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Potentially unnecessary and wasteful clinical trial research detected in cumulative meta-epidemiological and trial sequential analysis

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Abstract

Objective: The objective was to estimate the presence and extent to which potentially unnecessary and therefore maybe wasteful clinical trials regarding relevant interventions and outcomes in major clinical areas had been conducted.

Study Design and Setting: From current Cochrane collaboration systematic reviews in major medical fields (e.g., cardiovascular disease, cancer, psychiatry), 13 different comparisons were sampled. A cumulative meta-analysis was conducted for each and trial sequential analysis applied to determine when in the course of evidence accrual evidence was found sufficient to reach a reliable conclusion. Trials published afterward were considered potentially unnecessary. Sensitivity analysis is performed, for example, to determine if findings could be explained by a delayed perception of published findings when planning new trials.

Results: In 8/13 cases, potentially unnecessary research was detected to an extent of between 12% and 89% of all participants in trials that might not have been needed. In three of these cases with high proportions (69–89%) of potentially unnecessary research, this finding was found basically unchanged in sensitivity analysis, when only trials published 3 or 5 years after sufficient evidence had already been published were considered potentially wasteful.

Conclusions: The reasonableness of claims to relevance of additional trials needs to be much more carefully evaluated in the future. Cumulative, information size bases analysis might be included in systematic reviews. Research policies to prevent unnecessary research from being done need to be developed.

Keywords: Sequential analysis; Meta-analysis; Research waste; Clinical trials; Meta-epidemiology; Research process analysis; Research policy

1. Introduction

The question of possible ‘‘waste’’ in health research has gained considerable momentum recently [1,2]. Doubts about whether a seemingly ever-increasing output of research and publications is really adequate in terms of reasonableness of research processes and ultimately patient benefit are hardly new though [3]. In the area of randomized clinical trials in humans, in particular subjected to regulatory oversight, the number of human research subjects should not be extended beyond what is strictly necessary. If subjects are included in trials that are unnecessary, as the underlying research question has already been answered, a problematic situation regarding efficiency (‘‘waste’’) and ethics may arise. Therefore, the objective of the present study was to develop and test a method to estimate the presence and extent to which potentially unnecessary and therefore may be wasteful clinical trials in human subjects had been conducted in the past and derive some suggestions and conclusions dependent on the findings.

The effort of trying to answer the question ‘‘How do we ever keep up?’’ with increasing research output [4] has contributed to the increasing use of systematic reviews with or without meta-analysis and even led to the use of meta-reviews or overviews of reviews. Systematic review approaches are often today a de facto standard if decisions for treatment have to be made including regulatory, reimbursement, guideline-based, or individual decisions. Still today, many if not most systematic reviews of medical interventions frequently arrive at cautious conclusions, explicitly state or suggest that current knowledge is unsatisfactory, sometimes even if quite a number of trials have been identified and included. Unnecessary research and lack of research may thus well coincide. Although it seems probable that research is indeed insufficient in many (and likely even the majority of) cases, it is also quite possible

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What is new?

- A method was developed to test for potentially unnecessary clinical trials to explore the currently much debated question of ''research waste''.
- The method is based on methods already used in meta-analysis and in clinical trial interim analysis.
- It could be used in systematic reviews with formal meta-analysis as a diagnostic tool regarding the research process.
- The presence of ''research waste'' seems likely in clinical trials.
- The subject needs to be looked into more closely and research policies should address the issue.

that research resources are used unsatisfactorily in a substantial number of others. The present analysis was designed to detect such cases. Also it might not always be easy to distinguish one from the other, for example, in terms of different opinions of what constitutes necessary replication as opposed to questionable duplication [1].

Systematic reviews with quantitative meta-analysis undertaken to answer specific questions are used in the present analysis as a starting point for the quantitative analysis of the existence and the extent of (potential) research waste. Trials in these reviews are conducted and published over time, and cumulative meta-analysis, first applied more than 2 decades ago [5], captures this characteristic. It follows the course of research over time regarding the effect estimator, including statistical issues, potential trends, and reversals. If cumulative meta-analysis has subsequently been used, it was not always clear what kind of information on the research process it could provide. An overview of cumulative meta-analysis published up to 2012 concluded inter alia that unnecessary research might have been avoided, if prior research had been taken into account [6]. Detailed findings were diverse though, for example, including early result reversals and inconclusive results after a number of trials. No concept or formal method was developed or used to delineate conclusions about too few or too much research and no other systematically derived measures for the time course of evidence accrual were applied.

To determine quantitatively what constitutes likely unnecessary and thus potentially wasteful research in a cumulative process, first it seems reasonable to determine what constitutes ''sufficiency'' of evidence in such a process. To find that latter point in terms of trials published over time, the question of ''How much research will be needed?'' can be asked in terms of how many research subjects will be needed, in a fashion similar to the one that can be used in individual trial sample size calculations [7,8]. The critical assessment in terms of potential waste or potential unnecessary research may be based on a comparison to a hypothetical, ideal, prospective research process that might have taken place. This can be done in terms of the number of participants that would have been sufficient to determine the presence or absence of a particular effect worthwhile investigating, or to be reasonably expected from what is already known.

2. Methods

The most recently published reviews of interventions (excluding diagnostic reviews, overviews, and reviews using multiple treatment comparison methods) which had included at least five trials in a quantitative meta-analysis from each of 13 Cochrane review groups in major fields of clinical medicine, not including, for example, public health, health service organization, and patient/provider–related issues in health care (Web Appendix 1 at www.jclinepi.com) were identified. From each review, the comparison and outcome for which the largest number of trials had been included in a single meta-analysis for which a common effect estimator had been calculated by the review authors formed the database of the current analysis (Table 1).

2.1. Cumulative meta-analysis and trial sequential analysis

For each thus chosen outcome, intervention, and comparator, a cumulative meta-analysis was conducted. Each year in which a trial from the entire set of trials in the respective meta-analysis had been published served as a time point for the cumulative analysis. All analysis for each time point (year) included all trials published up to this year. All meta-analyses were conducted using the DerSimonian and Laird-random effects meta-analysis model [9]. Continuous outcomes were analyzed using the standardized mean difference (SMD, Cohens d), analysis of dichotomous outcomes used the Mantel-Haenszel odds ratio (OR). In the primary analysis, it was determined if the set of trials regarding the outcome, intervention, and comparator in each case was adequate to conclude with reasonable certainty whether a significant difference between test and control intervention exists or can be ruled out. Inadequacy/insufficiency was defined in two complementary ways: either the set of available trials could be found inadequate in terms of the number of trials and trial participants being too few to determine if either a significant difference or its absence could be observed, amounting to a potential lack of research. Alternatively, it could already be determined from a subset of trials conducted up to a certain time point. Subsequently published trials might then have been unnecessary and may therefore constitute potential research waste.