ETHICS OF RESEARCH PRACTICE IN CLINICAL MEDICINE

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A half a century ago Archibald Cochrane, British physician and researcher, emphasized the necessity for critical assessment and a more elaborated approach to biomedical research results. Evidence-based medicine, which is designed to protect a patient from using scientifically unjustified technologies in healthcare, was widely developed subsequently. However, it soon became evident that numerous essential scientific researches contain a substantial proportion of costly but less informative and unjustified trials. They do not add any significant knowledge (wastes or unnecessary spending in research). In 2014, like-minded investigators have joined together in the international community of Evidence-based research. They suggested a plan of actions and algorithm for evidence-based research denoting the liability of all subjects. It is essential that the processes were under supervision of the scientific and medical society.

Keywords: clinical trials, novel medicines, Cochrane, ethics

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ЭТИКА ИССЛЕДОВАТЕЛЬСКОЙ ПРАКТИКИ В КЛИНИЧЕСКОЙ МЕДИЦИНЕ

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Полвека тому назад британский врач и исследователь Арчибальд Кокрейн выдвинул идею о необходимости критической оценки и более тщательного подхода к результатам биомедицинских исследований. Позднее широкое развитие получила новая парадигма — доказательная медицина (evidence-based medicine), которая призвана защитить пациента от применения научно необоснованных технологий в здравоохранении. Однако вскоре стало очевидно, что внутри большого массива важных научных исследований имеется значительная часть дорогостоящих, но мало информативных, необоснованных исследований, которые не добавляют каких-либо существенных знаний (отходы или пустые растраты в исследованиях). В 2014 г. исследователи-единомышленники объединились в международное сообщество Научно-обоснованных исследований и предложили план действий за научно-обоснованные исследования, их алгоритм, обозначив ответственность всех участников исследовательского процесса. Важно, чтобы эти процессы были постоянно под вниманием научного и медицинского сообщества.

Ключевые слова: клинические испытания, новые лекарства, Кокрейн, этика

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The idea that ethical principles regulate the rights of patients, potential risks for them associated with the use of various medical technologies (and interventions in general) and participation in clinical trials, rights of physicians who render medical assistance or participate in clinical trials performing various functions is customary and habitual for the medical community.

Clinical trials of effectiveness and safety of interventions (and medicinal products in particular) are traditionally taken as the fundamentals of evidence-based medicine. The paradigm of evidence-based medicine has brought a silent revolution in international healthcare since the Cochrane Collaboration was founded in 1993. It was developed to produce systematic reviews of clinical research results properly selected and critically assessed in accordance with healthcare problems of the previous century as viewed by Archibald Leman Cochrane (Archie Cochrane). His name was subsequently given to the Collaboration.

His fundamental legacy included a thought about the necessary provision of equal and just fair medical assistance using only the methods the effectiveness of which was proven in properly planned and conducted trials [1]. Archie Cochrane made a decisive contribution to the development of systematic reviews and randomized clinical trials as methodology assessing effectiveness of interventions and clinical epidemiology as science. In his legendary critical review he defined systematic reviews which started bearing his name soon: "*It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials*" [2].

The simple principles formulated by A. Cochrane gained worldwide recognition, whereas Cochrane systematic reviews are recognized as a gold standard of high-quality scientific research even today [3].

In 1996, David Sackett who was a founder of the first Department of Clinical Epidemiology at McMaster University, developed the ideas and defined evidence-based medicine as '*the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient*' [4]. It means medical practice where physicians use interventions (diagnostic, therapeutic, etc.) integrating individual clinical expertise, views and needs of their patients with the best available external clinical evidence from systematic research. Dr. Sackett warned his contemporaries that practice can rapidly be out of date to the detriment of patients if no modern or actual best proof (scientific research) are found.

But even then, it was obvious for founding fathers of evidence-based medicine that ethics of research practice in clinical medicine is coming to the foreground though attributes of ethical expertise of clinical trials including detailed informed consents are used [5]. In 1994, Douglas Altman, professor of medical statistics in Oxford University who was a pioneer of the Cochrane collaboration, wrote as follows: 'We need less research, better research, and research done for the right reasons. *What should we think about a doctor who uses the wrong treatment, either wilfully or through ignorance, or who uses the right treatment wrongly (such as by giving the wrong dose of a drug)? Most people would agree that such behaviour was unprofessional, arguably unethical, and certainly unacceptable. What, then, should we think about researchers who use the wrong techniques (either wilfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common. This is surely a scandal'* [6].

