Medical Education

Waste of Research. Is There Any Solution? “Beginning from the Beginning” instead of “Beginning from the End”

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Abstract

There have always been challenges concerning tackling knowledge to practice. It is estimated that 85% of the investment in health research are wasted. Due to low quality, not all systematic review and meta-analysis are placed at the top of the hierarchy of evidence. Many individual clinical trials do not have the essential standards; therefore, conducting systematic reviews based on these low-quality individual studies is unreliable as they cannot be applied in healthcare decision-making and lead to resource waste. To overcome this great issue, several organizations have been worked hard to improve data extraction from only well-developed individual studies. However, it is not sufficient.

It is time to stop and look back all years behind. It is time to reconsider our efforts to make the best conclusion in order to prohibit the huge waste of energy, time, and resources. The old viewpoint “the Beginning from the End” must be replaced with the new one “the Beginning from the Beginning”. It means, we must do all struggles to conduct clinical trials in a standard high-quality format from the beginning as much as we could. Although, it does not seem easy, it might be possible by funding a high discipline, well-respected organization that is engaged in this critical issue. The supposed organization must define standards, flexible criteria for clinical trials, and all investigators must perform clinical trials under the supervision of this organization. Providing a considerable financial resource to grant the researches of the low- and middle-income countries to do clinical trials based on the designed protocol, considering an independent, high discipline journal for publishing well-conducted clinical trials regardless of their results, teaching researchers, considering another efficient policy to rank the journals rather than “impact factor” could help achieve this far-reach goal.

Keywords

waste; research; systematic review; meta-analysis

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Introduction

There has always been concern about tackling knowledge to practice, and the scope to which research knowledge is utilized [1, 2]. Among the sets of evidence, systematic review and meta-analysis play key parts in evidence transferring [3], policy formulation, the development of clinical practice guidelines, and informing routine decision-making in clinical practice [4]. Therefore, failure to use their

findings diminishes healthcare competence and compromises quality of life [4].

Meta-analysis, a quantitative statistical method which integrates the results of several independent studies, plays a key role in evidence-based medicine. Meta-analysis is placed at the top of the hierarchy of evidence, in which clinical evidence is ranked based on the strength of the freedom from various sorts of biases [5].

Unfortunately, the uptake of evidence from systematic reviews has not been consistent [6]. There are several obstacles to take in evidence from systematic reviews including those affecting knowledge, attitude and behavior [4].

Upsettingly, despite the growing prominence of precise guidelines (such as the PRISMA statement [7] and the AMSTAR checklist [8]), as well as the expanding profile of evidence-based practice organizations that focus on systematic reviews, the average quality of systematic reviews in many areas has not meaningfully improved over time [9, 10] or has even gone downhill [11]. The evidence-based practice organizations have not been triumphant at highlighting the importance of conducting reviews and reporting them precisely and scrupulously. As a result, we face a lot of poorly conducted systematic reviews despite persistent attempts in the opposite direction [12].

Systematic Review and Meta-Analysis

Systematic review involves a comprehensive and detailed search strategy in all available databases with the aim of reducing bias by identifying, appraising, and synthesizing all relevant studies on a specific matter [43].

Meta-analysis is conducted to quantitatively analyze the results of the previous researches in order to derive conclusions about that body of research [43].

Stages of Meta-Analysis

Formulating the Review Question

A short and descriptive title consists of unambiguous declaration of participants, interventions, comparisons, outcomes and study design (PICOS) should be presented [13, 14].

Searching for and Including Primary Studies

An in-depth search for primary studies including all general and subject-specific databases, hand search, contact with authors, and pharmaceutical

companies to locate and achieve them should be performed [15].

The finding of ongoing studies, and studies awaiting publication could secure the basis for evidence-based search [16, 17].

Controlling Quality of Evidence

Low-quality individual studies could end in inappropriate results in systematic reviews [18].

A sophisticated quality measurement using general critical appraisal guides and design-based quality checklists must be carried out for selected studies in order to discover heterogeneity, enlighten decisions regarding appropriateness of meta-analysis, assess the strength of assumptions and make proposals for future research [18].

Data Extraction

The data must be reviewed in terms of size, and format of each variable and outcome. Data combining, then, must be considered based on the heterogeneity or homogeneity [43].

Data Analysis

Before starting any analysis, the investigators must evaluate the direction, size, homogeneity of effects, and strength of evidence. The data will be qualitatively and quantitatively reviewed. If the data are not suitable for combination, the results and characteristics of individual studies should be listed in a descriptive form. Conversely, if the data are proper to be combined, the quantitative assessment and analysis should be performed [43].

