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Review Article

COMPASSIONATE USE OF INVESTIGATIONAL DRUG DURING EMERGENCY CONDITIONS AND ASSOCIATED ETHICAL ASPECTS, CHALLENGES, AND BENEFITS

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ABSTRACT

"Compassionate Use," also known as expanded access, is a method by which patients with a life-threatening or seriously debilitating disease that has no satisfactory treatment alternatives can gain access to new drugs outside the context of a clinical trial. Compassionate use (CU) of unlicensed drugs serves the need of patients with the serious debilitating disease in the absence of alternative approved therapies. CU does allow limited access to new products currently in clinical trials. However, it must be remembered that there are strict guidelines to follow. As with any new drug-device or treatment, there are strict guidelines determined by the Food and Drug Administration and study sponsor, especially for CU. This article contains the use of an investigational drug in emergencies, which are the ethical aspects for getting approval, the major challenges in taking a compassionate drug, and the benefits for dying patients.

Keywords: Compassionate use of a drug, Emergency use of an investigational drug, Ethical aspects, Benefits, Limitations.

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INTRODUCTION

The word compassionate use (CU) indicates such medications, strategy, and treatments which are under clinical trials and may be used in some specific critical conditions when there are no treatment options available [1,2]. These treatment options up till now have not been approved by the Food and Drug Administration (FDA) for global use. Even though the use of CU is firmly restricted there are certain conditions when the patient who is not considered as a suitable candidate in the clinical trial can register into the study. CU is generally approved when a new drug entity or a device is in Phase III of the clinical trial which was executed by the FDA in 1987 [3]. Nowadays, more than a few expressions are available such as compassionate drug use, expanded access (EA), pre-approval access, and special access and are used convertible to expose such use of drugs. EA is the official used term that was selected by the United States (US) FDA [4]. The World Health Organization (WHO) denoted CU as such a program which is planned to offer potentially life-saving investigational treatments to patients who suffer from a disease that has no adequate approved therapy or which cannot go through a clinical trial [5]. However, there are some significant differences between rules and regulations in individual countries, which is mainly the approval from IRB (institutional review board) for CU in several countries such as (US, Spain, and Italy), but not in others like (Canada, the UK, France, and Germany). Nonetheless, CU is different from standard clinical care and should be subject to review by research ethics committees (REC). CU truly involves considerable research aspects due to unapproved drugs with unconfirmed safety and efficacy in human beings. There is a very narrow number of drugs accessible for CU, or pharmaceutical companies might only have adequate drugs for utilizing in clinical trials. Some drug companies supply the drug-free of cost and some might apply the charge to the patients. The majority of insurance companies do not pay for the expenses of the new investigational drugs themselves not even with CU purposes. A federal law was accepted in 2018 that gave the patients a different approach to access unaccepted drugs, without having the approval from FDA. This way is generally referred to as "Right to Try" which does not replace EA program (EAPs) but offers another manner to get right of entry in unapproved drug use.

BACKGROUND OF COMPASSIONATE DRUG USE

Usually, a drug is made commercially available after to be proved through complete clinical trial procedures to be safe enough and efficacious. However, a certain condition has arrived to change this conventional path and thus the concept of the use of investigational drugs has been introduced, which is still a pending decision by USFDA. The CU was started with the human immunodeficiency virus (HIV) epidemic in the 1980s. During this time to control this infection, patients were allowed to take unapproved antiretroviral drugs as their last hope for survival [6,7]. The pharmaceutical company "Glaxo-Well come" had provided Anti-HIV drugs, zidovudine [8] to 22,000 patients free of cost in the 1990s, while the drug was undergoing Phase III clinical trials. From that time, the CU has been only rising. Another history was found in the 1980s the administration of an investigational antibiotic drug for the straight therapeutic effect of a patient [9]. Patients having multidrug-resistant (MDR) tuberculosis (TB) or having pre-extensively drug-resistant (pre-XDR) and XDR-TB, and those who failed in second-line therapy, are very critical for the treatment [10]. To avoid this problematic situation, the initiation of CU (combined use of both delamanid and bedaquiline) appeared due to novel mechanisms of action that can be recommended for the alternative treatment for those having developed resistance to pre-existing anti-TB medication [11]. Otsuka Pharmaceutical Co., Ltd. and European Respiratory Society TB Consilium and Médecins Sans Frontièresdeveloped the first CU program in 2014 [12]. An annex of the "Guidelines for the programmatic management of drug-resistant TB" was published by the WHO in 2008 in which various mechanisms of experimental TB drugs were discussed. The major objective of this guideline was to promote the development of CU for needy patients [13]. Bedaquiline was made available for CU for MDR-TB patients in India since 2012; however, access to this drug has not been easy [14].

