetta Lohner 1The Conduct and Reporting of Cardiovascular Disease Research: An Analysis of Randomized Controlled Trials Published in 2017 and Evaluation of Change over 5Years.* ***Medical Conference for PhD Students and Experts of Clinical Sciences: Book of abstracts Pécs, Hungary:*** *University of Pécs Doctoral Student Self-Government, (2018) 111 p. pp.6-6,1p*

Odgerel Baasan1*, Omar Freihat PhD1, Dávid Nagy PhD2, Szimonetta Lohner,MD, PhD1, 2 A descriptive analysis of randomized controlled trials of cardiovascular disease research published in 2017.* ***10 th INTERDISCIPLINARY DOCTORAL CONFERENCE 2021 BOOK OF ABSTRACTS****. Pécs, Hungary : Doctoral Student Association of the University of Pécs (2018) 361 p. pp.110-110 , 17*