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# Compassionate use of unauthorized drugs: Legal regulations and ethical challenges

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ABSTRACT

Compassionate use (also referred to as expanded access) is therapeutic use of unauthorized drugs outside of clinical trials. The objective of this review is to discuss practical aspects of the current legal regulations concerning compassionate use that have been introduced in the European Union, the USA (both the Food and Drug Administration regulations and Right-to-try laws), Canada and Australia. We also present main ethical challenges associated with use of unauthorized drugs such as possible difficulties with obtaining informed consent and fair patient selection. Moreover, we discuss guidelines, especially those contained in the Declaration of Helsinki, which may aid doctors in the ethical conduct of compassionate treatments.

## 1. Introduction

In clinical practice there are certain situations when all authorized drugs have proven ineffective or cannot be used. In such cases, the only treatment option may be unauthorized drugs, especially investigational drugs under clinical development. In general, the access of patients to these drugs is restricted due to concerns over their safety and efficacy. Therefore, until recently, patients could receive these drugs mostly after enrolling in a clinical trial. However, in some cases it is possible to use an unauthorized drug outside of clinical trials. Such treatment is most often termed compassionate use or expanded access [1]. While in the USA the Food and Drug Administration (FDA) prefers the term expanded access [2], according to the terminology adopted in the European Union (EU) regulations, therapeutic use of unauthorized drugs in programs involving groups of patients is referred to as compassionate use [3]. Unlike clinical trials, the primary objective of compassionate use is not to investigate a drug's efficacy and/or safety, but to obtain direct therapeutic benefit in a given patient [4].

Over the years, compassionate use has evolved to become a very complex enterprise involving a number of different stakeholders including drug manufacturers, regulatory agencies, physicians, patients and patient advocacy groups [5,6]. Current compassionate use programs may involve large number of patients, sometimes exceeding thousand [7,8]. Compassionate use has been applied in a variety of different medical specialties including but not limited to oncology, hematology, infectious diseases, gastroenterology, transplantology and ophthalmology [9]. According to the FDA's data, the number of requests for compassionate use has increased twofold from 2005 through 2014 (most recent data covering the years 2015–2018 have not yet been published) [9]. Growing interest in compassionate use is a result of several factors including the development of new drugs for serious unmet medical needs, high activity of patient advocacy groups and wider availability of data about new treatments in the Internet [6].

The main objective of this paper is to discuss practical aspects of legal regulations concerning compassionate use that have been introduced in the EU, the USA, Canada and Australia, as well as to present main ethical challenges associated with therapeutic use of investigational drugs.

This review is based on articles selected from Medline through PubMed (years 2014–2019, search terms ‘compassionate use’ and ‘expanded access’; where appropriate, references from these articles were also included).

## 2. Legal regulations

### 2.1. European union

In the EU the legal framework for compassionate use was introduced by Article 83 (1) of Regulation (EC) No 726/2004 of the European Parliament and of the Council (Table 1); in principle,

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**Table 1**
Main features of compassionate use in the European Union, the USA, Canada and Australia.

| | European Union | USA | Canada | Australia |
|---|---|---|---|---|
| Name | Compassionate use | 1) Expanded access/compassionate use (EA/CU)[a]<br>2) Right-to-try law (RTT) | Special access | 1) Authorized Prescriber Scheme (APS)<br>2) Special Access Scheme (SAS) |
| Investigational drugs | + | EA/CU +<br>RTT + | + | + |
| Investigational medical devices | – | EA/CU +<br>RTT + | – | + |
| Authorization | Individual Member States | EA/CU – FDA<br>RTT – | Health Canada | Therapeutic Goods Administration |
| Bioethics committee/IRB approval | ± [b] | EA/CU +<br>RTT – | – | APS +[c]<br>SAS - |
| Informed consent | ± [d] | EA/CU +<br>RTT + | + | + |

[a] The term preferred by the FDA is expanded access.
[b] Bioethics committee approval is not required by the Regulation (EC) No 726/2004, but is required in some Member States, especially in Italy.
[c] As an alternative to bioethics committee approval, endorsement by a specialist is acceptable.
[d] Informed consent is not required by the Regulation (EC) No 726/2004, but may be required in some Member States which developed national regulations for compassionate use.