PHASES OF CLINICAL TRIAL AND COMPASSIONATE DRUG USE

Clinical trial mainly focuses on the efficacy and safety of the new drug moiety for prevention, prophylaxis, or treatment for any disease. It is a study that prospectively assigned human volunteers to several interventions to measure the response and effects on the biological system [15]. There are four phases of clinical trials, Phase I, II, III,

and IV [16]. Phase I starts when FDA permits to begin clinical trials in human volunteers. In general, not more than 100 patients enlisted in the Phase I trial. If Phase I passes without any major problems, then Phase II can start where several 100–300 patients are allowed to participate. During this phase, additional information is gathered about the safety, efficacy, and side effects of the treatment. In Phase III, thousands of patients may be enrolled, and the new drug, device, or treatment is usually compared to an already approved therapy. Only during this Phase III, CU is allowed by the FDA [17]. Phase IV studies are done after approval from the FDA for the testing drug, device, or treatment has been established for commercial use.

ENROLLMENT CRITERIA FOR COMPASSIONATE DRUG USE

There are two ways to get approval for CU. The first one is if the drug or device has shown an effective result but currently under clinical trials and has not yet been permitted by the FDA. To fulfill the expanded use criteria, there should not be available any alternative approved therapy and the new therapy must not hinder the standard clinical trial method. The second way is if a patient is unable to take part in clinical trials then permission may be given to receive the new drug or device to dying patients [1]. The other criteria must be followed including the physician, must, believes that CU may be advantageous, even life-saving. All current established and alternative treatments have been applied and become unsuccessful. CU should be applied during the Phase III clinical trial and the study sponsor should agree with the use of the drug or device.

CU PROGRAMS (CUPs) IN SEVERAL COUNTRIES

USFDA

The prerequisite for expanded use of the drug is mentioned under subpart 1 of part 312 in the Code of Federal Regulations. Three key criteria are there, under which the FDA gives allowance for CU: The first one is EA for extensive use, second EA for transitional size populations, and third EA for separate dying patients [18]. EA is synchronized by the USFDA who permits the patients to use investigational drugs [19]. The physician can fill the form which was approved by the FDA for CU of the drugs. The responsibility of a physician is to get permission from IRB approval (21 CFR part 56), but this type of approval is not necessary in case of emergency EA. In 2018, a second alternative option was approved for CU of drugs which are under Phase I clinical trial. In this case, no authorization is required from the FDA or IRB, only the patients have to pay only the costs for investigational drugs or devices to the respective companies [20]. It was the last stage in the steps of introducing Right To-try laws in individual states. Basically the main motto of this law is to improve the access of patients to investigational bio-actives by reducing the FDA's oversight [21].

European Union

The word, CU is mentioned in Article 83 No. 2 of the Regulation (EC) No. 726/2004 of the European Parliament and the European Council. EMA takes the duty of providing recommendations for investigational use of drugs through the Committee for Medicinal Products for Human Use (CHMP) that are non-binding as member states can set up their own rules and actions. Member States must inform them about the rules and regulations of compassionate drug use. Germany, Netherlands, Norway, and Spain have already made their national guiding principle [22]. Regulations of the European Parliament and of the Council are obligatory for all Member States. However, this article formulates two most effective necessities for CU: First one is a chronically or severely enervate disorder, or a life risking disorder of patients who cannot be dealt with satisfactorily with a certified medicinal product, and second one is the medicinal product should be both the problem of an utility for a centralized advertising and marketing authorization or undergoing clinical trials [23]. To give detailed information about the Art. 83 (1), the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has provided rules and regulation on the CU of Medicinal Products. The guideline stated that particular regulations are constant with Art. 83 (1) are to be made by distinct Member of States. However, Several European countries have already developed national rules and regulations concerning CU [24]. According to CHMP guidelines, the patients must consider to enlist their names in clinical trials before participating in a CUP. This guideline stated that CU must not hinder the progress of clinical trials which are very much significant for safety and efficacy of any therapeutics. In addition, Art. 1 allows transient use of an unapproved drug spreading of any pathogens, toxins, chemical agents, or nuclear radiation suddenly [25].