Like-minded investigators of those years hoped that substantial implementation of methodology of systematic reviews and thorough critical assessment of research to include evidence in synthesis will be enough to overcome these problems. However, the scandal continued to worsen as soon as numerous trials and systematic reviews of doubtful quality appeared. This shows clear understanding of redundancy and uselessness of research in medicine and healthcare. The fact was most clearly expressed in a 2005 essay written by John Ioannidis, professor of Stanford University. He made a significant contribution to evidence-based medicine and clinical epidemiology examining own research practice in medicine and social sciences, being the founder of the so-called meta-research. His essay named 'Why most published research findings are false' [7] was the most read article in history of the Public Library of Science (PLOS) as of 2020 with more than three million of views.

The progressive medical and healthcare society has a perception of waste in research, which do not correspond to ethical principles of research practice. The ideas were clearly expressed in the background paper by Iain Chalmers and Paul Glasziou from the Center for evidence-based medicine of the Department of Medicine at the University of Oxford [8]. Sir Iain Chalmers is also a founder of the Cochrane Collaboration, the James Lind Library, the James Lind Initiative and Testing Treatments Interactive. The publication starts with citation of an investigator with myeloma published in the *British Medical Journal* [9]. He complains that the results of four randomized trials on his disease have not been published for several years since conference abstracts were presented. The citation is clear and representative. It states as follows: "*Research results should be easily accessible to people who need to make decisions about their own health. Why was I forced to make my decision knowing that information was somewhere but not available? Was the delay because the results were less exciting than expected? Or because in the evolving field of myeloma research there are now new exciting hypotheses or drugs to look at. How far can we tolerate the butterfly behaviour of researchers, moving onto the next flower well before the previous one has been fully exploited?"* [9].

I. Chalmers and P. Glasziou state [8] that waste in research and presentation of results are inevitable and tolerable. They brought together evidence from numerous research and revealed to the world the level of waste in research, which at least seems surprising.

The authors considered four stages of research and displayed cumulative losses expressed in monetary terms: dividends from research-invested tens of billions of dollars are wasted annually due to the problems that can be solved. The authors mention the problems and suggest solutions within the four stages of research, though a single simple solution is lacking. The solutions include selection of an incorrect research question; conducting unnecessary or poorly planned trials; unsuccessful timely publication of results or lacking publication; bias or useless result reporting (publications).

Though the authors were mainly guided by clinical trial design data, they assume that the problems can be applied to other medical trials as well. It is believed that the modest attempts to comprehend and improve the quality and methodology of research and publish the results would significantly increase the dividends i. e., benefit for patients and entire society. They recommend how to solve the problem and display the steps that have already been followed in Great Britain in this direction. Thus, the programs assessing medical technologies of the National Institute of Healthcare Research require or order (finance) systematic reviews prior to taking a decision about financing the primary trials, publish all research results in the form of online monographies, whereas all study protocols have been freely available since 2006.

Appeal of I. Chalmers and P. Glasziou that not just wasted investments but also a human being and human health are important were further developed in the concept of evidence-based research.

The concept and term 'evidence-based research' were accepted in 2009. It seemed to be redundant. The term was created to determine the focus area of a group of like-minded investigators who opposed a widely accepted practice of ignoring a set of results of earlier studies in favor of scientific interests and ambitions to the novel systematic approach of evidence-based research [10–18]. The concept means using systematic methods to search for and detect all previous trials for a specific research issue presenting references to earlier trials when novel trials are justified, developed and discussed. In other words, the essence of this approach consists in the obligatory use of systematic reviews, which have been either conducted or developed independently prior to any novel clinical trial.

It is essential, as numerous analyses of published trials to detect their possible belonging to wastes have shown that the ignoring is a common practice even among clinical trials published in most respected medical journals and considered as qualitative trials by their methodology [19–26]. In these publications, the authors ignore the systematic approach selectively citing earlier trials and being guided by own strategic intentions and preferences. This is basically a conflict of interests.

The research practice is a serious problem mainly due to the risks it bears in relation to prevented harm for study subjects. It is also a source of wastes.

To overcome the challenges, like-minded investigators have united in 2014 in Bergen, Norway, to create the international community of Evidence-based research (EBRNetwork, http://ebrnetwork.org). They developed a mission statement where their goal was formulated as 'No novel trial without a systematic review of existing evidence and effective development, renewal and distribution of systematic reviews' and offered a plan of actions for evidence-based trials and their algorithm denoting the liability of all subjects.

The application was published in the *British Medical Journal* in 2016 [27], and in the *Kazan Medical Journal* in 2019 (in Russian) [28] (translated by Cochrane, Russia). Initially, partners were colleagues from Australia, Canada, Netherlands, Norway, Great Britain and the USA. The concept of evidence-based research was officially recognized in 2018 and financed in 2018–2022 with the support of the European Cooperation in Science and Technology of Horizon 2020 EU program. The program brought together subjects (universities) from over than 40 countries of the world.