Regulations of the European Parliament and of the Council are mandatory for all Member States. However, this article formulates only two general requirements for compassionate use: 1) a chronically or seriously debilitating disease, or a life threatening disease of patients who cannot be treated satisfactorily with an authorized medicinal product, and 2) the medicinal product must be either the subject of an application for a centralized marketing authorization or be undergoing clinical trials [10]. In addition, to provide more detailed guidance on implementation of Art. 83 (1), the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued Guideline on Compassionate Use of Medicinal Products [3]. According to this Guideline, specific regulations consistent with Art. 83 (1) are to be developed by individual Member States [3]. In fact, many European countries have already introduced national regulations concerning compassionate use [11]. However, detailed discussion of these regulations is beyond the scope of this article.

While this is not explicitly required by Art. 83, according to the above-mentioned Guideline by CHMP patients should always be considered for enrollment in a clinical trial before being offered inclusion in a compassionate use program. This Guideline underscores that compassionate use should not slow down the progress of clinical trials which are essential for collection of data about safety and efficacy of drugs [3].

Moreover, Art. 1 of Directive 2004/27/EC of the European Parliament and of the Council [12], amending Art. 5 of Directive 2001/83/EC, permits use of unauthorized drugs in single patients under direct responsibility of a healthcare professional. According to the terminology adopted by the CHMP, such treatment is termed compassionate use on a named patient basis [3]. In addition, Art. 1 permits temporary use of an unauthorized drug in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation [12].

### 2.2. USA

In the USA therapeutic use of investigational drugs outside of clinical trials is permitted under expanded access regulations (Table 1). Expanded access is overseen by the FDA and relevant requirements are contained in the Code of Federal Regulations (CFR) Title 21 Part 312 Subpart I “Expanded access to Investigational Drugs for Treatment Use” [13]. Under the FDA regulations, there are three main categories of expanded access: (1) for individual patients including for emergency use, (2) for intermediate-size patient populations, and (3) treatment IND (investigational new drug) or treatment protocol intended for widespread treatment use [13].

The main requirements for all expanded access uses include the following: (1) a serious or immediately life-threatening disease where no comparable or satisfactory alternative therapy is available, (2) the potential benefits justify the potential risks and the potential risks are not unreasonable in the context of the disease, (3) there is no threat to the initiation, conduct, or completion of clinical investigations to support marketing approval of the expanded access use (in principle, expanded access is a pathway intended for patients who are unable to enroll in a clinical trial). Moreover, a doctor who directs the treatment must report adverse drug events to the sponsor, as well as obtain informed consent of the patient and the institutional review board (IRB) approval [13]. Specific requirements pertaining to individual categories of expanded access will not be discussed here in detail. In addition, the FDA regulations enable therapeutic applications of medical devices [14]; however, detailed discussion of them is out of scope of this paper.

On May 30, 2018, in the USA the federal Right to Try Act of 2017 was signed into law, providing patients with life-threatening diseases an alternative pathway to access investigational drugs which completed Phase I of a clinical trial without a necessity for authorization from the FDA [15]. This was the final stage in the process of introducing Right-to-try laws in individual states. In general, these laws aim to facilitate the access of patients to investigational drugs by eliminating the FDA's oversight [16]. However, they have been heavily criticized by experts for a number of reasons. For instance, according to the opponents of these laws, unreasonable use of drugs remaining at a very early stage of clinical development may not only not help, but also can deteriorate a patient's condition. Furthermore, the introduction of Right-to-try laws can disturb the proper functioning of the whole FDA-overseen system of drug regulation [16,17].

### 2.3. Canada

In Canada, therapeutic use of unauthorized drugs including biologicals (but not medical devices) is permissible in Special Access Programs (SAP; Table 1). The legal basis for these programs is contained in the Food and Drug Regulations, Sections C.08.010 and C.08.011. Basic information about these programs are available in the Guidance Document for Industry and Practitioners – Special Access Program for Drugs developed by the Canadian regulatory agency Health Canada [18]. Under SAP rules, an unauthorized drug can be used in serious or life-threatening diseases, especially in emergency cases when conventional therapies have failed, are unsuitable or unavailable. The use of an unauthorized drug must be supported by some credible evidence of its safety and efficacy, and a doctor should obtain informed consent of the patient. Moreover, a doctor has a duty to report

on the results of the treatment with an unauthorized drug including any adverse drug reactions both to the SAP and the manufacturer of the drug [18].