What are the Problems with Systematic Reviews and Meta-Analysis?

Heterogeneity

Any kind of variability among studies included in a systematic review is called heterogeneity. Clinical heterogeneity arises from different characteristics of participants involved in different individual studies, types and timing of outcome measurements, and different intervention characteristics that could

result in significant statistical heterogeneity, inaccurate summary effects and associated conclusions, and misleading decision makers, etc. [20].

On the other hand, the methodological heterogeneity is predicated upon the study design and risk of bias [19].

Another kind of heterogeneity being the consequence of clinical and/or methodological diversities is called statistical heterogeneity which is the variability in the intervention effects being evaluated in different studies [19].

Heterogeneity or non-comparability of the exposures/interventions, outcomes and study subjects in the primary studies is an inherent limitation of meta-analysis that could interfere with the authenticity or interpretation of the final summary effect measures. More stringent inclusion/exclusion criteria to improve homogeneity across primary studies might be helpful, but at the expense of external generalization and applicability [21].

Bias

Selection Bias

This bias is the consequence of missed studies. A source of this type of bias is publication bias. As only 50% of studies conducted have been ever published. In addition, statistically significant findings are more feasible, and earlier to be published than studies with non-significant findings [21, 22, 23]. Therefore, ignoring the unpublished, statistically non-significant data will bias a systematic review toward positive findings [24].

Information Bias

This type of bias occurs during retrieving information from individual studies for inclusion in systematic reviews. Different effect sizes from the primary studies could not be probably translated into single effect size in a correct manner. In fact, small-study effect is due to the tendency for small trials to show larger treatment outcomes than large trials [21].

A meta-epidemiological study consisting of 13 meta-analyses of 153 osteoarthritis trials has showed larger estimated benefits of treatment in small trials with fewer than 100 patients per trial as compared with larger trials [25].

In another meta-epidemiological study of 163 meta-analyses, it has been demonstrated that treatment outcomes were larger in the meta-analysis of all trials than in single most accurate study [26].

Importantly, moderate-size trials are also prone to larger effect size [27].

Is There Any Solution for the Above Problems?

All the problems abovementioned have made researchers and organizations to find solution for producing much more precise systematic review and meta-analysis.

Several organizations which are based on evidence-based practice have been contemplated into this regard.

The Cochrane Collaboration

The Cochrane Collaboration is the leading resource for systematic reviews in health care by using high-quality information, and up-to date assessment of the effects of health-care interventions based on predefined methodology in order to minimize the bias across in all parts of the process [28, 29].

The Joanna Briggs Institute (JBI)

JBI is an international non-for-profit research and development center within the Faculty of Health and Medical Sciences at the University of Adelaide, South Australia that produces systematic reviews [30].

The Center for Reviews and Dissemination (CRD)

CRD based at the University of York concentrates on generating policy relevant research by synthesizing evidence, assembling and analyzing data, at least in part, by producing high quality systematic reviews from multiple research studies [30].

Evidence for Policy and Practice Information and Co-Ordinating Centre (EPPI-Centre)

The objective of this center is developing methods for systematic reviews and research syntheses,

conducting reviews, supporting others to undertake reviews, and providing guidance and training in this area [30].

The AllTrials Campaign

This is a new campaign established to encourage reporting and registering both ongoing and old clinical trials in order to catch and collect them all together. The need for such a campaign has been originated from the fact that only half of clinical trials are being reported, at least in part, due to the negative results of clinical trials. Many systematic reviews suffer from publication bias. Nobody knows how much these biases have affected the decisions for public health during the several past decades [31].

ClinicalTrials.gov

ClinicalTrials.gov is an easy access web-based resource maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). ClinicalTrials.gov contains information about medical studies in human volunteers [32].

Waste of Research, a Serious Setback

Sholuck entitled the headline in his article, “The Paradox of Health Services Research: If It Is Not Used, Why Do We Produce So Much of It?” [33].

Regrettably, the rate of the uptake of research evidence in practice is very low, as it is estimated to take an only 14% of research for an average of 17 years to be translated into practice [34].

Upsettingly, health-care professionals and policy makers just occasionally use systematic reviews to guide decision-making [35, 36, 37, 38, 39].