WHO

A novel term was given by the WHO throughout the Ebola outbreak named Monitored Emergency Use of Unregistered and Experimental Interventions' (MEURI), for the experimental purpose that was done outside the clinical trials at the time of emergency that is lead by specific ethical criteria, as the expert group stated that CUCU has another meaning [26]. It was declared that these interventions should be reviewed and approved by regulatory agencies (ethics committee, and informed consent form [ICF]) to avoid undesired results.

India

According to Draft Amendments in the New Drug and Clinical Trial Rules, 2019, the investigational drug can be allowed in some particular conditions such as life-threatening disease or disease which causes everlasting disability. A manufacturer has to make an application to make an issue of license for the manufacture investigational drug when it is allowed for use under the rule of 96E. The Central Licensing Authority (CLA) has decided to change the draft type monitoring necessities like an assessment of manufacturing area of new investigational drug which is authorized by CLA, required requirements must be submitted quarterly information on status and store of unapproved new drugs that are imported, utilized, shattered, or provided to certified patients from the hospitals. The National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017 issued by the Indian Council of Medical Research (ICMR) have not mentioned compassionate drug use; yet, in the section of research throughout emergencies and disasters, certain necessities are approved from the WHO regulation on MEURI to notify the situation for using experimental interventions in emergency cases [27].

Canada

Canada has approved that the therapeutic use of unapproved drugs including biologicals (but not medical devices) is allowable in Special Access Programs. The legal policy of this program is under Food and Drug Regulations (Sections C.08.010 and C.08.011). General instructions are available in the Guidance Document for Industry and Practitioners – Special Access Program for therapeutics made by the Canadian regulatory agency Health Canada. According to SAP rules, an investigating drug can be utilized in life-threatening disease conditions, mainly in emergency cases while no therapies are left or unsuitable or unavailable. This CU should be supported by some probable evidence of its safety and efficacy, and a doctor or any health clinic must have the ICF for the interested patients. A doctor has the responsibility to keep all the information and data and must reveal about the results associated with compassionate drug use to both the SAP and the manufacturer of the drug [28].

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). According to APS, a registered medical practitioner has the authority to utilize unapproved investigated therapeutics for deadly disease. The application for CU must be authorized by a bioethics committee. In the SAS, unapproved bio actives can be utilized in exceptional clinical situations in a single patient on a case-by-case basis. It must be sure that all the treatment options have already been considered thereafter only compassionate programs can be conducted. Above all, the doctor must sign the ICF from the patient and should provide the information regarding the adverse effects, safety

and efficacy of the program. In general, three types of SAS are there. Category A involved the treatment of critically ill patients suffering from life-threatening diseases. SAS Category B is an application step which is accessed by physicians and considers about the basic criteria of category A and if the therapeutic is not allowed for the supply under Category C. It is mandatory for the Category B application to be accepted by the Australian regulatory agency - Therapeutic Goods Administration.

JUSTIFICATION FOR CUPs

Justice or fairness

The first promising reason for using this program indicates maybe for the ethical opinion of justice or fairness. Though there are various ways to express justice (such as distributive, egalitarian, libertarian, etc.). Yet, for this purpose "justice" is used to indicate the need for CU. This specific program may be a crucial option for terminally ill patients who just want to get rid of the deadly disease. Patients may be aware of various ongoing clinical trials through health-care professionals, although there is another to search for such trials online through many websites like "My Tomorrow" [29]. Though many patients have the expectation to participate in the CUPs but luckily very few of them become successful to pass the clinical trial. As, Phases I and II clinical trials do not incorporate a lot of participants, thus only a preferred number of dying patients can participate. Second, the clinical trial for a definite drug might not be conducted in their surrounding area. Sometimes it becomes very difficult for a terminally ill patient to travel a long distance to participate in the trial. Third, a lot of terminally ill patients may not fit for the criteria to participate in a trial. In maximum cases, a significant number of potential candidates is excluded due to create a homogeneous group. Patients having so poor physical condition are often-disqualified or some patients who are taking so many other medications (creating confounding factors) [30]. It is also important to mark that patients who are participating in the clinical trial must receive the experimental drug rather than placebo. Patients who can participate in the trial are determined by different factors such as distance to the trial center, the number of participants permissible in the trial, the situation on which the drug is tested, and the patient's physical state.