### 2.4. Australia

In Australia, there are two schemes that enable doctors to use unauthorized medicines, biologicals and medical devices – the Authorized Prescriber Scheme (APS) and the Special Access Scheme (SAS) [19,20; Table 1]. In the APS, a doctor is granted authority to use a specified unauthorized drug (or a class of drugs) to specific patients with a certain disease. An application for the use of an unauthorized drug needs to be approved by a bioethics committee or endorsed by a specialist in a discipline relevant to the proposed treatment. Important issues that are evaluated include the qualifications and relevant experiences of the doctor, access to facilities necessary to perform the treatment, evidence to support the proposed treatment, clinical justification including whether other therapeutic alternatives have been tried and why the unauthorized drug is being proposed as well as global regulatory status of the drug. In addition, informed consent of the patient is required [19].

In the SAS, unauthorized drugs can be used in exceptional clinical circumstances in single patients on a case-by-case basis. Before the use of an unauthorized drug, all authorized treatment options are expected to have already been considered. Moreover, the doctor must obtain informed consent from the patient. There are three main categories of SAS. SAS category A is a notification pathway intended for treatment of patients with potentially life-threatening diseases. SAS category B is an application pathway that can be accessed by doctors if patients do not meet the requirements of category A and if the drug is not authorized for supply under category C. Category B applications must be approved by the Australian regulatory agency - Therapeutic Goods Administration (TGA). An application has to contain, among others, a thorough clinical justification including reasons why authorized drug cannot be used in a given patient, as well as sufficient data about the safety and efficacy of the unauthorized drug. SAS category C is a notification pathway that enables doctors to use drugs which are deemed to have an established history of use [20].

## 3. Compassionate use: ethical considerations

There is a number of important ethical problems related to therapeutic use of unauthorized drugs. These include: (1) Risks and potential benefits associated with the treatment; (2) Fair patient selection; (3) Informed consent, (4) Social responsibility of doctors, (5) Ethical review of compassionate use requests, and (6) Ethical guidelines pertaining to the use of unauthorized treatments.

### 3.1. Risks and potential benefits of compassionate treatment

In the field of medical ethics, discussion about risks and potential benefits of compassionate use is relevant to two main principles - non-maleficence and beneficence. According to the principle of non-maleficence a doctor should do no harm to his/her patients, while beneficence essentially relies on the efforts to improve the patient's state of health. These values may become somewhat problematic when using investigational drugs. It is known that the likelihood that a drug starting clinical trials will be eventually approved is very low; in fact, some investigational drugs fail even at advanced stages of clinical development, sometimes due to inadequate safety and/or efficacy [21,22]. Therefore, some authors even argue that treatment with investigational drugs (with *de facto* uncertain safety and/or efficacy profile) cannot be consistent with the principles of beneficence and non-maleficence [23]. However, we believe that such an opinion is oversimplified. In our view, the doctor should carefully consider the risk/benefit ratio associated with potential treatment on a case-by-case basis. These considerations should involve three main aspects: (1) available data about the safety and efficacy of the drug; (2) course of the disease and prognosis; (3) additional issues, especially how compassionate treatment will affect other aspects of the patient's care (in particular, whether unwarranted hope for cure will not distract the patient from palliative care, if applicable [24]). If, overall, the risk/benefit ratio is favorable, treatment with an investigational drug seems to be reasonably consistent with the principles of non-maleficence and beneficence.

### 3.2. Fair patients selection

One of the key ethical challenges in compassionate use is how to ensure fair patient selection [25]. Compassionate use programs intended for groups of patients have certain inclusion and exclusion criteria; some of these programs have been registered at ClinicalTrials.gov and their criteria are available at the respective website [26]. However, to the best of our knowledge, no study has yet been performed to analyze these criteria. Selection of patients may be even more complicated when compassionate treatment is performed by doctors in individual patients, when there are no pre-specified inclusion and exclusion criteria. Complexity of the patient selection process in such situations was discussed in a recent paper [6]. It reports on the activity of the Compassionate Use Advisory Committee (CompAC), the first-of-its-kind independent and interdisciplinary committee established at an academic medical ethics department in order to provide to a pharmaceutical company recommendations regarding patient selection for compassionate treatment. Fairness in patient selection was achieved by creation of a single route of entry for patient requests, evaluation of each request based on uniform information, blinding of the committee members to some important information which might cause bias (names of patients, their race, gender and ethnicity, names of doctors, countries of origin) as well as creating rapid response to all requests. An important factor was also independence of the committee from the drug's manufacturer. Moreover, the CompAC has developed a set of specific criteria (largely clinical and to a lesser extent social) as a basis for patient selection. Detailed discussion of these criteria is out of scope of this paper. As indicated by the members of CompAC, these criteria were formulated for a particular drug and disease, and for other treatments other approaches may be better to achieve fair patient selection [6].

