ELDERLY PATIENTS IN RANDOMIZED CLINICAL TRIALS: ETHICAL ISSUES

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Considering patients of elderly and senile age, pronounced discrimination continues to be observed, expressed in their insufficient inclusion or non-inclusion in randomized clinical trials. As a result, the clinical recommendations based on the results of such studies cannot be fully applicable to this category of patients. The problems of inclusion/non-inclusion of older people in clinical trials are numerous. The reasons for their occurrence and solutions affect, among other things, the ethical sphere. Compliance with basic ethical principles such as respect for persons, beneficence and justice should underlie the decision to include a patient in a study. In general, when evaluating these ethical principles from the point of view of the well-being of the entire population of elderly and senile patients, it is necessary to rethink the principles according to which this category of patients was excluded from clinical trials.

Keywords: elderly patients, randomized clinical trials, ethical principles

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ПОЖИЛЫЕ ПАЦИЕНТЫ В РАНДОМИЗИРОВАННЫХ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЯХ: ЭТИЧЕСКИЕ АСПЕКТЫ

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В отношении пациентов пожилого и старческого возраста продолжает наблюдаться выраженная дискриминация, проявляющаяся в их недостаточном включении либо невключении в рандомизированные клинические исследования. Как следствие, формируемые на основании результатов подобных исследований клинические рекомендации не могут быть в полной мере применимы по отношению к рассматриваемой категории пациентов. Проблемы включения/невключения пожилых людей в клинические исследования многочисленны. Причины их возникновения и пути решения затрагивают в том числе этическую сферу. Соблюдение основных этических принципов, таких как уважение личности, благодеяние и справедливость, должно лежать в основе принятия решения о включении пациента в исследование. В целом, оценивая данные этические принципы с точки зрения благополучия всей популяции пациентов пожилого и старческого возраста, необходимо переосмыслять принципы, согласно которым данная категория пациентов исключалась из клинических исследований.

Ключевые слова: пожилые пациенты, рандомизированные клинические исследования, этические принципы

Вклад авторов: О. И. Бутранова — анализ литературы, сбор, анализ, написание текста публикации; С. К. Зырянов — анализ, интерпретация данных.

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The principles of evidence-based medicine underlie all modern clinical guidelines for managing patients, regardless of nosology, and their observance guarantees the best result in terms of outcomes. But is this true in the case of elderly and especially senile patients? The principles of the hierarchy of evidence put on the first-place systematic reviews and meta-analyses, as well as randomized clinical trials (RCTs). The proportion of elderly and senile patients in the total volume of RCTs is very small: for example, from January 1990 to December 2002, only 84 RCTs were found including patients over 80 years of age, of which 75 studied the effectiveness of therapy, and 9 — safety [1]. For comparison, over the same period, the total number of RCTs in young and adult patients was about 50,000. Most of the cardiovascular drugs, hypoglycemic drugs, and many others are used mainly by patients of older age groups. At the same time, according to Konrat C, et al (2012), in most RCTs estimating effects of drugs which are mainly used in the treatment of diseases specific to elderly patients, the proportion of participants over 65 was less than half. This pattern was typical for 62.2% RCTs of pioglitazone, 40.9% RCTs of risedronate, 37.9% RCTs of rosuvastatin, and 70.2% RCTs of valsartan [2]. An analysis of phase III clinical trials carried out by the National Institutes of Health, USA, from 1965 to 2015, found a significant disproportion between the studied nosologies and the participant profile, manifested in the inclusion of relatively young patients in studies on diseases typical of the elderly (chronic heart failure, osteoarthritis, etc.). In particular, it was demonstrated that in 67% of the studies the mean and/or median age was less than expected for the disease or condition of interest. Based on their analysis, the authors suggested that the results of these studies cannot be extrapolated to the general population of older people [3]. The COVID-19 pandemic has affected mainly the elderly and senile patients, while the age of patients included in RCTs studying

