World Journal of Meta-Analysis

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DOI: 10.13105/wjma.v2.i4.154

World J Meta-Anal 2014 November 26; 2(4): 154-161
ISSN 2308-3840 (online)

Russian clinical research policy does not guarantee results availability

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Received: May 14, 2014 Revised: August 11, 2014
Accepted: September 4, 2014
Published online: November 26, 2014

Abstract

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

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 International Clinical Trials Registry Platform and clinicaltrials.gov 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 2062 registered research protocols comprising 2017 international and 45 protocols sponsored by the Russian funding agencies. The number of the studies enrolling Russian subjects increased dramatically from three 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 two (4.4%) of exclusively Russian studies were published. Posting of patient outcomes was available for 16% of the trials that recruited trial participants in the Russian territory including one study funded exclusively by Russian sponsors. Investigators terminated 99 studies of 38111 participants and did not provide the results in clinicaltrials.gov or in published manuscripts. 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.

Key words: Clinical Research; Meta-analysis; Research standards; Publication bias; Medicine; Legal

Core tip: 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.

Shamliyan TA, Avanesova AA. Russian clinical research policy does not guarantee results availability. *World J Meta-Anal* 2014; 2(4): 154-161 Available from: URL: http://www.wjgnet.com/2308-3840/full/v2/i4/154.htm DOI: http://dx.doi.org/10.13105/wjma.v2.i4.154

INTRODUCTION

Scientific research improves global health care best when

international legal and ethical regulations guarantee stakeholders access to the complete and unbiased information it generates[1-4]. Similarly, complete and readily available information about the results from international studies is required for comprehensive syntheses of evidence[5]. Voluntary publication of only selected studies that show impressive results threatens the validity of research. Mandatory study registration and posting the results in trial registry as well as free public access to the publications[6-9] help address this problem[10-12].

Several American initiatives have contributed to transparent public control of clinical studies. First, the United States Congress mandated the registration in ClinicalTrials.gov of all drug trials "for serious or life-threatening diseases"[13-16]. Second, the Food and Drug Administration Amendments Act (FDAAA) mandated posting of applicable trial results on ClinicalTrials.gov within 12 mo of trial's completion[17]. FDAAA applicable trials include all interventions regulated by the FDA and phase Ⅱ to phase Ⅳ recruiting subjects in the United States[18-21].

Finally, the International Committee of Medical Journal Editors and the World Association of Medical Editors required a registration status for all submitted manuscripts reporting the results of clinical trials[22]. Since then many countries launched the national trial registries reporting the minimum protocol information defined by the 20-item World Health Organization Registration Data Set[23]. The World Health Organization International Clinical Trials Registry Platform (ICTRP) permits a single search across all national trial registries in nine languages[23].

The Russian legislation adopted the international standard in biomedical research and committed itself to meet the highest standards and the integrity of clinical research[24-26]. 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.

A contract research organization (http://www.synrg-pharm.com) and the Association of Clinical Trials Organizations, a non-commercial organization of the companies that engage clinical trials (http://acto-russia.org) provide inconsistent information about ongoing and completed clinical studies in the territory of the Russian Federation. Our objectives were to review Russian legal and ethical regulations of clinical research and to examine from the reliable sources the trends in conducting and availability of the results from the clinical studies that enrolled Russian subjects.

MATERIALS AND METHODS

We analyzed Russian legislation and ethical regulations about drug and devices approval, clinical research registration and the results availability.

We searched the ICTRP and clinicaltrials.gov to find all registered studies that had an investigational site in the territory of the Russian Federation. We retrieved all studies from trial registries in August 2012. We retrieved all available fields as defined at http://prsinfo.clinicaltrials.gov/definitions.html and reported by principal investigators. We further categorized interventions according to classification from clinicaltrials.gov. We marked and separately analyzed a subgroup of the studies that were sponsored exclusively by the Russian sponsors. We defined studies as randomized controlled clinical trials if the field with study designs described random allocation of the subjects into the treatment groups. We defined studies as pharmacokinetics, efficacy, safety, or efficacy and safety studies per investigators definitions of study goals. We analyzed the target enrollment in recruiting and actual number of the enrolled subjects in completed or terminated studies per the numbers provided by the principal investigators.