### 3.3. Informed consent

Informed consent of the patient is one of the requirements of compassionate use listed in the regulations introduced in the USA, Canada and Australia [13,18–20]. While it is not required explicitly by Art. 83 (1) of the Regulation (EC) No 726/2004 of the European Parliament and of the Council [10], according to the Guideline on Compassionate Use of Medicinal Products developed by the CHMP specific requirements for compassionate use are to be introduced by individual Member States [3]; thus, it is very likely that informed consent is required by regulations adopted in individual European countries. In fact, it is hard to imagine a reasonable doctor performing treatment with an unauthorized drug with uncertain safety and efficacy without informed consent. However, for a number of reasons obtaining informed consent for compassionate use can be difficult [4,5 and references therein]. First, drugs used in compassionate use remain at different stages of clinical development and therefore available data about their efficacy and safety may be limited. Second, compassionate treatment is ordinarily performed in patients with serious (or even life-threatening) diseases who cannot be treated satisfactorily with authorized drugs. Since an unauthorized drug provides the last chance for them, they are very likely to overestimate potential benefits of the treatment and to underestimate its risks [4,5]. Therefore, particular efforts must be taken to ensure that the patient has been provided with all available data about the drug (including uncertain benefits and risks), has understood

them and can make a rational decision regarding eventual treatment.

### 3.4. Social responsibility of doctors

Compassionate use by its nature creates a conflict between the needs of some patients and those of the whole society. On the one hand, for patients with serious diseases who cannot be treated satisfactorily with authorized drugs, investigational drugs may provide a “last resort” treatment. However, too widespread use of these drugs might adversely affect functioning of the complex regulatory system whose overall objective is to provide safe and effective drugs to the society [1,27]. This is particularly important in view of the introduction of Right-to-try laws which are likely to result in a larger number of patients wishing to use investigational drugs. To be considered safe and effective, and be available for standard clinical care, each drug has to complete clinical trials. Using on a large scale unauthorized drugs with uncertain safety and efficacy would have challenged this paradigm of the current drug regulation systems. Therefore, compassionate treatment should be performed only in exceptional cases; specific conditions and criteria are contained in relevant legal regulations.

An important problem reflecting the above-mentioned conflict is a relation between compassionate use and clinical trials. Compassionate treatment is performed primarily for the benefit of individual patients [1]. By contrast, the overall objective of clinical trials is to develop generalizable knowledge about drugs which will be important for all future patients [28]. Patients are likely to prefer compassionate treatment than clinical trials because participation in clinical trials is associated with some burdens and patients may be allocated to a control group and to not receive the investigational drug. In fact, actual cases of clinical trials were reported in the literature, where progress of the trial was hampered due to inclusion of too many patients to compassionate use programs [29]. This is why, in some regulations, it is stated explicitly that only patients who cannot be enrolled in a clinical trial can be considered for compassionate treatment [3,13]. In other cases, even if this is not a formal requirement, a doctor should always consider enrolling a patient in a clinical trial prior to offering compassionate treatment.

### 3.5. Ethical review of compassionate use requests

Since compassionate use is associated with a number of important ethical problems, one could ask whether it should be subject to ethical review similarly to clinical research. Whether or not compassionate use requests should be reviewed by bioethics committees is a controversial question. Currently this is required in very few countries including the USA, Italy and Australia (APS programs only, but as an alternative to bioethics committee approval, an endorsement from a specialist is acceptable) [4]. There are no primary papers on bioethics committee review of compassionate use requests in other countries. Bioethics committee involvement in review of compassionate use requests is controversial for two main reasons. First, there are solid arguments both for and against independent ethical review of these requests. Second, so far bioethics committees have been involved largely in review of clinical research and there are no clear rules of evaluating compassionate use requests [4,30].