In 2019, the Kazan State Medical University was included into the program as an observer. The program was extended until 2023 because of the pandemic.

The COVID-19 pandemic exacerbated the problem of waste in research; infodemic developed in research practice. Thus, about 11 and over 65 systematic reviews per day were published globally in 2010 [29] and in 2019, respectively. As of May 2021, only one database contained about 9,000 generalized evidences related to COVID-19 only. It means that about 21 reviews per day were devoted to the coronavirus infection since the WHO had announced the pandemic [29].

Nevertheless, as emphasized in a paper in the *Nature*, fundamental principles of evidence-based medicine should be immutable, whereas its principles, processes and methods should be developed under novel conditions. When the Cochrane Collaboration was founded in the last century, its founders were well aware that systematic reviews should be subjected to regular update taking into account all last trials: '*But the proposal of Archie Cochrane made 50 years ago stating that decisions should be based on rigorous evidence are currently more important than ever*' [29].

So, modern clinical practice relies upon evidence-based facts and achievements more and more. It increasingly refers to meta-analyses and systematic reviews. Currently, the goal is to keep making progress in the direction without numerous unnecessary, costly and ethically unjustified biomedical experimental and clinical trials, which can mislead a physician. Local ethics committees, editorial boards of biomedical journals, experts of scientific funds that determine research financing should pay attention to that.

References

1. Cochrane AL. Effectiveness and Efficiency. London: Nuffield Provincial Hospitals Trust, 1972.
2. Cochrane AL 1931–1971: a critical review, with particular reference to the medical profession. In: Medicines for the year 2000. London: Office of Health Economics. 1979; 1–11.
3. Grimshaw J. So what has the Cochrane Collaboration ever done for us? A report card on the first 10 years. Canadian Medical Association Journal. 2004; 171 (7): 747–749. DOI: 10.1503/cmaj.1041255.
4. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. British Medical Journal. 1996; 312 (7023): 71–72. DOI: 10.1136/bmj.312.7023.71.
5. Matthews R, Chalmers I, Rothwell P, Douglas G. Altman: statistician, researcher, and driving force behind global initiatives to improve the reliability of health research. British Medical Journal. 2018; 361: k2588. DOI: 10.1136/bmj.k2588.
6. Altman DG. The scandal of poor medical research. British Medical Journal. 1994; 308: 283. DOI: 10.1136/bmj.308.6924.283.
7. Ioannidis J. Why Most Published Research Findings Are False. PLoS Med. 2005; 2 (8): e124. DOI: 10.1371/journal.pmed.0020124
8. Chalmers I, Glasziou PP. Avoidable waste in the production and reporting of research evidence. The Lancet, 2009; 374: 86–89. DOI: 10.1097/AOG.0b013e3181c3020d.
9. Liberati A. An unfinished trip through uncertainties. British Medical Journal. 2004; 328: 531. DOI: 10.1136/bmj.328.7438.531.
10. Robinson KA, Goodman SN. A systematic examination of the citation of prior research in reports of randomized, controlled trials. Annals of Internal Medicine. 2011; 154: 50–55. DOI: 10.7326/0003-4819-154-1-201101040-00007.
11. Clarke M, Chalmers I. Discussion sections in reports of controlled trials published in general medical journals: islands in search of continents? Journal of the American Medical Association. 1998; 280: 280–282. DOI: 10.1001/jama.280.3.280.
12. Clarke M, Alderson P, Chalmers I. Discussion sections in reports of controlled trials published in general medical journals. Journal of the American Medical Association. 2002; 287: 2799–2801. DOI: 10.1001/jama.28721.2799.
13. Cooper NJ, Jones DR, Sutton AJ. The use of systematic reviews when designing studies. Clinical Trials. 2005; 2: 260–264. DOI: 10.1191/1740774505cn090oa.
14. Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? Clinical Trials. 2005; 2: 218–229, discussion 229–32. DOI: 10.1191/1740774505cn085oa.
15. Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. Lancet. 2010; 376: 20–21. DOI: 10.1016/S0140-6736(10)61045-8.
16. Sheth U, Simunovic N, Tornetta P 3rd, Einhorn TA, Bhandari M. Poor citation of prior evidence in hip fracture trials. Journal of Bone and Joint Surgery American. 2011; 93: 2079–2086. DOI: 10.2106/JBJS. J.01274.
17. Habre C, Tramer MR, Popping DM. Elia N. Ability of a meta-analysis to prevent redundant research: systematic review of studies on pain from propofol injection. British Medical Journal. 2014; 348: g5219. DOI: 10.1136/bmj.g5219.
18. Sawin VI, Robinson KA. Biased and inadequate citation of prior research in reports of cardiovascular trials is a continuing source of waste in research. Journal of Clinical Epidemiology. 2016; 69: 174–178. DOI: 10.1016/j.jclinepi.2015.03.026
19. Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. Journal of the Royal Society of Medicine. 2007; 100: 187–190. DOI: 10.1258/jrsm.100.4.187.
20. Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. British Medical Journal. 2009; 339: b2680. DOI: 10.1136/bmj.b2680.
21. Bastiaansen JA, de Vries YA, Munafo MR. Citation distortions in the literature on the serotonin-transporter-linked polymorphic region and amygdala activation. Biological Psychiatry. 2015; 78: e35–36. DOI: 10.1016/j.biopsych.2014.12.007.
22. Thornley C, Watkinson A, Nicholas D, Volentine R, Jamali HR, Herman E, Allard S, Lewine KJ, Tenopir C. The role of trust and authority in the citation behavior of researchers. Information Research. 2015; 20: 677.
23. Perino AC, Hoang DD, Holmes TH, Santangeli P, Heidenreich PA, Perez MV, Wang PJ, Turakhia MP. Association between success rate and citation count of studies of radiofrequency catheter ablation for atrial fibrillation: possible evidence of citation bias. Circulation, Cardiovascular and Quality Outcomes. 2014; 7: 687–692. DOI: 10.1161/CIRCOUTCOMES.114.000912.