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 calculated descriptive frequency statistics and compared results availability (in clinical.trials.gov or journal papers) by subject demographics, conditions, examined treatments, study design, funding, and recruitment status. We calculated odds ratios with 95%CI for posting of the results and publication using logistic regression with STATA or SAS 9.1 software (SAS Institute Inc., of Cary, North Carolina, United States).

RESULTS

Rapidly developing clinical research legislation in the Russian Federation consists of several federal laws[25-27] and Government Decrees[28-32] adopted during 2010-2012. 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 most recent decree from the Ministry of Health and Social Development at December 30, 2011 "On approval of the technical tests, toxicology studies, and clinical trials of medical devices in order of their registration" outlined requirements for the preclinical trials (Phase 0-2) emphasize examination of the safety and tolerance with investigative drugs[38]. Amendments B and G recommend protocols and tabulate safety assessment methods as a basis for design and execution of the clinical trials. The Ministry of Health and Social Development is responsible for the control over the clinical research and oversee clinical studies design and execution[35,39].

Clinical trials in the Russian Federation can be conducted by the foreign medical and pharmacist professionals after accreditation and certification according to the article 100 of the Federal Law N 323[26]. The sponsors must request the trial approval from the Council on Ethics of Ministry of Health and Social Development[34-37].

Table 1 Posting the results in clinicaltrials.gov

Study characteristic	Has results	No results available	Total	Percent with the results
Subject age				
Child	21	78	99	21.21
Child/adult	6	37	43	13.95
Child/adult/senior	28	117	145	19.31
Adult	17	192	209	8.13
Adult/senior	260	1301	1561	16.66
Senior	3	2	5	60.00
Subject sex				
Both	293	1536	1829	16.02
Female	22	131	153	14.38
Male	20	60	80	25.00
Total	335	1727	2062	16.25
Sponsorship				
Industry	322	1566	1888	17.06
Industry combined with non-industry sources	12	63	75	16.00
Non industry sponsors	1	98	99	1.01
Examined Interventions				
Behavioral	0	9	9	0.00
Biological	14	115	129	10.85
Device	0	17	17	0.00
Dietary supplement	1	3	4	25
Drug	315	1468	1783	17.67
Genetic	0	1	1	0.00
Other	0	22	22	0.00
Procedure	0	31	31	0.00
Radiation	0	1	1	0.00
Phases of clinical trials				
Phase 1	1	42	43	2.33
Phase 1/phase 2	3	31	34	8.82
Phase 2	58	429	487	11.91
Phase 2/phase 3	8	43	51	15.69
Phase 3	221	936	1157	19.10
Phase 4	38	133	171	22.22
Recruitment				
Active, not recruiting	25	339	364	6.87
Approved for marketing	0	2	2	0.00
Available	0	3	3	0.00
Completed	288	744	1032	27.91
Enrolling by invitation	0	20	20	0.00
No longer available	0	1	1	0.00
Not yet recruiting	0	25	25	0.00
Recruiting	0	481	481	0.00
Suspended	0	3	3	0.00
Temporarily not available	0	1	1	0.00
Terminated	22	100	122	18.03
Interventional	327	1624	1951	16.76
Observational	8	96	104	7.69

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. Russian law mandates trial sponsors to provide life and health insurance to all enrolled human subjects[32]. The current legislation does not well articulate the transparent process of medical and statistical review of the new medicine and devices as well as availability of the results from clinical studies for the public.

