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LETTERS TO THE EDITOR

Outcomes that patients perceive and value are systematically unassessed in randomized clinical trials of endocrine-related illnesses: a systematic review

1. Introduction

For patients and clinicians to use evidence to shape care, that evidence should directly estimate the effect of interventions on outcomes that patients perceive and value (i.e., patient-important or direct outcomes); however, surrogate outcomes (i.e., indirect outcomes) appear to be used every time more in clinical research [1,2]. The use of surrogate outcomes in clinical research is appealing as they allow for smaller, briefer, and less expensive trials intended to allow clinicians and researchers to elucidate how and to what extent an intervention affects health. The relationship between surrogate and patient-important outcomes, however, is not linear and is often less certain than physiologic plausibility suggests. *De facto*, evidence from large trials has repetitively shown that improving surrogate markers does not always translate into positive patient-important outcomes [3−9]. To our knowledge, the extent of endocrine-related randomized controlled trials (RCTs) assessing patient-important outcomes remains uncertain. Therefore, we conducted a systematic review to assess the types of outcomes in RCTs of endocrine-related illnesses published in top endocrinology journals.

2. Methods

We systematically searched in MEDLINE for RCTs evaluating treatments for endocrine-related diseases and published in top medical journals between 2014 and 2016. We excluded Phase 1 trials. For each RCT, two reviewers, working independently and in duplicate, reproducibly (kappa $>$ 0.6) determined the kind of outcomes measured (i.e., patient-important, surrogate, or laboratory/physiological). We defined patient-important outcomes as any event or outcome that is directly related to an improvement, prevention, or reduction in patient's mortality, quality of life, functional status, symptoms, or overall health.

3. Results

Inclusion criteria were met by 297 full-text studies. Of the 297 eligible RCTs, 209 (70%; 95% confidence interval [CI] 65−75%) did not assessed a patient-important outcome, 17 (5.7%; 95% CI, 3−8.4%) included them as primary outcomes, 54 (18.2%; 95% CI, 13.5−22.6%) as secondary outcomes, and 17 (5.7%; 95% CI, 3.4−8.4%) as both primary and secondary outcomes. The rate was similar in the 206 RCTs evaluating a drug intervention, of which 21 (10%; 95% CI, 6−14%) listed a patient-important outcome as a primary endpoint (Table 1).

4. Discussion

Only 1 out of every 10 RCTs published in top endocrinology journals included patient-important outcomes as primary outcomes, and only 30% assessed patient-important outcomes at all. This finding was observed in RCTs in all fields of endocrinology irrespective of study size, design, and funding. Hence, it is clear that at least for endocrinology treatment decisions between patients and clinicians are not based, in most cases, on what matters most to both of them, threatening with this the whole idea of patient-centered care. Also, the lack of patient-important outcomes in research reduces the trustworthiness of the evidence used to guide clinical decisions and practice guidelines [10−13]. It is imperative to change current policies to ensure that patient-important outcomes are the common denominator and not the exception [14,15]. Future research agencies should promote the conduction of large-scale clinical trials that prioritize patient's preferences and needs rather than to focus on markers with little or no impact on patient's health.

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Table 1
Description of 297 included randomized trials and their primary and secondary outcomes