24. Jannot AS, Agoritsas T, Gayet-Ageron A, Perneger TV. Citation bias favoring statistically significant studies was present in medical research. Journal of Clinical Epidemiology. 2013; 66: 296–301. DOI: 10.1016/j.jclinepi.2012.09.015.
25. Fiorentino F, Vasilakis C, Treasure T. Clinical reports of pulmonary metastasectomy for colorectal cancer: a citation network analysis. British Journal of Cancer. 2011; 104: 1085–1097. DOI: 10.1038/sj.bjc.6606060.
26. Robinson KA. Use of prior research in the justification and interpretation of clinical trials. Johns Hopkins University, 2009.
27. Lund H, Brunnhuber K, Juhl C, Robinson K, Leenaars M, Dorch BF, Jamtvedt G, Nortvedt MW, Christensen R, Chalmers I. Towards evidence-based research. British Medical Journal. 2016; 355: i5440. DOI: 10.1136/bmj.i5440.
28. Lund H, Brunnhuber K, Juhl C, Robinson K, Leenaars M, Dorch BF, Jamtvedt G, Nortvedt MW, Christensen R, Chalmers I. Towards evidence-based research. Kazan Medical Journal. 2019; 100 (5): 733–739. DOI: 10.17816/KMJ2019-733.
29. Evidence-based medicine: how COVID can drive positive change. Nature. 2021; 593 (7858): 168. DOI: 10.1038/d41586-021-01255-w.