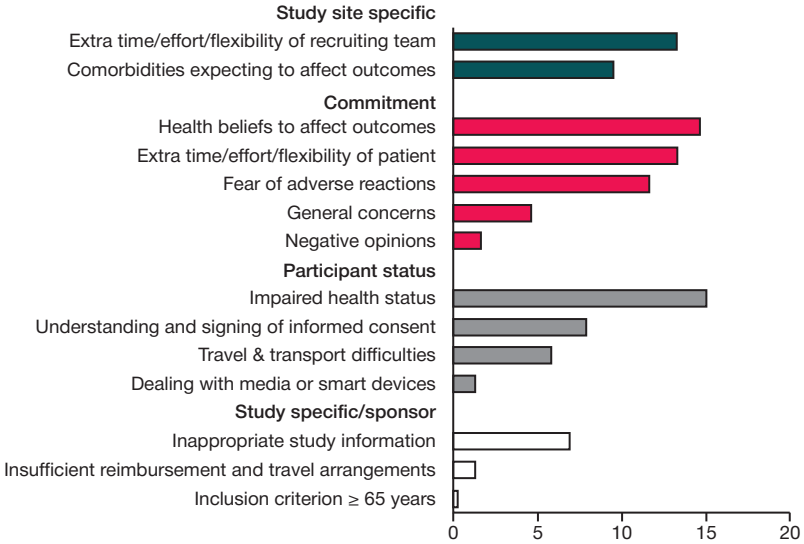

Fig. 1. Comparative assessment of the significance of problems associated with the inclusion of elderly patients in RCTs. Mean number of points awarded per item (standard error range: 0.17–9.17) (reproduced from [8]).

the efficacy and safety of drugs aimed at the treatment of COVID-19 was 20 years younger than the average age of patients included in observational studies [4]. If we consider RCTs of diseases that are common not only among the elderly, but also in other age groups, here the recruitment of participants is almost always limited to young patients. In the analysis of 32 RCTs of atopic dermatitis (n = 4547), the average age of participants was 34.4 (+5.4) years, while only 31% of the RCTs included patients older than 65 years [5]. In recent years, there has been some increase in the trend to include older patients in RCTs, but this affects only patients slightly older than 65 years, patients of the 75 plus age group still have a minimal representation in the structure of RCT participants. An analysis of RCTs published in one of the journals with a high impact factor between March 2019 and March 2021 found that only 8.3% of the studies had an average age of participants over 75 years [6].

In addition to the insufficient inclusion of older patients in RCTs, the problem is the qualitative characteristics of those older people who were nevertheless included in the studies. An analysis of data from UK phase III/IV trials (n = 116) of new drugs for the treatment of chronic diseases found that the proportion of older patients participating in studies with 2 or more comorbidities was in most cases about 30%, which is below the average values for population of elderly patients [7].

The global exclusion of elderly and senile patients from RCTs is in many ways unjustified and even dangerous, since in the future the results of RCTs are used as the basis for developing therapeutic strategies for this category of patients. A balanced assessment of the ethical principles for including or not including elderly and senile people in RCTs can serve as one of the tools aimed at improving the quality of care for elderly and senile patients.

ETHICAL ISSUES OF THE INCLUSION OF OLDER PATIENTS IN RCTS

The conclusion made by the multidisciplinary expert panel regarding the problems associated with the inclusion of older patients in RCTs stated that the key barrier to inclusion is poor health and a higher prevalence of acute or chronic comorbidities in this age group. In general, the experts identified four groups of recruitment problems: related to the study site, to the commitment, to patient/participant status and to the study/sponsor. Figure 1 represents the average scores assigned by experts to each of the problems (a 20-point scale was used), as well as the details of their compounds [8].

From the patient's point of view, the risk of health damage leads to reluctance to take the study drug, which may lead to violations of the regimen prescribed in the study protocol. As a result, the outcomes in such patients will distort the overall results, which corresponds to the point of view of the RCT organizers, who are negative about the prospect of including older patients.

The common opinion of many researchers is that the problems of including elderly patients in RCTs are associated with the patient's inability to understand the purpose of the study and its stages, the inability to follow the protocol, and, most importantly, the inability in many cases to give an informed consent (IC) to participate in the study. [9].