The Director of the State Department for the regulation of drugs Marat Sakaev stated in the International Conference "Ethics Review of Clinical Research in Pharmaceuticals" that 677 accredited medical organizations could conduct clinical research in Russia (http://www.coe.int/t/dg3/healthbioethic/conferences_and_symposia/Speaker_comp_enx.pdf).

He emphasized the importance of further improvement in the legislation and ethical regulations of the clinical research: "Despite the fact that in Russia, clinical studies have not as common as in the United States and the European Union, every year more and more Russian citizens to receive and accept the invitation to participate in clinical trials. In this regard, the formation of a clear system of state regulation and control in this area, not only to protect the rights, safety and health of patients participating in clinical studies, but the guarantee of the reliability of information on the safety and efficacy of drugs, obtained in clinical trials".

We found 2693 registered protocols (2062 protocols in clinicaltrials.gov) including 2017 international studies recruiting Russian subjects and 45 studies sponsored exclusively by the Russian funding agencies. The number of the studies enrolling Russian subjects increased dramatically from three studies in 2002 to 252 studies in 2012 (Figure 1). The studies enrolled 2409570 subjects. Most studies (92%) were funded exclusively by industry, were interventions (94.6%), examined drugs (87%) and enrolled exclusively adults (86%) of both genders (89%). Half of the studies were completed while 6.5% were initiated but not completed. Few studies provided clear reasons for termination.

The studies funded exclusively by the Russian sponsors more often employed interventional design (84%) with random allocation of the subjects to the treatment groups (73%), and aimed to examine efficacy (16%) or efficacy and safety (53%) with the treatments. Eleven studies did not provide goals of the studies. Most studies were phase 3 (42%) or phase four (24%) clinical trials. The trials funded by the Russian agencies recruited 43163 subjects.

Results availability in trial registries

Among all registered presented in the ICTRP, only clinicaltrial.gov provides postings of baseline participant's characteristics, flow, and post-treatment outcomes. The results were available only for 16% of the studies that recruited Russian participants including one study sponsored by Russian funding agency (Table 1). Odds of posting the results varied among individual sponsors and by study characteristics (Table 1). Industry sponsors posted the results more often than not for profit sponsors (OR = 20, 95%CI: 3-125) (Figure 2). Completed studies had posted results more often than initiated but not completed studies (OR = 1.8, 95%CI: 1.1-2.9). Interventional and drug studies posted the results more often than observational studies or studies of non-pharmacological interventions (Figure 2). The posted post-intervention outcomes were available only for 524214 (22%) enrolled participants.

Results availability in peer reviewed journals indexed in Medline

The results were published only for 383 (19%) of in-

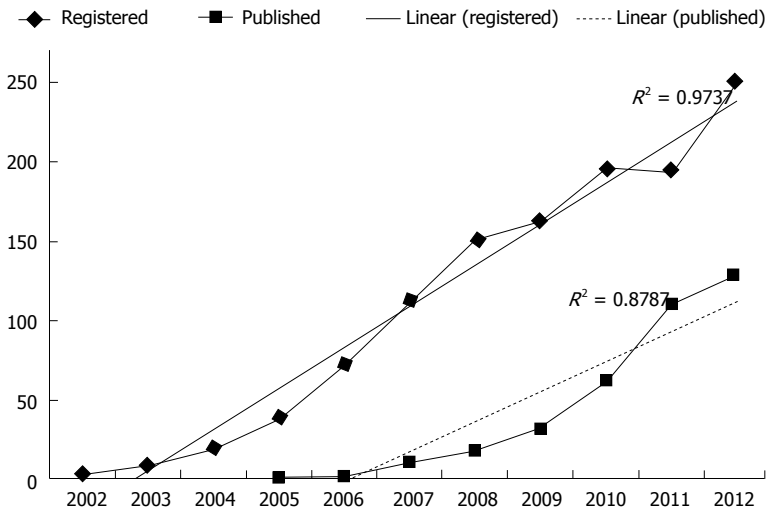

Figure 1 Registration and publication of the clinical studies enrolling subjects in the Russian Federation. Horizontal axis- years of the registration or publication; Vertical axis - the number of the studies.

