ETHICAL ASPECTS OF CREATING CLINICAL GUIDELINES FOR PRACTITIONERS

Dreytser ED[1], Mudrova AV[1] ✉, Pavlov CS[2]

[1] The First Moscow State Medical University of the Ministry of Health of Russia (Sechenov University), Moscow, Russia

[2] Botkin City Clinical Hospital, Moscow, Russia

Clinical guidelines represent documents that contain structured information based on scientific evidence on prevention, diagnosis, treatment and rehabilitation, and regulate professional activities of the medical community. Starting from January 1, 2025, it is planned to switch to the mandatory use of clinical recommendations approved by the Ministry of Health of the Russian Federation, while the year of 2024 is an interim period for their application. However, various methodological and ethical issues arise while developing and discussing clinical recommendations. They include a conflict of interests of the authors, as well as aspects of its disclosure and settlement, accessibility of clinical recommendations for patients, as well as the discrepancy between the provisions of the recommendations and their evidence base such as results of systematic reviews and meta-analyses. Resolution of these problems will significantly improve the quality of clinical recommendations, and increase patient awareness of diseases and treatment approaches. This review analyzes a wide range of methodological problems related to the development of clinical recommendations, examines regulatory acts and ethical principles issued by government agencies, professional communities and international organizations, and makes suggestions to reduce the level of bias and, as a result, to increase the degree of evidence of clinical recommendations.

Key words: clinical recommendations, systematic review, meta-analysis, conflict of interest, systematic error, Cochrane

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✉ **Correspondence should be addressed:** Anastasia V Mudrova
Svetlogorsky proezd, 5, sq. 58, Moscow, 125476, Russia; moodrova.a@yandex.ru

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ЭТИЧЕСКИЕ АСПЕКТЫ СОЗДАНИЯ КЛИНИЧЕСКИХ РЕКОМЕНДАЦИЙ ДЛЯ ПРАКТИКУЮЩИХ ВРАЧЕЙ

Е. Д. Дрейцер[1], А. В. Мудрова[1] ✉, Ч. С. Павлов[2]

[1] Первый МГМУ им. И. М. Сеченова Минздрава России (Сеченовский Университет), Москва, Россия

[2] Городская клиническая больница им. С. П. Боткина ДЗМ, Москва, Россия

Клинические рекомендации представляют собой документы, которые содержат базирующуюся на научных доказательствах структурированную информацию по вопросам профилактики, диагностики, лечения и реабилитации и регламентируют профессиональную деятельность врачебного сообщества. С 1 января 2025 года планируется переход на обязательное использование клинических рекомендаций, одобренных Министерством здравоохранения Российской Федерации, в то время, как 2024 год является промежуточным периодом их применения. Однако при разработке и обсуждении клинических рекомендаций возникают различные методологические и этические проблемы. Среди них можно выделить конфликт интересов авторов, а также аспекты его разглашения и урегулирования, вопрос доступности клинических рекомендаций для пациентов, а также несоответствие между положениями рекомендаций и их доказательной базой — результатами систематических обзоров и метаанализов. Урегулирование перечисленных проблем значительно повысит качество клинических рекомендаций, а также увеличит осведомленность пациентов о заболеваниях и подходах к лечению. В данном обзоре приводится анализ широкого спектра методологических проблем, связанных с разработкой клинических рекомендаций, рассматриваются нормативно-правовые акты и этические принципы, изданные государственными органами, профессиональными сообществами и международными организациями, и высказываются предложения для снижения уровня предвзятости и, как следствие, повышения степени доказательности клинических рекомендаций.

Ключевые слова: клинические рекомендации, систематический обзор, метаанализ, конфликт интересов, систематическая ошибка, Cochrane

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✉ **Для корреспонденции:** Анастасия Васильевна Мудрова
Светлогорский проезд, д. 5, кв. 58, г. Москва, 125476, Россия; moodrova.a@yandex.ru

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Clinical recommendations are documents regulating the professional activity of a doctor and containing structured information based on scientific evidence on prevention, diagnosis, treatment and rehabilitation, including patient management protocols (treatment protocols), medical intervention options and a described sequence of actions of a medical professional taking into account the course of the disease, the presence of complications and concomitant diseases, and as well as other factors affecting the results of medical care. Starting from January 1, 2025, it is planned to switch to the mandatory use of clinical recommendations approved by the Ministry of Health of the Russian Federation [1]. The year of 2024 is a transitional period for the application of clinical recommendations [2].