Modern provisions on the protection of the patient as participant of a clinical trial were set out in the Helsinki Declaration of 1964, which is advisory in nature. In the Russian Federation, the Rules of Good Clinical Practice of the Eurasian Economic Union are currently used as a regulatory document. Actually, the use of the imperative of consent to the implementation of medical or diagnostic procedures is an achievement of the 20th century and states like: "every person in adulthood and in his right mind has the right to determine what to do with his body" [10]. With regard to research practice, the "Berlin Codex" was the first normative document [11], and the doctrine of informed consent, close to the modern one, was formulated in the late 1940s. within the framework of the Nuremberg Code [12]. It is important to note the three basic ethical principles of research practice formulated in the Belmont Report [13]:

- respect for the individual;
- beneficence;
- justice.

The IC procedure demonstrates the principle of respect for the individual, while its signing, as well as the actual participation in the RCT of an elderly person, requires a detailed assessment by the doctor of all the pros and cons in relation to such principles as beneficence and justice. Assessment of the capacity of an elderly patient before signing an IC is an important step that can determine the success of participation

in the study as a whole. There are various tests aimed at assessing the main components of the mental capacity [14], including the degree of understanding (receiving and processing information), value of judgments (evaluating information in an individual context), reasoning ability (comparing alternatives and understanding the consequences) and the ability to make choices (determining one preferred option and a message about the choice).

The actual process of signing an IC can act as an additional stress factor for the patient, increasing the state of anxiety. There is discussion of the possibility of an alternative to a written signature for older patients, such as the use of a seal, thumbprint, head nodding and handshake [15]. Such alternatives may help to reduce stress in the elderly patient associated with the provision of a written signature [16], but the legitimacy of such alternatives is debatable. Disorders in the mental sphere represent a significant problem: the progression of dementia and cognitive decline act as a factor limiting the patient's ability to participate in the study. The signing of the IC by the legally authorized representative is a possible option, but, from an ethical point of view, quite controversial, since in this case the personal desire or unwillingness of the patient remains unknown.

Additional problems in conducting RCTs arise in the case of the participation of elderly and senile patients who are residents of nursing homes, suffering from dementia, or who are in the intensive care unit (ICU). The ability to perceive information and value judgments in such patients is significantly reduced, which leads to the inability to sign the IC. In this regard, data from an analysis of 269 RCTs involving elderly patients in the ICU setting are of interest. The results found that in 8 out of 269 RCTs, the protocol noted the refusal to use IC, in 5 — exemption from the procedure for signing IC, in other 9 information about the IC procedure was not indicated, but its presence was assumed [17]. Of the 256 RCTs with IC, 70.7% had written consent, 1.2% had both written and oral consent, 1.6% had only oral consent, and 26.5% did not specify the type of consent.

The signing of an IC by an elderly patient does not guarantee his participation in the study. The rate of non-participation among elderly after signing consent has been shown to be higher than in younger patients. In the work of Hempenius L et al (2013), refusal to participate in the study was noted in 16.8% of elderly patients, while problems with patient transportation and procedure planning caused only 3.7% of participants to be excluded from the study [18]. In this regard, an important stage is the explanatory work provided by the doctor, which necessarily includes building a trusting relationship with the patient and is aimed at reducing anxiety and negative expectations of the elderly person.

Another problem is premature discontinuation of the study, which is typical for the elderly and senile; according to published data, the proportion of such patients can reach 30% [19], which can lead to difficulties in the final analysis of the data.

RECOMMENDATIONS FOR ETHICAL INCLUSION OF ELDERLY PATIENTS IN RCTS

Age-related changes in organs and systems, senile asthenia, impaired cognitive functions, the presence of polymorbidity and, as a result, polypharmacy limit the possibility of including elderly and senile patients in RCTs. At the same time, these conditions are widespread in real clinical practice, and therefore the inclusion of such patients is highly desirable in terms of obtaining highly reliable results that could be directly implemented in real schemes for managing elderly and senile patients. Assessing the risks and problems of including older patients in RCTs, it can be noted that their non-inclusion, the introduction of strict age limits, the declaration of polymorbidity and senile asthenia as non-inclusion criteria lead to an obvious distortion of such fundamental ethical principles as beneficence and justice. This is especially true in relation to the further receipt of modern high-quality medical care by the general population of elderly and senile people.

