Format for ANSWERING REVIEWERS

July 6, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11295-edited- revised.doc).

Title: Russian clinical research policy does not guarantee results availability

Author: Avanesova Anna A., Shamliyan Tatyana A.

Name of Journal: *World Journal of Meta-analysis*

ESPS Manuscript NO: 11295

The manuscript has been improved according to the following suggestions of reviewers.

Comments from the editor

Comment 1. TITLE

Title should be less than 12 words.

Response 1. We revised the title as" Russian clinical research policy does not guarantee results availability" (9 words)

Comment 2. A short running title of less than 6 words should be provided

Response 2. We provided a short running title: Russian clinical research policy

Comment 3. Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. Thank you!

Response 3. We provided one corresponding address following the recommended format.

Comment 4. Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-59080039, Fax: +86-10-59080039.

Response 4. We provided requested format for telephone and fax numbers.

Comment 5. An informative, structured abstracts of no less than 246 words should accompany each paper. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim in the form: "To investigate/study/…; MATERIALS AND METHODS (no less than 80 words); RESULTS (no less than 120 words): You should

present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Response 5. We provided the structured abstract following your recommendations as follows:

AIM To investigate results availability from clinical studies enrolling Russian subjects and Russian clinical research policy.

MATERIALS AND METHODS We analyzed Russian legislation and ethical regulations about drug and devices approval, clinical research registration and the results availability.
In August 2012 we searched the World Health Organization portal of trial registries and clinicaltrials.gov with key words "Russian Federation" to find all registered studies that had an investigational site in the territory of the Russian Federation. To find publication status, we searched the PubMed and Scirus bibliographical databases with trial registration number to find journal publications of the registered studies.

RESULTS We identified 2,062 registered in clinicaltrials.gov studies including 2,017 multinational studies and 45 studies funded exclusively by the Russian sponsors. The number of the studies enrolling Russian subjects increased dramatically from 3 studies in 2002 to 252 studies in 2012 . Most studies (92%) were funded exclusively by industry, were interventions (94.6%), examined drugs (87%) and enrolled exclusively adults (86%) of both genders (89%).

Only 383 (19%) of multinational studies and 2 (4.4%) of exclusively Russian studies were published. The results were posted for 16% of the studies that enrolled subjects in the Russian territory including 1 study funded exclusively by Russian sponsors. Ninety nine studies of 38,111enrolled subjects were terminated and neither posted the results in clinicaltrials.gov nor published the results in journal articles. Federal laws require clinical study registration and conflict of interest disclosure. However, routine monitoring of compliance to clinical research policy is not available.

CONCLUSION Russian legislation does not guarantee the availability of clinical research results. Russian legislation should mandate transparent evidence- based market approval of the drugs and devices.

Comment 6. Please list 5–10 key words for each paper, selected mainly from Index Medicus, which reflect the content of the study. Each key word is separated by a semicolon.

Response 6. We provided requested key words as follows: Clinical Research; Meta-analysis; Research

standards; Publication bias; Medicine, legal

Comment 7. Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Response 7. We identified clinical studies that enrolled Russian subjects and found very low rate of the publication of the results in peer reviewed clinical journals or posting of the results in trial registry, clinicaltrials.gov. We concluded that Russian legislation does not guarantee the availability of clinical research results. The Russian legislation should be revised to mandate transparent evidence- based market approval of the drugs and devices based on high quality clinical evidence applicable to the Russian population.

Comment 8. Please put the reference numbers in square brackets in superscript at the end of ciatation content or after the cited author's name.

Please check across the text.

Response 8. We reformatted references following your recommendations.

Comment 9. Please write the COMMENTS section at here. See the requirements as fellows:

COMMENTS

Background

To summarize concisely and accurately the relevant background to the article to enable the readers to gain some basic knowledge about the article and better understand its significance.

Research frontiers

To briefly introduce the hotspots or important areas in the research field related to the article.

Innovations and breakthroughs

To summarize and emphasize the differences, particularly the advances, achievements, innovations and breakthroughs, from the other related or similar articles so as to allow the readers to catch up the major points of the article.

Applications

To summarize the actual application values, the implications for further application and modification, or the perspectives of future application of the article.

Terminology

To concisely and accurately describe, define or explain the specific, unique terms that are not familiar to

majority of the readers, but are essential for the readers to understand the article.