In the process of developing and discussing clinical recommendations by experts, a number of methodological and ethical problems arise. They include a conflict of interests of the authors, availability of clinical recommendations to patients, discrepancy between the clinical recommendations and the initial evidence base, results and conclusions of systematic

reviews, which belong to the most evidence-based method of analyzing scientific data. This paper examines a wide range of methodological problems related to the creation of clinical recommendations.

MATERIALS AND METHODS

The available literature devoted to the creation of clinical recommendations and the methodological and ethical problems that arise in this case is analyzed. We also reviewed the regulatory and ethical framework governing the development and implementation of clinical guidelines. These include relevant laws, regulations, guidelines and ethical principles issued by government agencies, professional communities and international organizations. Key documents regulating this area include materials published by the World Health Organization (WHO), the Association of American Medical Colleges (AAMC), the NICE Advisory Committee and the Clinical Guidelines Committee of the American College of Physicians of the American College of Physicians (ACP) [3–5]. For clarity, we used the findings and data from systematic reviews developed by the Cochrane Community Hepatobiliary Group (CHBG) included in a number of international clinical recommendations.

Below we provide a detailed analysis of regulatory legal acts and case studies on the ethical issues of forming clinical recommendations, and make suggestions on how to reduce the level of bias. Potential systematic errors in the selected literature and research topics represent a limitation of our research.

RESULTS AND DISCUSSION

Ethical aspects of writing systematic reviews

The review examines the ethical aspects of writing systematic reviews taking Cochrane research as an example. Cochrane systematic reviews are rightfully recognized as research of the highest quality, which are resistant to bias due to a strict standardized methodology.

Conflict of interest statement

A conflict of interest is a declaration by the author, which contains provisions reflecting a personal direct or indirect interest that affects or potentially has an impact on the proper, objective and impartial performance of official duties. By strength, conflicts of interest are divided into conflicts of high, moderate and low strength, they are divided into active and inactive ones by activity, and into financial and intellectual ones by type [4]. Conflict of interest is one of the main ethical aspects affecting the content of clinical recommendations. To identify a conflict of interest, it is necessary to disclose all possible conflicts of interest.

Members of the Cochrane Community are required to declare any potential conflicts of interest annually and/or when circumstances change. The members of the Management Board declare all potential conflicts of interest over the previous ten years. For other positions, the corresponding period is three years [6]. A conflict of interest is declared with the help of questionnaires. They are compiles and filled in using the Convey Global Disclosure System, created by the Association of American Medical Colleges (AAMC).

The main questions of the questionnaire relate to accepting offers from commercial organizations with a financial interest in the field of research by the applicant/his spouse/partner/relative, owning shares or parts of the shares in a commercial organization with a financial interest in the field of research, owning planned, issued or pending patents for products related to the field of research.

Accessibility of information for patients

An important ethical aspect of the compilation of systematic reviews includes accessibility of information to patients. To do this, a patient-oriented summary is created for each review. A team of volunteers is engaged in translating it from English into other languages [7]. This form makes it possible to inform patients about the methods of treatment and diagnosis of their diseases, which increases the rate of awareness [8].

Ethical aspects of making clinical recommendations

An algorithm for resolving conflicts of interest in the preparation of clinical recommendations

The main ethical principles of creating clinical recommendations are transparency, proportionality, and impartiality. Transparency means that all information about participants and solutions for managing conflicts of interest is freely available. According to the principle of proportionality, the strategy of interest conflict management should be strengthened as their severity increases. Conflict of interest should be assessed in an impartial manner [4].

The Clinical Guidelines Committee of the American College of Physicians recommends the following algorithm for dealing with conflicts of interest. Authors of clinical recommendations fill in questionnaires about the presence of interests before starting work on clinical recommendations, during which the authors are required to declare new conflicts of interest. It is also necessary to fill in a questionnaire on conflicts of interest a year after writing clinical recommendations. A panel of experts evaluates conflicts of interest and divides them into groups depending on their strength.

Low-level conflicts of interest include any inactive high-level conflict (for example, the author was a member of the advisory board of a pharmaceutical company, but resigned last year), any intellectual interest, which is only relatively related to a clinical topic (for example, the author participates in writing a weight loss manual and during the previous three years participated in a study evaluating the effect of various diets on cardiovascular diseases). In this case, the author can freely participate in writing clinical recommendations.

Moderate conflicts of interest include intellectual interest, which can lead to a cognitive bias (for example, the author involved in the creation of clinical recommendations for blood pressure control has been researching drugs for hypertension for the previous 3 years), relationships with organizations that can profit from cooperation with recommendations, but are not interested in clinical conclusions of the recommendations (for example, patent interest in software related to clinical decision-making). Experts with medium-strength conflicts of interest can participate in the discussion, but they are not entitled to be authors of recommendations and participate in voting.