The traditional approach to planning RCTs includes the introduction of age restrictions, it is believed that patients over 70–75 years of age will not be able to comply with the requirements of the protocol and have a high risk of premature discontinuation of the study. On the other hand, older patients may have more free time to participate in RCTs and, provided that cognitive functions are preserved, they may be sufficiently involved in the process of providing data about themselves and fulfilling the requirements corresponding to the stages of the study [20]. Evidence has been published showing the benefit of removing the upper age limit for enrolling patients in RCTs and reducing the list of exclusion criteria in terms of improving the quality of evidence obtained in RCTs [21].

Considering possible options for solving the problems associated with the inclusion / non-inclusion of older people

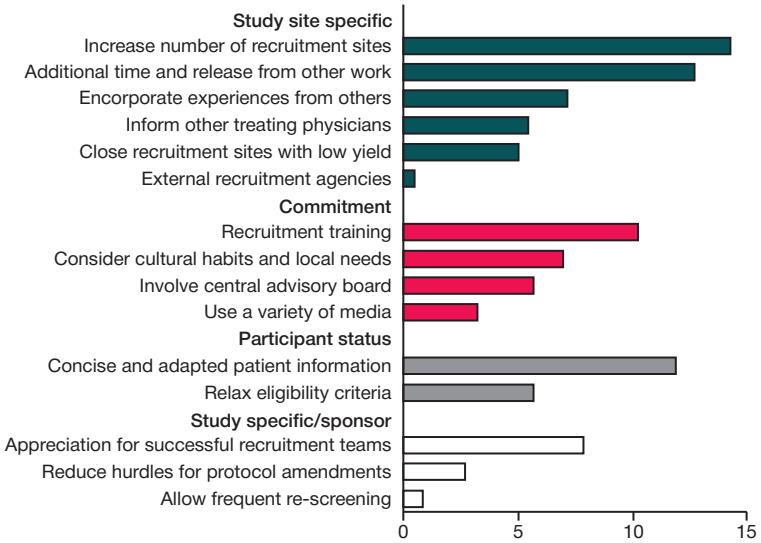

Fig. 2. Comparative assessment of the significance of options for solving problems associated with the inclusion of elderly patients in RCTs (in points) (from [8]).

in RCTs, it is worth noting the results of a survey of experts involved in conducting studies involving this category of patients. According to their collegiate opinion, the most important thing for a larger recruitment of older participants is the inclusion of more research centers, as well as the allocation of more time to staff with their release from other duties, staff motivation, expressed in financially expressed gratitude for the successful inclusion of patients. Great importance is attached to the reduction and simplification of information about the study provided to patients (Fig. 2). Taking into account the expert opinion presented, it can be noted that the problems are solvable, and the solution lies mainly in the area of increasing the funding of RCTs involving elderly patients (increasing the cost of including additional research centers, attracting additional staff).

Ethical issues of participation of elderly and senile patients in RCTs affect both the patients themselves and the researchers. The use of the "do no harm" principle should be fundamental at all stages, including screening, signing an IC, and actually participating in the study. The existing discrimination of older people in relation to inclusion in RCTs can be regarded as a violation of equal rights, however, the patient's misunderstanding of the objectives of the study and the conditions for participation may lead to a violation of such an ethical principle as a beneficence, expressed in the final impact of the study on health and quality of life indicators in elderly persons. The development and implementation of new medical technologies is aimed at providing high-quality and safe care to patients, this process is impossible without RCTs. The non-inclusion of elderly patients in RCTs is a fundamentally significant mistake leading to a global decrease in the effectiveness of the technologies used, which means that in relation to the population of elderly patients, we are faced with a violation of all three basic ethical principles simultaneously: respect for the individual, beneficence and justice.