Peer review

To provide the comments from peer reviewers that most represent the characteristics, values and significance of the article, and allow the readers to have an objective point of view toward the article.

Response 9. We provide Comments section following your recommendations.

Background

Scientific research improves global health care best when international legal and ethical regulations guarantee stakeholders access to the complete and unbiased information it generates. The Russian legislation adopted the international standard in biomedical research and committed itself to meet the highest standards and the integrity of clinical research. The actual legislation in relation to the trends in clinical research involving Russian subjects as well as study sponsorships, types, and results availability has not been examined yet.

Research frontiers

International efforts should be made to ensure consistent public access to results of multinational clinical research. Public trust in clinical research depends on transparent and complete information about all funded studies. Registration of clinical research in The World Health Organization International Clinical Trials Registry Platform (ICTRP) and posting results of registered studies on Clinicaltrials.gov has improved public access to the evidence somewhat, but not nearly enough. All multinational studies, complete, terminated, or suspended, and regardless of country specific market approval, should report participant flow and treatment outcomes on ClinicalTrials.gov. Evidence-based decisions in health care in the US, Russia, and other countries can only be possible with complete and accessible information about the benefits and harms of available healthcare interventions.

Innovations and breakthroughs

Our study found dramatically increasing number of registered studies enrolling Russian subjects. However, the results are available from a very small proportion of the registered studies that enrolled Russian subjects. Many publications of the Russian randomized trials do not mention registration.

Our study demonstrated that existing international clinical research policy and Russian research regulations do not guarantee availability of the results from human studies. All clinical studies enrolling human subjects on the territory of the Russian Federation should be routinely monitored for the registration status and for posting of results on ClinicalTrials.gov and the Russian trial registry.

Applications

Our findings demonstrate that existing international, and specifically Russian clinical research, regulations and ethical policy does not guarantee public access to the results from all clinical studies enrolling Russian subjects and therefore should be revised. Based on our analysis of the Russian legislation, policy, and trends in clinical research, we propose Russian policy changes that can enhance integrity of human research and safety and quality of evidence based health care in accordance with the international ethical principles.

First, ethical approval and national and multinational studies conduct should be done by the clinical research professionals with internationally recognized training and certification in clinical research. Second, compliance with the Russian regulation to register all approved clinical studies should be routinely monitored and available to the public.

Third, rapidly developing Russian legislation should address mandatory posting the results from clinical studies in the national and international trial registries to guarantee results availability for all clinical research in the territory of the Russian Federation.

Forth, Russian scientific peer reviewed journals should adopt the international standards in publishing only registered clinical studies. Finally, transparent evidence based market approval based on high quality clinical evidence applicable to the Russian population should be introduced and routinely monitored including conflict of interest by policy and coverage decision makers.

Terminology

Definitions of the data elements from www.clinicaltrials.gov

Field name	**Definition of the data element**
NCT ID	The ClinicalTrials.gov identifier
Other IDs	Other identification numbers assigned to the protocol, including unique identifiers from other registries and NIH grant numbers
Title	Official name of the protocol provided by the study principal investigator or sponsor
Acronym	Acronym or initials used to identify this study
Funded	Funding source as industry, NIH, U.S. Federal Government, Network, or other
Sponsors	Name of primary organization that oversees implementation of study and is responsible for data analysis
Recruitment	# Enrolling by invitation: participants are being (or will be) selected from a predetermined population # Active, not recruiting: study is ongoing (i.e., patients are being treated or examined), but participants are not currently being recruited or enrolled # Completed: the study has concluded normally; participants are no longer being examined or treated (i.e., last patient's last visit has occurred) # Suspended: recruiting or enrolling participants has halted prematurely but