Any active relationship (financial or other) with high-risk organizations is considered a strong conflict of interest (for example, an expert is currently a member of the advisory board of a pharmaceutical company). If the expert is ready to eliminate the conflict of interest, then he can be allowed to develop a clinical recommendation. If the expert is unable or unwilling to reduce the severity of the conflict of interest, he is excluded from participation [4].

Inconsistency of the provisions of clinical recommendations with the results of systematic reviews

The provisions of clinical recommendations may quite often not correspond to the results of systematic reviews. Participants of the Cochrane Community hepatobiliary group conducted a study comparing data from 7 systematic reviews prepared by the Cochrane Community and 62 provisions of 9 clinical recommendations of AASLD, EASL, NICE and BSG professional communities. The following topics were included in the study: ascites, hepatorenal syndrome, prevention and treatment of spontaneous bacterial peritonitis, primary and secondary prevention and treatment of bleeding from varicose veins of the esophagus. The consistency between the conclusions of the authors of the recommendations and the independent assessment was 0.145 (95% CI: 0.077 to 0.256), therefore, disagreement was found in 85.5% of the statements of the recommendations and the initial data of systematic reviews [9]. Thus, the strength of the recommendations was overestimated, which suggests the need to introduce mandatory disclosure of conflicts of interest for compilers of clinical recommendations.

Not all international and Russian professional communities adhere to the policy of disclosing conflicts of interest. Some experts prefer the results of their own research when making clinical recommendations, and this is an important ethical issue. This ethical problem can be solved by introducing a mandatory questionnaire on the alleged conflicts of interest.

The skill of searching for and evaluating systematic errors is currently not a criterion for selecting compilers of clinical recommendations, which may also lead to a selective choice of the provisions of clinical recommendations. To resolve this contradiction, it is possible to introduce mandatory testing and determine the qualifications of potential authors of clinical recommendations. It is also possible to use systematic error assessment tools such as GRADE and AMSTAR 2 when evaluating systematic errors in clinical recommendations. GRADE (Grading of Recommendations, Assessment, Development, and Evaluations). GRADE is a transparent system for the development and presentation of summaries of evidence, through which a systematic approach to making recommendations for clinical practice is possible. This is the most widely used tool for evaluating the quality of evidence and making recommendations: GRADE is officially supported by more than 100 organizations around the world, including Cochrane [10]. AMSTAR 2 is a tool for determining the methodological quality of systematic reviews of intervention studies [11].

Clinical recommendations for patients

An equally important ethical task is to create information about clinical recommendations accessible to patients, following the example of summaries created by the Cochrane Community, or a free version of UpToDate for patients and their relatives [7, 12]. Thanks to adapted clinical guidelines, it is possible to raise awareness about the prevention and treatment of their diseases, which can help patients protect their rights when receiving medical care. It is advisable to ensure access to paid Internet services that allow to look through the abbreviated versions of clinical recommendations, for example, Reclin for Russian doctors and the Up-to-Date English-language resource [11, 12]. Such platforms are aimed at practitioners who do not have enough time to familiarize themselves with the full version of clinical recommendations. It is possible to solve the problem of insufficient patient awareness by creating similar free resources for a wide audience.

CONCLUSIONS

A clinician does not have the time and methodological skills to analyze systematic errors in clinical recommendations. Experts who compile the recommendations need to conduct a thorough methodological analysis of systematic errors, since the conclusions of the practical guidelines directly affect the process of making a medical decision. The international experience in making recommendations for clinical practice indicates that a number of conclusions of the recommendations do not reflect the results of systematic reviews, whereas overestimation of the strength of the evidence base has a negative impact on the health of patients and the healthcare system. It is advisable to include a patient-oriented section in the clinical recommendations so that they can get clear, accessible and comprehensive information about their diagnosis and save the time resource of outpatient doctors.