Beneficence

The explanation for CUPs results in positive hope for the seriously dying patients with experimental drugs that could save or extend their lives. However, these programs can be risky in two aspects. First, there is a straight risk for the intervention of active compound one who takes to have unsafe effects on them, and second, there is a danger that by involvement in the CUPs patients is demoralized for the profit of researchers or pharmaceutical companies.

Autonomy

By giving this facility to the dying patients with an experimental drug (besides randomized clinical trials [RCTs]) might advance the autonomy and create those RCTs more ethically. Kodish (1991) once argued that clinical trials will be justified ethically if the involvement or the experimental drug in the trial is also accessible outside of the RCT [31]. If an intervention is obtainable both within and outside of an experimental trial then participants will have the choice to either in the RCT or the CUP. Schuklenkthus argues that not giving the experimental medications through CUPs can be amounted to coercing dying people into participating in particular trial designs. At the same time as such, CUPs might result in a proper autonomy since it offers patients with two options where they earlier had only one coercive alternative.

USE OF COMPASSIONATE DRUG IN VARIOUS PANDEMICS

In nCOVID-19

The quick and immediate arrangements for helpful care and RCTs are the only way that can be efficient and secure treatments for nCOVID-19 and future pandemics. Based on the previous clinical trial data, the FDA has approved the emergency use of remdesivir for the prevention of severe nCOVID-19 in both adults and children [32]. It is a nucleotide analog prodrug that results from the inhibition of viral RNA polymerases and also results in promising *in vitro* activity against SARS-CoV-2.The current study showed clinical progress in 68% of the infected patients with the supervision of remdesivir for 10 days [33]. Lately, the Central Drugs Standard Control Organization (CDSCO) also agreed to the emergency use of this drug in suspected or laboratory-confirmed nCOVID-19 infected patients [34]. Although Chloroquine, hydroxychloroquine, azithromycin, lopinavir, and ritonavir have various side effects such as QT prolongation, hepatitis, acute pancreatitis, and anaphylaxis [35,36]; in this critical situation lifesaving become a more important priority than those adverse effects. Yet, having some potential harm, steroids and IL-6 inhibitors are administered to nCOVID-19 infected patients in several countries.

Ebola virus

Drugs such as GS-5734, REGN monoclonal antibody combination Zmapp, and mAb114 had been permitted for CU by the Ethics Committee in Africa all through the Ebola outbreak and found to be effective [37]. The ICF was approved by the infected patients with the secure observation of any undesirable effects [38]. Post-exposure prophylaxis with the rVSV-ZEBOV vaccine was also acceptable for CU on the persons who get in touch with infected patients [39].

In henipavirus

The m102.4 (human MAb-monoclonal antibody) was permitted for compassionate drug use when it was found defensive against the virus in animal models [40]. This monoclonal antibody was administered to either Hendra virus or Nipah virus-infected patients individually [41]. The result was found to be effective in a recent clinical trial (neutralizing virus infection) which allowed the administration of m102.4 through a CUP [42]. This antibody has been obtainable in Australia from 2010 for CU and just completed Phase I clinical trials and approved for CU in typically ill patients. Based on the trial, it was suggested that a single dose of 20 mg/kg of m102.4 can be given or two-doses might be divided by 48 h gaping, to patients having clinical symptoms of infection. On the other hand, the antiviral drug remdesivir showed efficacy in nonhuman primates while administered as post-exposure prophylaxis and can be corresponding to immunotherapeutic treatments. The drug ribavirin had been used in patients having initial Malaysian Nipah Virus infection but its efficiency was unclear.