Doctors who consider use of investigational drugs and have any ethical concerns might also consult clinical ethics committees (also termed hospital ethics committees). In general, these committees exist in many European countries, the USA, Canada and Australia, and their main role is to advice clinicians regarding different ethical challenges encountered during clinical practice [31]. Indeed, some compassionate use requests have been put forward to these committees [32]. However, to the best of our knowledge, there are no data available in the literature about how ethics committees handle such requests.

### 3.6. Ethical guidelines pertaining to the use of unproven treatments

Important ethical guidance about the use of unproven drugs is contained in the Declaration of Helsinki [33]. Although the Declaration, in principle, concerns clinical research, its last paragraph (Par. 37) pertains to experimental treatments [34]. According to this paragraph a doctor may use an unproven intervention in cases when proven interventions do not exist or have been ineffective. Prior to use of an unproven intervention, the doctor should consult an expert and obtain informed consent from the patient. Such interventions can be used when they, in the doctor's judgement, can bring about positive therapeutic effects in the patient. In addition, the Declaration indicates a necessity to investigate the safety and the efficacy of the unproven intervention and to disseminate new data that have been collected during the treatment [34]. However, the Declaration of Helsinki is not a legally-binding document. Therefore, guidance from par. 37 cannot replace legal regulations pertaining to compassionate use. Moreover, some bioethicists criticized par. 37 of the Declaration for promoting use of unproven treatments without proper oversight [35].

Guidelines about use of unproven treatments are also contained in some national codes of medical ethics [33]. These may be also used by doctors who consider therapeutic use of unauthorized drugs. However, detailed discussion of these guidelines is out of scope of this article.

## 4. Conclusions

The EU, the USA, Canada and Australia have introduced legal regulations which enable doctors to use unauthorized drugs (in practice these are most often investigational drugs undergoing clinical trials); in addition, in the USA and Australia treatment with investigational medical devices is permitted. While there are some differences between regulations adopted in individual countries, in principle compassionate treatment can be performed in patients with serious including life-threatening diseases in whom all authorized treatment options have failed. For these patients compassionate use may provide the “last resort” treatment. However, therapeutic use of drugs with uncertain safety and efficacy is associated with a number of ethical dilemmas. Doctors who consider compassionate use should be aware of these problems; guidelines which might aid them in ensuring high ethical standards of such treatment are contained in the Declaration of Helsinki and some national codes of medical ethics.

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## Declarations of interest

None.

## References

[1] Caplan AL, Bateman-House A. Should patients in need be given access to experimental drugs? Expert Opin Pharmacother 2015;16(9):1275–9.
[2] https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm, Accessed date: 28 February 2019.
[3] European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation (EC) no 726/2004 Available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf; 2007, Accessed date: 28 February 2019.
[4] Borysowski J, Ehni HJ, Górski A. Ethics review in compassionate use. BMC Med 2017;15:136https://doi.org/10.1186/s12916-017-0910-9.

