Journal of Clinical Epidemiology 95 (2018) 63−72

Comparative evidence on harms in pediatric randomized clinical trials from less developed versus more developed countries is limited

Dario Tedesco[a,1], Mufiza Farid-Kapadia[b,1], Martin Offringa[b], Zulfiqar A. Bhutta[b,c,d], Yvonne Maldonado[e,f,g], John P.A. Ioannidis[f,h,i], Despina G. Contopoulos-Ioannidis[e,i,*]

[a]*Department of Biomedical and Neuromotor Sciences, University of Bologna, Via San Giacomo, 12, 40126, Bologna, Italy*
[b]*Department of Pediatrics, Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children University of Toronto, 555 University Avenue, Toronto, Ontario M5G-1X8, Canada*
[c]*Centre for Global Child Health, The Hospital for Sick Children, 686 Bay Street, Suite 11.9805, Toronto, ON, M5G-0A4, Canada*
[d]*Center of Excellence in Women and Child Health, The Aga Khan University, Stadium Road, P.O. Box 3500, Karachi, 74800, Pakistan*
[e]*Division of Infectious Diseases, Department of Pediatrics, Stanford University School of Medicine, 300 Pasteur Drive, Room G312, Stanford, CA 94305, USA*
[f]*Department of Health Research and Policy, Stanford University School of Medicine, 150 Governor's Lane, HRP Redwood Building, Stanford, CA 94305, USA*
[g]*Senior Associate Dean for Faculty Development and Diversity, Stanford University School of Medicine, Stanford, CA 94305, USA*
[h]*Department of Medicine, Stanford Prevention Research Center, Stanford University School of Medicine, 1265 Welch Road, Stanford, CA 94305, USA*
[i]*Meta Research Innovation Center at Stanford (METRICS), 1070 Arastradero Road, Palo Alto, CA 94304, USA*

Accepted 22 November 2017; Published online 28 November 2017

Abstract

Objectives: Evaluate comparative harm rates from medical interventions in pediatric randomized clinical trials (RCTs) from more developed (MDCs) and less developed countries (LDCs).

Study Design and Setting: Meta-epidemiologic empirical evaluation of Cochrane Database of Systematic Reviews (June 2014) meta-analyses reporting clinically important harm-outcomes (severe adverse events [AEs], discontinuations due to AEs, any AE, and mortality) that included at least one pediatric RCT from MDCs and at least one from LDCs. We estimated relative odds ratios (RORs) for each harm, within each meta-analysis, between RCTs from MDCs and LDCs and calculated random-effects-summary-RORs (sRORs) for each harm across multiple meta-analyses.

Results: Only 1% (26/2,363) of meta-analyses with clinically important harm-outcomes in the entire Cochrane Database of Systematic Reviews included pediatric RCTs both from MDCs and LDCs. We analyzed 26 meta-analyses with 244 data sets from pediatric RCTs, 116 from MDCs and 128 from LDCs (64 and 66 unique RCTs respectively). The summary ROR was 0.92 (95% confidence intervals: 0.78−1.08) for severe AEs; 1.13 (0.54−2.34) for discontinuations due to AEs; 1.10 (0.77−1.59) for any AE; and 0.99 (0.61−1.61) for mortality and for the all-harms-combined-end point 0.96 (0.83−1.10). Differences of ROR-point-estimates ≥2-fold between MDCs and LDCs were identified in 35% of meta-analyses.

Conclusion: We found no major systematic differences in harm rates in pediatric trials between MDCs and LDCs, but data on harms in children were overall very limited.

Keywords: Pediatrics; Comparative; Harms; Mortality; Randomized trials; Meta-analyses; Cochrane Database of Systematic Reviews

Conflict of interest statement: The authors have stated that they have no conflicts of interest.

Funding: This study was supported in part by a grant from the Meta-Research Innovation Center at Stanford (METRICS).

Ethical approval: Not applicable.

Transparency declaration: Dr. Contopoulos-Ioannidis (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

[1] Both authors contributed equally to this work.

* Corresponding author. Tel.: +1-650-723-5682; fax: +1-650-725-8040.