Reference

1. Federal'nyy zakon ot 21 noyabrya 2011 g. № 323-FZ «Ob osnovakh okhrany zdorov'ya grazhdan v Rossiyskoy Federatsii». Available from URL: https://minzdrav.gov.ru/documents/7025-federalnyy-zakon-323-fz-ot-21-noyabrya-2011-g (accessed: 12.05.2024). Russian.
2. Postanovleniye Pravitel'stva Rossiyskoy Federatsii ot 14.03.2024 № 299 Ofitsial'noye opublikovaniye pravovykh aktov. Available from URL: http://publication.pravo.gov.ru/document/0001202403220061 (accessed: 12.05.2024). Russian.
3. Jacoline Bouvy programme director medicines evaluation How NICE manages the potential conflicts of interests of patient experts. Blogs. News. NICE. Available from URL: https://www.nice.org.uk/news/blog/how-nice-manages-the-potential-conflicts-of-interests-of-patient-experts (accessed: 05.02.2024).
4. Qaseem A, et al. Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods from the Clinical Guidelines Committee of the American College of Physicians. Annals of Internal Medicine. 2019; 171(5): 354–361.
5. WHO handbook for guideline development, 2nd Edition. Available from URL: https://www.who.int/publications-detail-redirect/9789241548960 (accessed: 04.02.2024).
6. Conflict of interest declarations. Cochrane Community. Available from URL: https://community.cochrane.org/organizational-info/people/conflict-interest (accessed: 04.02.2024).
7. Plain language summaries. Cochrane Community. Available from URL: https://community.cochrane.org/style-manual/cochrane-review-specific/plain-language-summaries (accessed: 13.05.2024).
8. Nauchno-informatsionnoye obespecheniye issledovaniy i razrabotok v oblasti meditsiny: podkhody i resheniya. 2023; 5: 77–95. Russian.
9. Roberts D, Leung J, Gluud C, Nikolova D, Pavlov C, et al. Comparison of recommendations from cirrhosis Clinical Practice Guidelines and from Cochrane systematic reviews. 2022.
10. GRADE handbook. Available from URL: https://gdt.gradepro.org/app/handbook/handbook.html (accessed: 07.02.2024).
11. Reclin — Klinicheskiye rekomendatsii dlya vrachey, ordinatorov, studentov. Available from URL: https://reclin.ru/ (accessed: 14.05.2024). Russian.
12. Evidence-based Clinical Solutions for Healthcare. UpToDate. Wolters Kluwer. Available from URL: https://www.wolterskluwer.com/en/solutions/uptodate (accessed: 14.05.2024).

Литература

1. Федеральный закон от 21 ноября 2011 г. № 323-ФЗ «Об основах охраны здоровья граждан в Российской Федерации». Режим доступа: [Электронный ресурс]. URL: https://minzdrav.gov.ru/documents/7025-federalnyy-zakon-323-fz-ot-21-noyabrya-2011-g (дата обращения: 12.05.2024).
2. Постановление Правительства Российской Федерации от 14.03.2024 № 299 Официальное опубликование правовых актов. Режим доступа: [Электронный ресурс]. URL: http://publication.pravo.gov.ru/document/0001202403220061 (дата обращения: 12.05.2024).
3. Jacoline Bouvy programme director medicines evaluation How NICE manages the potential conflicts of interests of patient experts. Blogs. News. NICE. Available from URL: https://www.nice.org.uk/news/blog/how-nice-manages-the-potential-conflicts-of-interests-of-patient-experts (accessed: 05.02.2024).
4. Qaseem A, et al. Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods from the Clinical Guidelines Committee of the American College of Physicians. Annals of Internal Medicine. 2019; 171(5): 354–361.
5. WHO handbook for guideline development, 2nd Edition. Available from URL: https://www.who.int/publications-detail-redirect/9789241548960 (accessed: 04.02.2024).
6. Conflict of interest declarations. Cochrane Community. Available from URL: https://community.cochrane.org/organizational-info/people/conflict-interest (accessed: 04.02.2024).
7. Plain language summaries. Cochrane Community. Available from URL: https://community.cochrane.org/style-manual/cochrane-review-specific/plain-language-summaries (accessed: 13.05.2024).
8. Научно-информационное обеспечение исследований и разработок в области медицины: подходы и решения. 2023; 5: 77–95.
9. Roberts D, Leung J, Gluud C, Nikolova D, Pavlov C, et al. Comparison of recommendations from cirrhosis Clinical Practice Guidelines and from Cochrane systematic reviews. 2022.
10. GRADE handbook. Available from URL: https://gdt.gradepro.org/app/handbook/handbook.html (accessed: 07.02.2024).
11. Reclin — Клинические рекомендации для врачей, ординаторов, студентов. Режим доступа: [Электронный ресурс]. URL: https://reclin.ru/ (дата обращения: 14.05.2024).
12. Evidence-based Clinical Solutions for Healthcare. UpToDate. Wolters Kluwer. Available from URL: https://www.wolterskluwer.com/en/solutions/uptodate (accessed: 14.05.2024).