CONCLUSION

The exclusion of patients from RCTs on the basis of age, depending on the degree of cognitive impairment and polymorbidity, hinders scientific progress in the treatment of elderly and senile patients. Rethinking existing approaches to the inclusion of this category of patients in RCTs is essential to improve the efficacy and safety of developed therapeutic strategies and improve treatment outcomes, as well as to protect both the study participants themselves and researchers.

References

1. Le Quintrec JL, Bussy C, Golmard JL, Hervé C, Baulon A, Piette F. Randomized controlled drug trials on very elderly subjects: descriptive and methodological analysis of trials published between 1990 and 2002 and comparison with trials on adults. J Gerontol A Biol Sci Med Sci. 2005; 60 (3): 340–344. DOI: 10.1093/gerona/60.3.340
2. Konrat C, Boutron I, Trinquart L, Auleley GR, Ricordeau P, Ravaud P. Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. PLoS One. 2012; 7 (3): e33559. DOI: 10.1371/journal.pone.0033559
3. Lockett J, Sauma S, Radziszewska B, Bernard MA. Adequacy of Inclusion of Older Adults in NIH-Funded Phase III Clinical Trials. J Am Geriatr Soc. 2019; 67 (2): 218–222. DOI: 10.1111/jgs.15786
4. Prendki V, Tau N, Avni T, et al. A systematic review assessing the under-representation of elderly adults in COVID-19 trials. BMC Geriatr. 2020; 20 (1): 538. Published 2020 Dec 20. DOI: 10.1186/s12877-020-01954-5
5. Lam M, Zhu JW, Maqbool T, et al. Inclusion of Older Adults in Randomized Clinical Trials for Systemic Medications for Atopic Dermatitis: A Systematic Review [published correction appears in JAMA Dermatol. 2020 Nov 1; 156 (11): 1272. JAMA Dermatol. 2020; 156 (11): 1240–1245. DOI: 10.1001/jamadermatol.2020.2940
6. Mc Carthy CE, Murphy R, McAteer C, Okon M, O'Donnell M. 279 Inclusion of older patients in clinical trials: a review of a single, high impact, medical journal over a 2-year period. Age Ageing. 2022; 51(Suppl 3): afac218.246. Published 2022 Oct 25. DOI: 10.1093/ageing/afac218.246
7. Hanlon P, Hannigan L, Rodriguez-Perez J, et al. Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis. BMC Med. 2019; 17 (1): 201. Published 2019 Nov 12. DOI: 10.1186/s12916-019-1427-1
8. Buttgereit T, Palmowski A, Forsat N, et al. Barriers and potential solutions in the recruitment and retention of older patients in clinical trials-lessons learned from six large multicentre randomized controlled trials. Age Ageing. 2021; 50 (6): 1988–1996. DOI: 10.1093/ageing/afab147
9. Altawalbeh SM, Alkhateeb FM, Attarabeen OF. Ethical Issues in Consenting Older Adults: Academic Researchers and Community Perspectives. J Pharm Health Serv Res. 2020; 11 (1): 25–32. DOI: 10.1111/jphs.12327
10. Lombardo PA. Phantom tumors and hysterical women: revising our view of the Schloendorff case. J Law Med Ethics. 2005; 33 (4): 791–801. DOI: 10.1111/j.1748-720x.2005.tb00545.x
11. Anweisung an die Vorsteher Der Kliniken, Polikliniken und sonstigen Krankenanstalten über medizinische Eingriffe zu anderen ALS zu diagnostischen, Heilund Immunisierungszwecken vom 29 Dezember 1900. Zentralblatt für die gesamte Unterrichtsverwaltung Preußen 1901. [Accessed December 18, 2018]. Available from: http://goobiweb.bbf.dipf.de/
12. Mitscherlich A, Mielke F, editors. Medizin Ohne Menschlichkeit Dokumente Des Nürnberger Ärzteprozesses. Frankfurt aM: Fischer Taschenb, 1989.
13. HHS.gov [homepage on the Internet] The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. [Accessed April 18, 1979]. Available from: http://www.hhs.gov/ohrp/humansubject
14. Punchik B, Press Y, Samson T. Review of decision-making capacity (DMC) assessment tools for treatment among elderly patients with cognitive imparment. Harefuah. 2020 Sep; 159 (9): 672–677. Hebrew. PMID: 32955810.
15. Chen KM, Lin JN, Lin HS, et al. The effects of a Simplified Tai-Chi Exercise Program (STEP) on the physical health of older adults living in long-term care facilities: a single group design with multiple time points. Int J Nurs Stud. 2008; 45 (4): 501–507. DOI: 10.1016/j.ijnurstu.2006.11.008
16. Altawalbeh SM, Alkhateeb FM, Attarabeen OF. Ethical Issues in Consenting Older Adults: Academic Researchers and Community Perspectives. J Pharm Health Serv Res. 2020 Mar; 11 (1): 25–32. DOI: 10.1111/jphs.12327. Epub 2019 Oct 30. PMID: 33042231; PMCID: PMC7546426.
17. Southerland LT, Benson KK, Schoeffler AJ, Lashutka MA, Borson S, Bischof JJ. Inclusion of older adults and reporting of consent processes in randomized controlled trials in the emergency department: A scoping review. J Am Coll Emerg Physicians Open. 2022; 3 (4): e12774. Published 2022 Jul 29. DOI: 10.1002/emp2.12774
18. Hempenius L, Slaets JP, Boelens MA, et al. Inclusion of frail elderly patients in clinical trials: solutions to the problems. J Geriatr Oncol. 2013; 4 (1): 26–31. DOI: 10.1016/j.jgo.2012.08.004
19. Pitkälä KH, Juola AL, Kautiainen H, et al. Education to reduce potentially harmful medication use among residents of assisted living facilities: a randomized controlled trial. J