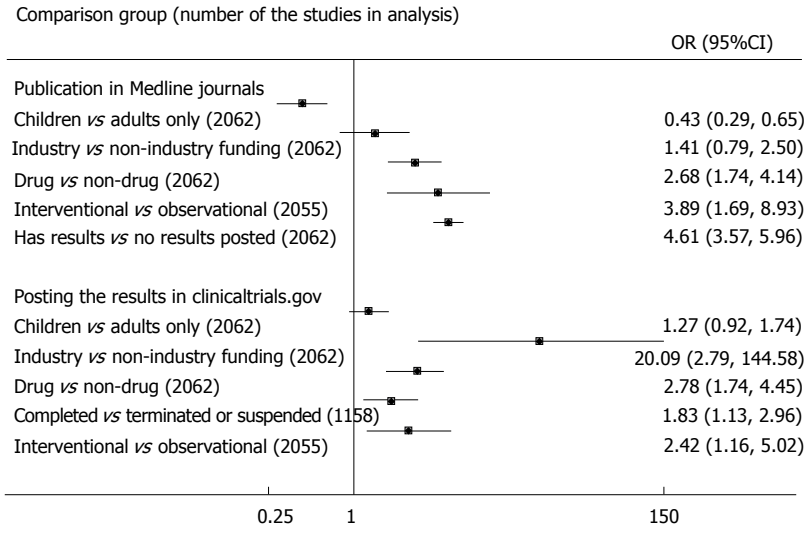

Figure 2 Odds of results availability as posted in clinicaltrials.gov or published in journals among study characteristics.

ternational studies and for two (4.4%) of the studies funding by the Russian agencies (Table 2). Journal manuscripts published the outcomes only for 902735 (38%) of the recruited participants (Table 3). Principal investigators terminated 99 studies of 38111 participants and did not provide the results in clinicaltrials.gov or in published manuscripts (Table 3). Principal investigators that posted the results in trial registry also published the results in peer reviewed journals (OR of journal publication of the studies with *vs* without results in clinicaltrials.gov 4.6, 95%CI: 3.6-5.9) (Figure 2). Pediatric studies were published less often than studies recruiting adults (OR = 0.43, 95%CI: 0.29-0.65) (Figure 2). Studies of pharmacological interventions (OR = 2.7, 95%CI: 1.7-4) published the results more often than studies examining non-drug treatments. Principal investigators conducting clinical trials published the results more often than principal investigators conducting observational studies (OR = 3.9, 95%CI: 1.7-8.9).

Principal investigators published manuscripts in 158 peer-reviewed journals available *via* PubMed search. The four journals including Lancet, New England Journal of Medicine, Current Medical Research and Opinions, and the Journal of Clinical Psychiatry published 24% of all studies enrolling Russian subjects. Only seven articles were led by Russian authors. Medline search found 821 published during last 10 years randomized controlled clinical trials with no registration information.

DISCUSSION

Our study found dramatically increasing number of registered studies enrolling Russian subjects. However, patient outcomes were not available from the majority of the registered studies that recruited Russian participants. 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. Comprehensive analyses of evidence are hindered by the substantial likelihood of publication bias. Publication of the results in peer-reviewed journals remains voluntary[6-9]. In contrast, posting of the results in Clinicaltrials.gov[40] provides public access to the subject flow, benefits with the treatments, and all adverse effects which