		Primary outcome			Secondary outcome		
Trial characteristics	**Total**	**Patient important**	**Surrogate**	**Laboratory or physiological**	**Patient important**	**Surrogate**	**Laboratory or physiological**
All included trials		34 (11.4)	187 (63)	76 (25.6)	72 (24.2)	180 (60.6)	45 (15.2)
Endocrinology branch							
Diabetes	198 (66.7)	25 (12.6)	123 (62.1)	50 (25.3)	51 (25.8)	124 (62.6)	23 (11.6)
Cardiovascular[a]	42 (14.1)	2 (4.8)	31 (73.8)	9 (21.4)	9 (21.4)	25 (59.5)	8 (19)
Bone	38 (12.8)	4 (10.5)	27 (71.1)	7 (18.4)	7 (18.4)	24 (63.2)	7 (18.4)
Thyroid	10 (3.4)	3 (30)	4 (40)	3 (30)	4 (40)	4 (40)	2 (20)
PGA	9 (3)	0 (0)	2 (22.2)	7 (77.8)	1 (11.1)	3 (33.3)	5 (55.6)
Trial design							
Parallel	231 (77.8)	30 (13)	161 (69.7)	40 (17.3)	62 (26.8)	144 (62.3)	25 (10.8)
Crossover	55 (18.5)	2 (3.6)	19 (34.5)	34 (61.8)	4 (7.3)	33 (60)	18 (32.7)
Cluster	6 (2)	1 (16.7)	5 (83.3)	0 (0)	4 (66.7)	1 (16.7)	1 (16.7)
Factorial	3 (1)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	1 (33.3)	0 (0)
Other	2 (0.7)	0 (0)	1 (50)	1 (50)	0 (0)	1 (50)	1 (50)
Type of intervention							
Drug vs							
Placebo	111 (37.4)	10 (9)	70 (63.1)	31 (27.9)	21 (18.9)	72 (64.9)	18 (16.2)
Active drug	78 (26.3)	7 (9)	54 (69.2)	17 (21.8)	18 (23.1)	47 (60.3)	13 (16.7)
Usual care	13 (4.4)	3 (23.1)	7 (53.8)	3 (23.1)	5 (38.5)	7 (53.8)	1 (7.7)
Other	4 (1.3)	1 (25)	3 (75)	0 (0)	0 (0)	4 (100)	0 (0)
ELC	18 (6.1)	2 (11.1)	12 (66.7)	4 (22.2)	8 (44.4)	9 (50)	1 (5.6)
Nutrition	26 (8.8)	0 (0)	15 (57.7)	11 (42.3)	3 (11.5)	14 (53.8)	9 (34.6)
Other interventions	47 (15.8)	11 (23.4)	26 (55.3)	10 (21.3)	17 (36.2)	27 (57.4)	3 (6.4)
Funding							
Non-for-profit sources	134 (45.1)	18 (13.4)	71 (53)	45 (33.6)	34 (25.4)	68 (50.7)	32 (23.9)
For-profit sources	124 (41.8)	13 (10.5)	92 (74.2)	19 (15.3)	28 (22.6)	87 (70.2)	9 (7.3)
Mixed sourced	35 (11.8)	2 (5.7)	22 (62.9)	11 (31.4)	9 (25.7)	22 (62.9)	4 (11.4)
Not reported	4 (1.3)	1 (25)	2 (50)	1 (25)	1 (25)	3 (75)	0 (0)

Abbreviations: ELC, education of lifestyle changes; PGA, pituitary-gonadal-adrenal.
[a] Lipids or metabolism. Values are numbers (percentages) unless otherwise stated.

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Don't forget about the "R" in cmRCT: reply to Groenwold and van Smeden

With great interest, we read the paper "*Investigation of the 'm' in the cmRCT design revealed dependence between trial results*" [1]. We were particularly triggered by the rather alarming title. Upon reading the paper, however, our worries disappeared. It seems that, while focusing on the "m" in cmRCT, the authors forgot to think about the "R."

The authors describe four scenarios for conducting RCTs within one cohort. In scenario 1, subjects can only participate in a single trial. In scenario 4, subjects can participate in multiple trials, and trial allocation in subsequent trials is irrespective of the treatment status in the previous trials. The authors state that these scenarios bear no risk for dependence between trials.

The risk occurs, they state, in the other two scenarios. However, neither of these two scenarios represents true RCTs, as in both scenarios participants do not have an equal probability to be allocated to the treatment arms. In scenario 2, subjects in the active treatment arm in trial 1 cannot participate in trial 2, while those receiving the control treatment in trial 1 can only receive control treatment in trial 2. It is completely clear that patients in both treatment arms of trial 2 are not interchangeable (a requirement for randomization), as the control arm of trial 2 may include controls of trial 1, while the intervention arm may not. In scenario 3, subjects in the active treatment arm in trial 1 can only receive the control treatment in trial 2, while controls in trial 1 can receive either the active and control treatment of trial 2. Also here, the two arms of trial 2 are not interchangeable, as the control treatment arm of trial 2 may include participants from the active treatment arm of trial 1, while the intervention arm may not.

There are multiple examples of scenario 1 trials, where cohort members participate in one trial only (www.twics.global/use-of-the-design). An example of scenario 4 is seen in the PLCRC cohort of colorectal cancer patients [2]. Here, participants of the cohort-based BOOST trial (impact of a radiation boost on pathological response in rectal cancer) may subsequently participate in the SPONGE trial (impact of a retractor sponge on postoperative complications) [3,4]. Since patients who have received a radiation boost are prone to postoperative complications, participants in the SPONGE trial are stratified according to their BOOST trial status.

The authors do not provide examples of scenario 2 or scenario 3 trials. To the best of our knowledge, these trials do not exist. It therefore seems that the authors are using a straw man argument by setting up a scenario that hasn't been seen in reality.

As long as the multiple RCTs running within one cohort are designed as randomized controlled trials, in which patients are eligible for a new trial only if they are eligible for all of its arms, there is no concern for dependency between trials. Dependence may occur when the principles of randomization (interchangeability between groups) are abandoned, and cmRCT becomes cmCT.

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