[5] Darrow JJ, Sarpatwari A, Avorn J, Kesselheim AS. Practical, legal, and ethical issues in expanded access to investigational drugs. N Engl J Med 2015;372:279–86.
[6] Caplan AL, Teagarden JR, Kearns L, Bateman-House AS, Mitchell E, Arawi T, et al. Fair, just and compassionate: a pilot for making allocation decisions for patients requesting experimental drugs outside of clinical trials. J Med Ethics 2018;44(11):761–7.
[7] Cappuzzo F, Soo R, Hochmair M, Schuler M, Lam KC, Stehle G, et al. Global named patient use program of afatinib in advanced non-small-cell lung carcinoma patients who progressed following prior therapies. Future Oncol 2018;14(15):1477–86.
[8] Plourde PV, Jeha S, Hijiya N, Keller FG, Silverman LB, Rheingold SR, et al. Safety profile of asparaginase *Erwinia chrysanthemi* in a large compassionate-use trial. Pediatr Blood Cancer 2014;61(7):1232–8.
[9] Jarow JP, Lemery S, Bugin K, Khozin S, Moscicki R. Expanded access of investigational drugs: the experience of the center of drug evaluation and research over a 10-year period. Ther Innov Regul Sci 2016;50:705–9.
[10] Regulation (EC) no 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726; 2004, Accessed date: 28 February 2019.
[11] Balasubramanian G, Morampudi S, Chhabra P, Gowda A, Zomorodi B. An overview of compassionate use programs in the European Union member states. Intractable Rare Dis Res 2016;5:244–54.
[12] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32004L0027; 2004, Accessed date: 12 March 2019.
[13] Electronic Code of Federal Regulations. Expanded access to investigational drugs for treatment use. https://gov.ecfr.io/cgi-bin/text-idx?SID=c7f297d02ba280e799a012f70d549fae&mc=true&node=pt21.5.312&rgn=div5#sp21.5.312.i; 2009, Accessed date: 12 March 2019.
[14] Electronic code of Federal Regulations. Treatment use of an investigational device. https://gov.ecfr.io/cgi-bin/retrieveECFR?gp=&SID=3fa5a60ded95cecaeea3523042dbb96e&mc=true&n=pt21.8.812&r=PART&ty=HTML#se21.8.812_136; 1997, Accessed date: 14 March 2019.
[15] Lynch HF, Zettler PJ, Sarpatwari A. Promoting patient interests in implementing the Federal Right to try act. JAMA 2018;320(9):869–70.
[16] Gabay M. RxLegal: a rapid review of right-to-try. Hosp Pharm 2018 Jul;53(4):234–5.
[17] Joffe S, Lynch HF. Federal Right-to-try Legislation – threatening the FDA's public health Mission. N Engl J Med 2018;378(8):695–7.
[18] Health Canada. Guidance document for industry and practitioners – special access programme for drugs. 2013. Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs/guidance-industry-practitioners-special-access-programme-drugs-health-canada-2008.html Accessed 2018-16-07.
[19] Therapeutic Goods Administration. Authorised prescribers. 2017. Available at: https://www.tga.gov.au/form/authorised-prescribers Accessed 2018-16-07.
[20] Therapeutic Goods Administration. Special access scheme. 2018. Available at: https://www.tga.gov.au/form/special-access-scheme Accessed 2018-16-07.
[21] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ 2016;47:20–33.
[22] Hwang TJ, Carpenter D, Lauffenburger JC, Wang B, Franklin JM, Kesselheim AS. Failure of investigational drugs in late-stage clinical development and publication of trial results. JAMA Intern Med 2016;176:1826–33.
[23] Raus K. An analysis of common ethical justifications for compassionate use programs for experimental drugs. BMC Med Ethics 2016;17(1):60.
[24] De Panfilis L, Satolli R, Costantini M. Compassionate use programs in Italy: ethical guidelines. BMC Med Ethics 2018;19(1):22. https://doi.org/10.1186/s12910-018-0263-8.
[25] Caplan AL, Bateman-House A, Waldstreicher J. Compassionate use: a modest proposal. Am Soc Clin Oncol Educ Book 2016;35:e2–4. https://doi.org/10.14694/EDBK_156130.
[26] Puthumana J, Miller JE, Kim J, Ross JS. Availability of investigational medicines through the US Food and Drug Administration's expanded access and compassionate use programs. JAMA Netw Open 2018;1(2):e180283https://doi.org/10.1001/jamanetworkopen.2018.0283.
[27] Walker MJ, Rogers WA, Entwistle V. Ethical justifications for access to unapproved medical interventions: an argument for (limited) patient obligations. Am J Bioeth 2014;14(11):3–15.
[28] Nardini C. The ethics of clinical trials. Ecancermedicalscience 2014;8:387.
[29] Lorigan P, Ascierto PA, Dummer R, Eggermont AM, Flaherty KT, Garbe C, et al. Expanded access programmes: patient interests versus clinical trial integrity. Lancet Oncol 2015;16(1):15–7. https://doi.org/10.1016/S1470-2045(14)71161-1.
[30] Folkers KM, Bateman-House A. Improving expanded access in the United States: the role of the institutional review board. Ther Innov Regul Sci 2018;52(3):285–93.
[31] Hajibabaee F, Joolaee S, Cheraghi MA, Salari P, Rodney P. Hospital/clinical ethics committees' notion: an overview. J Med Ethics Hist Med 2016;9:17.
[32] Brierley J, Larcher V. Compassionate and innovative treatments in children: a proposal for an ethical framework. Arch Dis Child 2009;94(9):651–4.
[33] Borysowski J, Ehni HJ, Górski A. Ethics codes and use of new and innovative drugs. Br J Clin Pharmacol 2019;85(3):501–7.
[34] World Medical Association. Declaration of Helsinki. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/; 2013, Accessed date: 28 February 2019.
[35] Asplund K, Hermerén G. The need to revise the Helsinki declaration. Lancet 2017;389:1190–1.