Swine flu

US FDA allowed an Emergency Use Authorization (EUA) for intravenous (IV) Peramivir (antiviral), to treat confirmed 2009 H1N1 influenza-A virus-infected

patients on October 23, 2009. The Centers for Disease Control and Prevention made the program to supervise Peramivir allotment to request clinicians under EUA [43,44]. In 2010, the CHMP gave a view on the CU of Tamiflu and IV Zanamivir to treat critically ill patients infected with H1N1 influenza [45].

Use in deadly illness: Isolated case

After the pre-approval process of antiretroviral drugs for CU, cancer researchers of the US soon became active. The researchers are trying to get investigational drugs to treat surely dying cancer patients. One organization named "Abigail Alliance" formed immediately after the death of a 21 years old Abigail Burroughs who was diagnosed with terminal squamous cell carcinoma of the head and neck. She lost her life in 2001 when she was denied two investigational drugs named Erbitux (Cetuximab) from "ImcloneSystem" and Iressa (Gefitinib) from "AstraZeneca" [46]. Rozek *et al*. described the findings from H1N1 trial registrations (15 H1N1 study registration records were included in ten interventional trials and five observational studies during the pandemic). CU eight several treatments were to be investigated such as oseltamivir, zanamivir, convalescent plasma, IV immunoglobulin, rosuvastatin, sirolimus, Chinese herbs, and vitamin supplementation (Vitamins A, C, and E). Among the 15 studies, nine were reported completed; four were terminated due to reducing the number of positive

cases; and the status of two were not recorded [47]. They described that most of the treatment studies were either retrospective observational studies or case series and few were prospective studies. The CU of such drugs resulted in relatively better effects, though, in enlisting A (H1N1) pdm09 infected patients in progressing or seasonal influenza studies of the 582 patients enlisted in a trial, about 439 patients were enrolled in this manner. Hence, it is suggested to conduct clinical trials for the bio actives to use in correlative diseases (like seasonal influenza) during epidemic situations to stop the outbreak [48].

Used in non-life-threatening conditions

CU of a drug is not limited to cancerous patients. In phase, two clinical trials approved drugs are used in cancer disease. This compassionate program is also used in some non-life-threatening conditions such as an incident in the US of LeClaire brothers, Austin and Max. The brothers were born having a genetic disorder named Duchenne Muscular dystrophy that caused the imbalance of the walk. The family was losing hope but soon found an experimental drug, named "Eteplirsen" which was being developed by the company Sarepta Therapeutics. Max, whose age is now 14 years old enlisted for the clinical trial in 2011. On the other hand, Austin, who is now 17 years old boy declined to participate in the trial (because he was using a wheelchair and thus failed to meet the criteria for enrollment in the program). But Austin enlisted his name in another clinical trial with the same drug after 3 years. Since that time when then, the brothers have observed a major development in their physical state. Drug Eteplirsengot approval letter in September 2016 by the US FDA following a White House petition that was signed by more than 100,000 people [49].