E-mail address: dcontop@stanford.edu (D.G. Contopoulos-Ioannidis).

https://doi.org/10.1016/j.jclinepi.2017.11.016

What is new?

Key findings

- Evidence for important clinical questions is increasingly generated in trials from less developed countries (LDCs), without long-standing tradition in clinical research practices. We studied the comparative rates of clinically important harms in pediatric trials performed exclusively in LDCs and exclusively in more developed countries (MDCs), targeting the same diseases/conditions and the same compared interventions.
- Although we perused the entire Cochrane Database of Systematic Reviews to identify meta-analyses on clinically important harms that included pediatric randomized clinical trials both from LDCs and MDCs, comparative data on clinically important harms from medical interventions in children were overall very limited.
- We found no statistically significant differences in the rates of clinically important harms between pediatric trials from LDCs vs. MDCs; however, differences of more than twofold in the point estimates of the relative harm rates between the two country settings were identified in 35% of meta-analyses.

What this adds to what was known?

- Despite spreading a broad net across the entire Cochrane Database of Systematic Review, our study was still underpowered to detect clinically significant harm differences between pediatric trials from the two country settings.

What is the implication and what should change now?

- Improved reporting of clinically important harms for children, also including requirements by regulatory agencies for harm reporting per country setting in international multi-site trials may increase the completeness of evidence on harms in children and improve the efficiency of global clinical research.

1. Introduction

Owing to the increasing cost of randomized clinical trials (RCTs) performed in more developed countries (MDCs), it is becoming increasingly more common that evidence for important clinical questions is generated in trials performed in less developed countries (LDCs). Overall, 17.6% (64,297 sites/364,955 total registered sites) of all the country sites of RCTs registered in clinicaltrials.gov are in LDCs [1]. India now participates in more than 7% of all global phase III trials [2]. Moreover, the number of trials from India and China registered in 2011 in clinicaltrials.gov, EU clinical trial registry or clinical trial registry of India increased compared to 2007 by 3.7% and 5.1%, for these two countries respectively, whereas the United States and EU showed a decline by 11.3% and 11.9% respectively [3]. Among 346 pediatric trials provided to the U.S. Food and Drug Administration for drugs and biologics approval between 2007 and 2010, developing countries or countries in transition participated in 22% of the studies contributing to 10% of the total number of patients [4]. Respectively, among 78 vaccine trials, such countries participated in 27% of the studies providing 52% of the patients [4]. Moreover, among 174 pediatric trials performed under the Pediatric Exclusivity Program between 1998 and 2007, 38% of patients were enrolled in the developing/transition countries [5].

Despite benefits from the globalization of clinical research [6,7], the generalizability of efficacy and safety results across different country settings needs systematic evaluation. There are uncertainties around quality of research in various settings [8−11]. Comparison of 307 randomized trials from China, 117 from India, and 304 from Western countries showed that Indian and Chinese trials were of much lower methodological quality [10]. Among 3,137 Chinese trials, 93% previously claimed by their authors to be randomized trials were mislabeled and only 207 were indeed randomized [9]. Most Chinese trials did not adhere to the CONSORT reporting guidelines and many trials from LDCs remained unregistered [10]. Only 56% of 670 surveyed researchers from developing countries report that their research was reviewed by a local institutional review board [12], and only 11% of published clinical trials conducted in China in 2004 report review by a research ethics review committee [11]. Few pediatric trials from middle/low-income countries mention the involvement of a data safety board or a local ethics committee [13]. The European Medicines Evaluation Agency in 2009 raised concerns about the transferability of results from clinical studies conducted outside Europe to European population [14,15]; Food and Drug Administration recently addressed similar issues in the United States [15,16].

We have previously shown differences in the reported mortality rates and primary efficacy outcomes in RCTs performed for the same diseases/conditions and the same compared interventions between MDCs and LDCs [17]. On average, results for experimental interventions were more favorable in LDCs [17]. Besides genuine difference between countries, selective outcome reporting, publication, language, and other biases [18−20] in the literature from LDCs with limited tradition on modern clinical research practices, may explain these discrepancies.

Another empirical evaluation also assessed the harms in trials from MDCs and LDCs but limited itself to