Table 2 Publication of the registered studies that enrolled Russian subjects

Study characteristics	Published	Unpublished	Total	Percent published
Age				
Adult	26	183	209	12.4
Adult/senior	327	1234	1561	20.9
Child	7	92	99	7.1
Child/adult	3	40	43	7.0
Child/adult/senior	18	127	145	12.4
Senior	2	3	5	40.0
Sex				
Both	352	1477	1829	19.2
Female	23	130	153	15.0
Male	8	72	80	10.0
Sponsorship				
Industry	354	1534	1888	18.8
Industry/National Institutes of Health	0	2	2	0.0
Industry/other	14	42	56	25.0
Industry/other/ National Institutes of Health	0	1	1	0.0
Industry/United States Fed	1	1	2	50.0
Other/industry	0	13	13	0.0
Other/National Institutes of Health/industry	0	1	1	0.0
National Institutes of Health	4	6	10	40.0
National Institutes of Health/other	0	1	1	0.0
Other	10	70	80	12.5
Other/National Institutes of Health	0	8	8	0.0
Interventions				
Behavioral	2	7	9	22.2
Biological	10	119	129	7.8
Device	1	16	17	5.9
Dietary supplement	1	3	4	25.0
Drug	359	1424	1783	20.1
Genetic	0	1	1	0.0
Other	2	20	22	9.1
Procedure	5	26	31	16.1
Radiation	0	1	1	0.0
Phases of clinical trials				
Phase 1	0	43	43	0.0
Phase 1/phase 2	3	31	34	8.8
Phase 2	68	419	487	14.0
Phase 2/phase 3	5	46	51	9.8
Phase 3	257	900	1157	22.2
Phase 4	40	131	171	23.4
Recruitment				
Active, not recruiting	51	313	364	14.0
Approved for marketing	1	1	2	50.0
Completed	285	747	1032	27.6
No longer available	1	0	1	100
Suspended	0	3	3	0.0
Temporarily not available	0	1	1	0.0
Terminated	23	99	122	18.9
Withdrawn	0	8	8	0.0
Study type				
Interventional	375	1576	1951	19.2
Observational	6	98	104	5.8
Posting the results in clinicaltrials.gov				
Has results	143	192	335	42.7
No results available	240	1487	1727	13.9

Table 3 Enrollment of the subjects in the registered clinical studies by study characteristics

Study characteristic	Sum	Mean	Std Dev	Median
Subject age				
Adult	122622	592	1334	353
Adult/senior	1817056	1181	2836	462
Child	35069	358	891	172
Child/adult	9727	226	335	100
Child/adult/senior	415280	2925	9863	450
Senior	9816	1963	2158	450
Subject sex				
Both	2224171	1232	3849	423
Female	132363	877	1388	419
Male	53036	689	1143	300
Sponsorship				
Industry	2130061	1142	3628	432
Industry/National Institutes of Health	465	465		465
Industry/other	123747	2250	4293	500
Industry/other/National Institutes of Health	8381	8381		8381
Industry/United States Fed	750	375	318	375
National Institutes of Health	30401	3040	5516	860
National Institutes of Health/other	280	280		280
Other	91308	1201	3831	145
Other/industry	17011	1309	2776	200
Other/National Institutes of Health	4166	521	477	335
Other/National Institutes of Health/ industry	3000	3000		3000
Interventions				
Behavioral	23514	2613	5846	400
Biological	116476	917	3958	288
Device	16116	948	2458	90
Dietary supplement	1712	428	605	150
Drug	2058994	1171	3623	448
Genetic	100	100		100
Other	27135	1292	3539	160
Procedure	8566	276	381	150
Phases of clinical trials				
Phases = phase 1	2412	56	63	36
Phases = phase 1/phase 2	3690	109	104	98
Phases = phase 2	149238	310	374	200
Phases = phase 2/phase 3	31469	629	960	295
Phases = phase 3	1443064	1267	2773	587
Phases = phase 4	234401	1379	3495	391
Recruitment				
Completed	1355817	1331	4549	460
Suspended	792	264	216	210
Terminated	110736	915	2501	284
Withdrawn	540	77	133	0
Study type				
Interventional	1845794	956	2415	404
Observational	563776	5421	11639	1069
Posting of the results in clinicaltrials.gov				
Study results = has results	524214	1570	4804	484
Study results = no results available	1885356	1109	3381	402
Terminated studies with no results available		102335	1034	2740
Terminated studies with posted results		8401	382	573
Terminated unpublished studies with posted results		3554	209	217
Terminated unpublished studies without posted results		38111	471	760
Publication				
Published	902735	2401	5662	670
Unpublished	1506835	909	2954	383