WELFARE AND LIMITATIONS WITH CU

The main significance of a compassionate drug use program is that the dying patient gets a chance to use investigational drugs as their last hope for life-saving. It is such a program, where the investigational drugs are allowed to take as an alternative treatment for their critical health issue [50]. This compassionate drug acts as a linker between the developmental phase and the closing approval of a drug which might help to improve the prolonged use of the drug. After administration, the efficiency and safety data can help the researchers for the further modification of the drug molecule. Getting such real evidence can be utilized instead of conventional clinical trial data when demanding regulatory approval. Patients suffering from fatal illness are generally expected to have health benefits and may have narrow relative risk (while the patient is already in a death situation). Unreasonable to incorporate all suitable in computed tomography (such as lengthy travel distance or severe additional criteria). The compassionate drug may be a promising way for the dying patients and an appropriate way to enlist the investigational drugs or devices. Another Advantage for CUPs is that it provides the pharmaceutical companies a vital experience about their pipeline drugs, not only the patients who could generally be disqualified but also the physicians and linked health-care professionals, due to its commercial launch. The inferences are of two types. First, it permits the pharmaceutical company to produce a wide key opinion system where the pipeline product can potentially be exposed when the company is looking for licensing authorization. Second, after treating the patient through a compassionate program it will be more familiar to the patients to pay for that product while it will be available in the market. In CUPs, one should be attentive to the potential of exploitation [51]. Conducting a compassionate program is not an easy process to become successful as the conducting association asks for an early allowance of drugs that have not yet been officially approved for CU. Hence, it requires appointing legal experts and needs to become a partnership with several external stakeholders which results in a long time duration. CUPs are expensive activities as the association having to subcontract to legal experts away from their usual sphere of the process in research and development and approving certified approval with such exterior associations seeking best for their "specialized" services [52]. Misunderstanding about therapeutic efficiency may lead to risks involved interventions and misleading of ICF process causes serious side effects that can damage the patient physically as well as economically. For example, we can take Chloroquine or hydroxychloroquine, azithromycin, and lopinavir-ritonavir have numerous numbers of side effects such as QT prolongation, hepatitis, acute pancreatitis, and neutropenia that results enhance the possibility of cardiac death while administered against nCOVID-19 and steroids showed the considerably enhanced risk of death and secondary infections in influenza-infected patients [53,54]. Without knowing the magnitude of the harm, the administration of compassionate drug use throughout a pandemic might result from discouraging patients to participate in RCTs. Sometimes harmful adverse effects may also occur during the clinical trials. Sometimes harmful adverse effects also occur during the RCTs, however these emergency drug associated clinical trials are conducted among small scale populations under strict rules and regulation. In this type of CUPs, now there is frequently no responsibility to state the adverse effects [55]. There is a risk that in CUPs the dying patients are treated as easy research participants. CU includes clinical trial practice, but some issues have been indicated that participating patients in the program have a limited commitment to exposing some necessary data including the effect and adverse reaction [56]. Due to the increase in terminally diseases cases, CUPs are now day used as studies. CUPs are not regulated as important as clinical trials and sometimes this increases the risk of patient safety. If pharmaceutical companies are permitted to charge patients either take them just as research participants for the company's profit, thus it results in the risk of exploitation.

THE ALTERNATIVE WAY FROM CUPS

Still, RCTs are not claimed as the best testing procedure of investigational drugs for dying people as the existence of a placebo control group and the little number of participants in CUPs does not count as the only alternative. As the designing and testing process of a drug is long enough; hence, there might be some new ways which can accelerate the drug approval process (such as using an Expansion Cohort Design instead of conducting different Phases I, II, and III) studies based on incoming data [57,58] which offers more flexibility and reduce time interval. When the approval process goes fast then more terminally ill patients can participate in the CUPs. Another option is single-patient trials where the patient is administered with experimental new drugs and the data are stored in a more scientific mode than in most existing CUPs [59]. Hence, an alternative option is possible [60].

ETHICAL ASPECTS FOR THE INVESTIGATIONAL DRUG IN CUPS

CUPs are often mentioned as a therapeutic process that is not planned properly, offering the treatment principle without sufficient informed consent or without monitoring any minor-major adverse effects. The CUP involves data collection to justify the efficacy, safety, risk-benefit of the investigational drug and the patient choice criteria, physicians' qualifications, and many other aspects as relevant for research purpose [61]. The principle of justice demands the need to ensure fairness in the selection of patients, transparency in procedures, and ensuring access to products available for CU. The principle of nonmaleficence and beneficence ensures the best procedures for adequate safety, monitoring, and protection from harm [62].

Ethics committee

This Ethical committee is required for the safety and protection of enrolled patients who are participating in the CUP. On the other hand, the responsibility of this committee is to review the protocols concerning emergency use in a few countries including the USA, Spain, and Italy. Informed consent for an investigational drug is enlisted in the system of the USA, Canada, and Australia [25,63]. The local ethics committee can assure about patient rights and can minimize the risks by providing them proper safety measures, supportive management, and the concept of any type of side effects. The ICMR has lately published National Guidelines for Ethics Committee reviewing biomedical and health research during the nCOVID-19 pandemic situation [64]. According to CDSCO of India, a novel drug can get approval outside India in cases of national emergency, extreme necessity, and epidemics, for rare drugs in exceptional diseases, and some certain situations

which have no approved therapy [65]. The rule 33A and 34A of the Drugs and Cosmetic Act (1940 and Rules, 1945) permit to introduce of a small number of new drugs through a government hospital or through independent medical organization for the treatment of terminally ill patients who are suffering from a disease which needs therapies for unmet health requirements [66]. According to the EMA's Guideline for CU of medicinal devices or drugs under (Article 83 of Regulation (EC) No 726/2004), which was made by the Committee for Medicinal Products for Human Use (CHMP) declared that CUPs conducted chiefly for the therapeutic occasion [22]. Both the US FDA and the EMA stated that the CUP and clinical trials program must be separate from each other [67]. The main role of REC is to defend the rights of biomedical investigate candidates [68]. The EMA stated that safety data must be recorded throughout the CUPs and also added that CUPs cannot replace RCTs for investigational justification.

