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REVIEWS

Comparative rates of harms in randomized trials from more developed versus less developed countries may be different

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Abstract

Objectives: We set up to evaluate the relative risk of harms in trials performed in less developed vs. more developed countries.

Study Design and Setting: Meta-epidemiologic evaluation using the Cochrane Database of Systematic Reviews. We considered meta-analyses with at least one randomized clinical trial (RCT) in a less developed country and one RCT in a more developed country. We targeted severe adverse events (AEs), discontinuations due to AEs, any AE, organ system–specific AEs, individual AEs, and all discontinuations due to any reason. We estimated the relative odds ratio (ROR) of harms between more and less developed countries for each topic and the summary ROR (sROR) across topics under each category of harms.

Results: We identified 42 systematic reviews (128 meta-analyses, 521 independent RCTs). Summary sRORs did not differ significantly from 1.00 for any harm category. Nominally significant RORs were found in only 6/128 meta-analyses. However, in 27% (35/128) of meta-analyses the ROR point estimates indicated relative differences between country settings >2-fold. Considering also ROR 95% confidence intervals, in 92% (118/128) of meta-analyses one could not exclude a 2-fold difference in both directions.

Conclusions: We identified limited comparative evidence on harms in trials from these two country settings. Substantial differences in the risk point estimates were common; the potential for modest differences could rarely be excluded with confidence.

Keywords: Comparative safety; Comparative harms; More developed countries; Less developed countries; Randomized trials; Meta-analyses

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1. Introduction

As the budget for and participation rates in randomized clinical trials (RCTs) in more developed countries are limited, it is becoming increasingly more common that clinical guidelines and clinical decision making about important questions of health interventions and health care will depend on evidence from trials performed in less developed countries [1]. With the globalization of clinical research, emerging countries are increasingly more actively involved in clinical trials [2–4]. Asian and Latin America regions have recently shown the largest annual increase in the number of registered clinical trials [5]. Trials done exclusively in less developed countries often have low methodological quality [6]. Only 56% of 670 surveyed researchers from developing countries reported that their research had been reviewed by a local institutional review board [7] and only 11% of published clinical trials conducted in China in 2004 report that their study protocol was reviewed by an ethical review committee [8].

Some reports are raising concerns for underreporting of adverse events from studies performed in developing countries [9]. For example, large differences in the reported rates of ciprofloxacin associated arthropathy were seen in children from North America compared with children from Latin America [9]. However, the frequency of this phenomenon has not been systematically studied. If results from trials performed in countries without a long-standing tradition in clinical research will be used to guide clinical decision making, an empirical large-scale evaluation of these trends is needed.

Although there are potential benefits from the globalization of clinical research, it is important to evaluate whether results are similar and possible to extrapolate across different settings. In a previous evaluation [10], we assessed differences in mortality and primary efficacy outcomes in RCTs performed on the same topic in more vs. less developed countries. We found that on average, trials in less developed countries tended to report more favorable results for the experimental intervention [10]. Sometimes genuine differences between country settings could explain differences in results; however, selective outcome reporting, publication, language, and other biases [11–13] in the literature coming from less developed countries was considered more likely to explain these discrepancies. It would be important to assess whether major harms outcomes are also similar or different in RCTs from more vs. less developed countries.

Very often the number of patients studied in prelicensure trials is small to allow the robust evaluation of both safety and efficacy outcomes [14]. Individual studies and even individual meta-analyses are on average underpowered to detect differences in reported rates of clinically important adverse events from different country settings [15]. Therefore, we performed a large-scale meta-epidemiologic evaluation of safety outcomes in trials from more vs. less developed countries.

2. Methods

2.1. Definitions of countries

The categorization of countries into more developed and less developed countries was done as previously described in our earlier article on comparative results for mortality and primary efficacy outcomes [10]. In brief, we considered more developed countries to be those with both long-standing established marker economies and long-standing tradition in clinical research as previously suggested [16]. Such countries included the United States, Canada, Australia, New Zealand, Israel, Japan, and Western European countries. All other countries except for those in Eastern Europe were considered as less developed. We excluded RCTs from Eastern European countries as these represent another unique type of countries in transition [17].

2.2. Harm-related end points

We targeted 6 main categories of harm-related end points [18], three of which were considered as primary end points because they combine adverse events of all types and they only include harms. We did not focus on mortality, as this was the focus in our previous article [10]. The primary end point categories were severe adverse events; discontinuations due to adverse events; and any adverse event. The secondary end point categories were organ system–specific adverse events; individual adverse events; and all discontinuations due to any reason (in some studies, discontinuations due to harm might not have been separately reported, but they could have been included under such a broader study end point; this end point would then be relevant for harms, although not fully specific). Under the categories of organ system–specific and individual adverse events, we considered several subcategories (e.g., gastrointestinal adverse events, hematologic adverse events and so forth; and headache, neutropenia and so forth, respectively). These end points were considered secondary because they either do not include all adverse events or they count also some events that are not due to adverse events.

We also considered a composite primary-harms end point (combined primary harms), where all three primary harm end points (severe adverse events, discontinuations due to adverse events and any adverse event) were considered together.

2.3. Eligible meta-analyses

We included meta-analyses that quantitatively synthesized evidence on harm-related end points and included at least one RCT from a less developed country and at least one RCT from a more developed country for the same compared interventions and the same type of harm-related end point. We focused on RCTs performed exclusively in more developed countries or exclusively in less developed