Am Med Dir Assoc. 2014; 15 (12): 892–898. DOI: 10.1016/j.jamda.2014.04.002
20. Bayer A, Tadd W. Unjustified exclusion of elderly people from studies submitted to research ethics committee for approval: descriptive study. Br Med J. 2000; 321 (7267): 992–993. DOI: 10.1136/bmj.321.7267.992
21. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. J Gen Intern Med. 2011; 26 (7): 783–790. DOI: 10.1007/s11606-010-1629-x

Литература

1. Le Quintrec JL, Bussy C, Golmard JL, Hervé C, Baulon A, Piette F. Randomized controlled drug trials on very elderly subjects: descriptive and methodological analysis of trials published between 1990 and 2002 and comparison with trials on adults. J Gerontol A Biol Sci Med Sci. 2005; 60 (3): 340–344. DOI: 10.1093/gerona/60.3.340
2. Konrat C, Boutron I, Trinquart L, Auleley GR, Ricordeau P, Ravaud P. Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. PLoS One. 2012; 7 (3): e33559. DOI: 10.1371/journal.pone.0033559
3. Lockett J, Sauma S, Radziszewska B, Bernard MA. Adequacy of Inclusion of Older Adults in NIH-Funded Phase III Clinical Trials. J Am Geriatr Soc. 2019; 67 (2): 218–222. DOI: 10.1111/jgs.15786
4. Prendki V, Tau N, Avni T, et al. A systematic review assessing the under-representation of elderly adults in COVID-19 trials. BMC Geriatr. 2020; 20 (1): 538. Published 2020 Dec 20. DOI: 10.1186/s12877-020-01954-5
5. Lam M, Zhu JW, Maqbool T, et al. Inclusion of Older Adults in Randomized Clinical Trials for Systemic Medications for Atopic Dermatitis: A Systematic Review [published correction appears in JAMA Dermatol. 2020 Nov 1; 156 (11): 1272. JAMA Dermatol. 2020; 156 (11): 1240–1245. DOI: 10.1001/jamadermatol.2020.2940
6. Mc Carthy CE, Murphy R, McAteer C, Okon M, O'Donnell M. 279 Inclusion of older patients in clinical trials: a review of a single, high impact, medical journal over a 2-year period. Age Ageing. 2022; 51(Suppl 3): afac218.246. Published 2022 Oct 25. DOI: 10.1093/ageing/afac218.246
7. Hanlon P, Hannigan L, Rodriguez-Perez J, et al. Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis. BMC Med. 2019; 17 (1): 201. Published 2019 Nov 12. DOI: 10.1186/s12916-019-1427-1
8. Buttgereit T, Palmowski A, Forsat N, et al. Barriers and potential solutions in the recruitment and retention of older patients in clinical trials-lessons learned from six large multicentre randomized controlled trials. Age Ageing. 2021; 50 (6): 1988–1996. DOI: 10.1093/ageing/afab147
9. Altawalbeh SM, Alkhateeb FM, Attarabeen OF. Ethical Issues in Consenting Older Adults: Academic Researchers and Community Perspectives. J Pharm Health Serv Res. 2020; 11 (1): 25–32. DOI: 10.1111/jphs.12327