Field name	Definition of the data element
	potentially will resume # Terminated: recruiting or enrolling participants has halted prematurely and will not resume; participants are no longer being examined or treated # Withdrawn: study halted prematurely, prior to enrollment of first participant
Conditions	Primary disease or condition being studied, or focus of the study. Diseases or conditions should use the National Library of Medicine's Medical Subject Headings (MeSH) controlled vocabulary when possible.
Study Types	Interventional or observational studies
Study Designs	Purpose, phase, treatment allocation, masking of the treatment status; type of primary outcome or endpoint that the protocol is designed to evaluate
Phases	Phase of investigation, as defined by the US FDA for trials involving investigational new drugs
Study Results	-Participant Flow - Baseline Characteristics - Outcome Measures and Statistical Analyses - Adverse Events Information - Administrative Information "Applicable clinical trials" generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE).
Interventions	- Drug (including placebo) - Device (including sham) -Biological/Vaccine -Procedure/Surgery - Radiation - Behavioral (e.g., Psychotherapy, Lifestyle Counseling) - Genetic (including gene transfer, stem cell and recombinant DNA) - Dietary Supplement (e.g., vitamins, minerals)
Outcome Measures	Specific key measurement(s) or observation(s) used to measure the effect of experimental variables in a study, or for observational studies, to describe patterns of diseases or traits or associations with exposures, risk factors or treatment.
Gender	Physical gender of individuals who may participate in the protocol
Age Groups	Age of participants
Enrollment	Number of subjects in the trial
First Received	Date the protocol information was received
Start Date	Date that enrollment to the protocol begins
Completion Date	Final date on which data was (or is expected to be) collected
Last Updated	Date the protocol information was updated
Last Verified	Date the protocol information was last verified
Primary Completion Date	The date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the prespecified protocol or was terminated

Field name	Definition of the data element
Why Study Stopped? (not available for downloading)	a brief explanation of why suspended, terminated or withdrawn studies have been halted or terminated

Peer review

Peer reviewer 1. This is a very interesting survey regarding the status of clinical research in Russian Federation and emphasizes that a transparent process to make available the results of all studies is still missing.

The only point not touched by authors regards the informed consent. Is it necessary to obtain it before any study related activities?

At page 5 design is mispelled deign.

The statement "Meta-analyses can provide valid actionable conclusions when the results from all conducted studies are available for independent analyses. " in the core tip and abstract is in my opinion misleading and should be eliminated

Peer reviewer 2. This is a very valuable study about the trend of publication of clinical research. The conclusion is supported by solid data analysis. Minor concerns:

1. Abstract is missing.

2. It should be described how many authors did the search, abstracted data, as well as how to solve disagreement when it occurs.

3. A funnel plot is highly recommended to show publication bias.

Comment 10. Please delete et al, and list all authors' names. Thank you!

Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI. PMID (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed) DOI (http://www.crossref.org/SimpleTextQuery/)

Response 10. We reformatted all references following your recommendations.

Comments from peer reviewers

Peer reviewer 1. This is a very interesting survey regarding the status of clinical research in Russian Federation and emphasizes that a transparent process to make available the results of all studies is still missing.

Comment 11. The only point not touched by authors regards the informed consent. Is it necessary to obtain it before any study related activities?

Response 11. We clarified that Russian legislation requires informed consent before any study activities:" Several regulatory documents address ethical approval of the clinical research involving human subjects according to the international standards including informed consent procedure. [33-37]"

"The principal investigators certified to conduct clinical research in Russia must request the trial approval from the local research ethics committee and obtain informed consent before enrollment of the subjects. "

Comment 12. At page 5 design is mispelled deign.

Response 12. We corrected this error.

Comment 13. The statement "Meta-analyses can provide valid actionable conclusions when the results from all conducted studies are available for independent analyses. " in the core tip and abstract is in my opinion misleading and should be eliminated

Response 13. We deleted this sentence.

Peer reviewer 2. This is a very valuable study about the trend of publication of clinical research. The conclusion is supported by solid data analysis. Minor concerns:

Comment 14. Abstract is missing.

Response 14. We provided a structured abstract

Comment 15. It should be described how many authors did the search, abstracted data, as well as how to solve disagreement when it occurs. A funnel plot is highly recommended to show publication bias.

Response 15. We clarify our methods as follows: "To find publication status, we searched the PubMed and Scirus bibliographical databases with trial registration number to find journal publications of the registered studies. Two researchers rechecked the publication status. We did not analyze the actual results of the studies reported in published articles. We did not abstract any data from the published articles, did not analyze reporting bias, and did not construct funnel plots to quantify publication bias."

We thank you for the excellent idea to quantify publication bias in multi-national research including Russian studies vs. American studies. We will test in the future the hypothesis that publication bias introduced by

withholding the results from multi-national studies can be larger than by withholding the results from US studies.

Thank you again for publishing our manuscript in the *World Journal of Meta-analyses*.

Sincerely yours,

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