Albeit, not all meta-analysis is placed at the top of the hierarchy of evidence due to the insufficient quality. Many individual trials included in the study do not consist of allocation concealment and blinding. Conducting systematic reviews based on the low-quality randomized clinical trials (RCTs) leads to unreliable results and could not be applied in decision making for public health [40]. In contrast, they waste resources, energy and time. For

instance, a meta-analysis of RCTs evaluating intensive glycaemic control in non-critically ill hospitalized patients showed a non-significant reduction in mortality (relative risk of 0.95 (95% CI 0.72 to 1.25). In most RCTs included in this meta-analysis, allocation concealment and blinding were not satisfactory. For this reason, despite the fact of having five RCTs, such evidence should not be rated high in any pyramid [40].

Nearly 85% of the investment in health research are wasted. Unluckily, such a negative sentiment due to the losses promotes a series of dedication to compensate such a huge loss. These attempts just lead to a vicious circle in which the investment losses keep persisting and are called the sunk cost fallacy. The attempts by the systematic review communities to extract valid information from small, poor-quality trials are an example of this fallacy [41].

More importantly, the abuse of trial participant humanism is unethical that is not defensible at all [41].

How Can Evidence-Based Practice Organizations Resolve the Problem?

Despite the efforts above-mentioned are necessary and should be satisfying, they are not sufficient at all. Nearly all the aforementioned organizations are concerned about registering all clinical trials regardless of their results, selecting the most precise and least biased clinical trials to produce more valuable systematic reviews. It seems that these efforts could partially cover the huge problems facing the production of well-conducted systematic reviews. For example, the recent efforts of the AllTrial Campaign tend to overcome unregistered clinical trials and, consequently, publication bias. The Cochrane systematic review, on the other hand, has so far tried to reduce the bias in systematic reviews by accurately evaluating, reviewing and selecting RCTs.

Now, what about lower-quality clinical trials which are excluded? What about the huge amount of cost, energy, and time of all researchers, volunteer participants, and funding organizations? What about the other types of biases which affect the re-

sults of systematic reviews leading in less precise, unreliable results that make harms to patients if come to practice?

How could the effect size, the issues with concealment allocation, blinding, randomization, and heterogeneity of individual studies be overcome?

It appears that employing many reviewers to search for, select, and grade the clinical trials in hope to retrieve at least a part of detriment is not the best strategy to perfectly use resources [41].

In reality, the current approach which has been conducted from the *end*, where all large well-designed and small less valuable-designed clinical trials have already been conducted, a lot of energy, resources, and huge amount of costs have already been utilized, and an enormous number of moments have already been taken to the *beginning*, where we had to retrieve more precise, well-designed clinical trials among the all of those with the huge number of extra-resource, energy and time has not been prosperous at all.

Isn't it the time to think about this drastic problem much more deeply? Isn't it the time to stop the waste of a lot of supplies? How could we have a set of homogenous clinical trials not in all, at least in most their aspects? Is there any key for this giant dilemma?

The answer is YES!

It is absolutely very difficult to reach, at least at the first glance. However, if we do not attempt now, we will never reach this goal at all.

First, we have to replace our old perspective from “the Beginning from the End” to “the Beginning from the Beginning” that aids avoiding the waste of knowledge.

To make the best future for medicine, we need a very strong, highly disciplined, well-respected organization being engaged in this critical issue.

The following steps might be helpful to facilitate gaining this purpose.

1. Thinking of a supreme organization with the above characteristics which conducts a rather flexible, specific, and comprehensive protocol for clinical trials, management, supervision, registration, control, and publishing almost all clinical trials across the globe.

2. All the small and large organizations involved in this subject matter should get together in order to evaluate the best strategy regarding this issue.
3. Election should be aimed at choosing one single organization or a preponderant committee as a supreme leader to take this responsibility.
4. Discussing the dilemmas facing clinical trials' design, operating, reporting, and publishing.

Conclusions

Improving human's health is the single goal of all investigations. Reaching this goal and saving time, energy, and resources as well, need to consider palliative solutions, as well as a curative and basic elucidation.

Considering a head organization which takes the responsibility for directorship, management, and control of all clinical trials based on a standard, designed protocol could be very useful to overcome many issues. Providing a considerable financial resource to grant the researches of the low- and middle-income countries to do clinical trials based on the designed protocol, considering an independent, high discipline journal for publishing well-conducted clinical trials regardless of their results, teaching researchers to understand the importance of doing a well-designed, well-conducted and well-reported clinical trials, considering another efficient policy to rank the journals rather than “impact factor” could help achieve this far-reach goal.

Conflict of Interest

The authors stated no conflict of interest.

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