participating subjects experienced. However, no Russian policy addressed mandatory posting the results neither in

clinicaltrials.gov, nor in Russian trial registry[28]. The Russian Government Decree mandated the registration of all clinical studies in the official web-based Russian trial registry that has not been opened for the public yet[28]. The Russian trial registry and clinicaltrials.gov should include the protocols and patient outcomes for all clinical studies recruiting human subjects on the territory of the Russian Federation.

Further efforts should be made to ensure consistent public access to results of international clinical research[41]. Principal investigators are obligated to provide accurate and complete information about patient outcomes from all funded and conducted studies[24]. Posting results of registered studies on Clinicaltrials.gov has improved public access to the evidence somewhat, but not nearly enough[18-21]. Thus far, systematic reviews of evidence have not raised the issue of how lack of access to results from incomplete studies compromises the validity of review conclusions and decisions in health care in the United States, Russia, and around the world[42]. All multinational studies, complete, terminated, or suspended, and regardless of country specific market approval, should report participant flow and treatment outcomes on ClinicalTrials.gov. Incomplete multinational studies should always post results along with reasons for suspension or termination. Public data should include information about who initiated termination or suspension of the studies, and why. Early discontinuation of trials for commercial reasons has been determined unethical[43,44]. Trials discontinued for safety reasons should be reported in detail as a source of valuable information about treatment harms[45,46]. Evidence-based decisions in health care in the United States, Russia, and other countries can only be possible with complete and accessible information about the benefits and harms of treatment[47,48].

Our study had several limitations. We did not contact the Russian regulatory ministry to obtain more accurate information about all approved clinical studies although no registration information in Russian publications of randomized clinical trials indicated low registration rates. We relied on information provided in trial registries by sponsors and did not contact sponsors or principal investigators regarding missing data or exact reasons for termination. We could not know reasons for poor results availability since trial registry do not have a variable indicating compliance with the United States federal law regarding posting the results.

Nevertheless, 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. There is a growing number of clinical studies in Russia, multinational and national, with a shortage of internationally certified clinical research professionals[49]. Russia has internal training courses on Research Ethics for members of the Council on Ethics of Ministry of Health and Social Development and short training opportunities for the principal investigators in the local universities[50]. 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[44].

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[28]. Third, the revised Russian legislation should mandate reporting the patient outcomes from all studies recruiting Russian participants. 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[51].

ACKNOWLEDGMENTS

We would like to thank Michael Berglin, B.S. for his help in editing this paper.

COMMENTS

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. Principal investigators are obligated to provide accurate and complete information about patient outcomes from all funded and conducted studies. Registration of clinical research in The World Health Organization International Clinical Trials Registry Platform 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 United Sttaes, 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

This study found dramatically increasing number of registered studies enrolling Russian subjects. However, patient outcomes were not available from the majority of the registered studies that recruited Russian participants. Many publications of the Russian randomized trials do not mention registration. This study demonstrated that existing international clinical research policy and Russian research regulations do not guarantee availability of the results from human studies. The Russian trial registry and clinicaltrials.gov should include the protocols and patient outcomes for all clinical studies recruiting human subjects on the territory of the Russian Federation.

Applications

These 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 the analysis of the Russian legislation, policy, and

trends in clinical research, the authors 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, the revised Russian legislation should mandate reporting the patient outcomes from all studies recruiting Russian participants. 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.

Peer review

This is a very valuable study about the trend of publication of clinical research. The conclusion is supported by solid data analysis.

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