10. Lombardo PA. Phantom tumors and hysterical women: revising our view of the Schloendorff case. J Law Med Ethics. 2005; 33 (4): 791–801. DOI: 10.1111/j.1748-720x.2005.tb00545.x
11. Anweisung an die Vorsteher Der Kliniken, Polikliniken und sonstigen Krankenanstalten über medizinische Eingriffe zu anderen ALS zu diagnostischen, Heilund Immunisierungszwecken vom 29 Dezember 1900. Zentralblatt für die gesamte Unterrichtsverwaltung Preußen 1901. [Accessed December 18, 2018]. Available from: http://goobiweb.bbf.dipf.de/
12. Mitscherlich A, Mielke F, editors. Medizin Ohne Menschlichkeit Dokumente Des Nürnberger Ärzteprozesses. Frankfurt aM: Fischer Taschenb, 1989.
13. HHS.gov [homepage on the Internet] The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. [Accessed April 18, 1979]. Available from: http://www.hhs.gov/ohrp/humansubject
14. Punchik B, Press Y, Samson T. Review of decision-making capacity (DMC) assessment tools for treatment among elderly patients with cognitive imparment. Harefuah. 2020 Sep; 159 (9): 672–677. Hebrew. PMID: 32955810.
15. Chen KM, Lin JN, Lin HS, et al. The effects of a Simplified Tai-Chi Exercise Program (STEP) on the physical health of older adults living in long-term care facilities: a single group design with multiple time points. Int J Nurs Stud. 2008; 45 (4): 501–507. DOI: 10.1016/j.ijnurstu.2006.11.008
16. Altawalbeh SM, Alkhateeb FM, Attarabeen OF. Ethical Issues in Consenting Older Adults: Academic Researchers and Community Perspectives. J Pharm Health Serv Res. 2020 Mar; 11(1): 25–32. DOI: 10.1111/jphs.12327. Epub 2019 Oct 30. PMID: 33042231; PMCID: PMC7546426.
17. Southerland LT, Benson KK, Schoeffler AJ, Lashutka MA, Borson S, Bischof JJ. Inclusion of older adults and reporting of consent processes in randomized controlled trials in the emergency department: A scoping review. J Am Coll Emerg Physicians Open. 2022; 3 (4): e12774. Published 2022 Jul 29. DOI: 10.1002/emp2.12774
18. Hempenius L, Slaets JP, Boelens MA, et al. Inclusion of frail elderly patients in clinical trials: solutions to the problems. J Geriatr Oncol. 2013; 4 (1): 26–31. DOI: 10.1016/j.jgo.2012.08.004
19. Pitkälä KH, Juola AL, Kautiainen H, et al. Education to reduce potentially harmful medication use among residents of assisted living facilities: a randomized controlled trial. J Am Med Dir Assoc. 2014; 15 (12): 892–898. DOI: 10.1016/j.jamda.2014.04.002
20. Bayer A, Tadd W. Unjustified exclusion of elderly people from studies submitted to research ethics committee for approval: descriptive study. Br Med J. 2000; 321 (7267): 992–993. DOI: 10.1136/bmj.321.7267.992
21. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. J Gen Intern Med. 2011; 26 (7): 783–790. DOI: 10.1007/s11606-010-1629-x