Литература

1. Cochrane AL. Effectiveness and Efficiency. London: Nuffield Provincial Hospitals Trust, 1972.
2. Cochrane AL 1931–1971: a critical review, with particular reference to the medical profession. In: Medicines for the year 2000. London: Office of Health Economics. 1979; 1–11.
3. Grimshaw J. So what has the Cochrane Collaboration ever done for us? A report card on the first 10 years. Canadian Medical Association Journal. 2004; 171 (7): 747–749. DOI: 10.1503/cmaj.1041255.
4. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. British Medical Journal. 1996; 312 (7023): 71–72. DOI: 10.1136/bmj.312.7023.71.
5. Matthews R, Chalmers I, Rothwell P, Douglas G. Altman: statistician, researcher, and driving force behind global initiatives to improve the reliability of health research. British Medical Journal. 2018; 361: k2588. DOI: 10.1136/bmj.k2588.
6. Altman DG. The scandal of poor medical research. British Medical Journal. 1994; 308: 283. DOI: 10.1136/bmj.308.6924.283.
7. Ioannidis J. Why Most Published Research Findings Are False. PLoS Med. 2005; 2 (8): e124. DOI: 10.1371/journal.pmed.0020124.
8. Chalmers I, Glasziou PP. Avoidable waste in the production and reporting of research evidence. The Lancet. 2009; 374: 86–89. DOI: 10.1097/AOG.0b013e3181c3020d.
9. Liberati A. An unfinished trip through uncertainties. British Medical Journal. 2004; 328: 531. DOI: 10.1136/bmj.328.7438.531.
10. Robinson KA, Goodman SN. A systematic examination of the citation of prior research in reports of randomized, controlled trials. Annals of Internal Medicine. 2011; 154: 50–55. DOI: 10.7326/0003-4819-154-1-201101040-00007.
11. Clarke M, Chalmers I. Discussion sections in reports of controlled trials published in general medical journals: islands in search of continents? Journal of the American Medical Association. 1998; 280: 280–282. DOI: 10.1001/jama.280.3.280.
12. Clarke M, Alderson P, Chalmers I. Discussion sections in reports of controlled trials published in general medical journals. Journal of the American Medical Association. 2002; 287: 2799–2801. DOI: 10.1001/jama.28721.2799.
13. Cooper NJ, Jones DR, Sutton AJ. The use of systematic reviews when designing studies. Clinical Trials. 2005; 2: 260–264. DOI: 10.1191/1740774505cn090oa.
14. Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? Clinical Trials. 2005; 2: 218–229, discussion 229–32. DOI: 10.1191/1740774505cn085oa.
15. Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. Lancet. 2010; 376: 20–21. DOI: 10.1016/S0140-6736(10)61045-8.
16. Sheth U, Simunovic N, Tornetta P 3rd, Einhorn TA, Bhandari M. Poor citation of prior evidence in hip fracture trials. Journal of Bone and Joint Surgery American. 2011; 93: 2079–2086. DOI: 10.2106/JBJS. J.01274.
17. Habre C, Tramer MR, Popping DM. Elia N. Ability of a meta-analysis to prevent redundant research: systematic review of studies on pain from propofol injection. British Medical Journal. 2014; 348: g5219. DOI: 10.1136/bmj.g5219.
18. Sawin VI, Robinson KA. Biased and inadequate citation of prior research in reports of cardiovascular trials is a continuing source of waste in research. Journal of Clinical Epidemiology. 2016; 69: 174–178. DOI: 10.1016/j.jclinepi.2015.03.026
19. Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. Journal of the Royal Society of Medicine. 2007; 100: 187–190. DOI: 10.1258/jrsm.100.4.187.
20. Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. British Medical Journal. 2009; 339: b2680. DOI: 10.1136/bmj.b2680.
21. Bastiaansen JA, de Vries YA, Munafo MR. Citation distortions in the literature on the serotonin-transporter-linked polymorphic region and amygdala activation. Biological Psychiatry. 2015; 78: e35–36. DOI: 10.1016/j.biopsych.2014.12.007.
22. Thornley C, Watkinson A, Nicholas D, Volentine R, Jamali HR, Herman E, Allard S, Lewine KJ, Tenopir C. The role of trust and authority in the citation behavior of researchers. Information Research. 2015; 20: 677.
23. Perino AC, Hoang DD, Holmes TH, Santangeli P, Heidenreich PA, Perez MV, Wang PJ, Turakhia MP. Association between success rate and citation count of studies of radiofrequency catheter ablation for atrial fibrillation: possible evidence of citation bias. Circulation, Cardiovascular and Quality Outcomes. 2014; 7: 687–692. DOI: 10.1161/CIRCOUTCOMES.114.000912.
24. Jannot AS, Agoritsas T, Gayet-Ageron A, Perneger TV. Citation bias favoring statistically significant studies was present in medical research. Journal of Clinical Epidemiology. 2013; 66: 296–301. DOI: 10.1016/j.jclinepi.2012.09.015.
25. Fiorentino F, Vasilakis C, Treasure T. Clinical reports of pulmonary metastasectomy for colorectal cancer: a citation network analysis. British Journal of Cancer. 2011; 104: 1085–1097. DOI: 10.1038/sj.bjc.6606060.
26. Robinson KA. Use of prior research in the justification and interpretation of clinical trials. Johns Hopkins University, 2009.
27. Lund H, Brunnhuber K, Juhl C, Robinson K, Leenaars M, Dorch BF, Jamtvedt G, Nortvedt MW, Christensen R, Chalmers I. Towards evidence-based research. British Medical Journal. 2016; 355: i5440. DOI: 10.1136/bmj.i5440.
28. Lund H, Brunnhuber K, Juhl C, Robinson K, Leenaars M, Dorch BF, Jamtvedt G, Nortvedt MW, Christensen R, Chalmers I. Towards evidence-based research. Kazan Medical Journal. 2019; 100 (5): 733–739. DOI: 10.17816/KMJ2019-733.
29. Evidence-based medicine: how COVID can drive positive change. Nature. 2021; 593 (7858): 168. DOI: 10.1038/d41586-021-01255-w.