Significance of ICF, distribution policy of investigational drug, and priority level

A CUP is conducted for dying patients due to having no FDA-approved drugs in the market. As these programs are conducted by the ethics committee, the participating patients do not have the access to check data or even do not have sufficient knowledge about the program [69]. Thus, patients who are ready to take the unapproved drug to save their life without having any concept about potential effects and the probable side effects must be guided by RECs through ICF. Information about the program, which medication is used, what are the side effects and benefits must be known by the patient and his family. They had to sign the ICF for the further processing of the program. In this program, sometimes some critical situations occur. The first is in cases where a treating physician is also a researcher. When the patients want to take part in biomedical research sometimes a conflict of interest is occurring when the particular research gets priority over the clinical concern of the patient [70]. Since CU often combines therapeutic and research aspects, a conflict of interest might arise, for example, from a physician's desire to "pioneer" the use of a novel intervention without paying sufficient attention to the patient's medical needs. The second situation that harbors the potential for abuse is associated with the interests of the commercial sales of drug manufacturers. The possibility exists that these manufacturers might use CUPs to distribute investigational drugs, thus generating increased demand for the drug following its eventual formal approval. The main motto of the ICF is to stop possible mistreatment and to make sure the patients that this compassionate program is only for the patient's profit. The RECs have wide experience of reviewing ICFs though they are chiefly concerned in the evaluation of various biomedical researchers, after all this consent form exactly told the choice about involvement in a program. Hence, these consent forms must be carefully reviewed by RECs. Where CU does not involve research (e.g. in the treatment of individual patients), an alternative solution might be there for standards. In CUPs, several collaborators take participants who have different roles and responsibilities. Not only regulators besides clinicians, ethics committees, concerned hospitals, patient encouragement boards, and others should work together to confirm the safety and efficacy of compassionate drugs. An additional consideration is very much desired for keeping the patient's interest. The shareholders should have adequate execution and controlling the plan for transparency in the process. Having additional responsibility to carry on proper compilation and allotment of confidential data with authorized authorities, during secure transparency, accuracy, defending patient identity, and doing all the work in a definite time frame [71]. In 2015, CU Advisory Committee (Comp.AC) was recognized for giving suggestions to pharmaceutical companies about the access of new drugs. For example, this committee advised Janssen to use "Daratumumab" as CU within multiple myeloma infected patients [72].

SOME ETHICAL PROBLEMS DURING THE PROGRAMME

There are a number of important ethical aspects associated with CU of drugs. These include proper patient selection, social duty of doctors, Ethical review of CU requests, and ethical guidelines pertaining to the use of unapproved drugs.

Proper patients selection

Patients selection is one of a major ethical challenges in CU program [73]. This programs are basically considerable for the patients having critical situation and also they are maintaining the proper inclusion and exclusion criteria; various programs also been registered at ClinicalTrials.gov and their criteria are also available at the website [74]. Although, no study has yet been developed to measure these criteria. This selection process becomes challenging when the compassionate program is conducted by personal health profession and when there is absence of pre-specified inclusion and exclusion criteria. CU Advisory Committee (Comp Ac) was established at an academic medical ethics department to deliver information to the pharmaceutical company about the patient selection criteria for conducting compassionate program. To achieve smooth patient selection process a single way of enrolling in this program has been requested and evaluation was based on uniform information, blinding of the committee representatives to some significant information that could cause bias (such as names of patients, gender and ethnicity, names of doctors, and countries of origin) as well as producing quick response to all requests. Moreover, the Comp AC has evolved a set of definite criteria (largely clinical and to a lesser extent social) as a basis for patient selection [75].

Social duty of physicians

The CU sometimes leads to a conflict between the critically ill patients and those of the total society. Application of large scale investigational drugs with uncertain safety and efficacy might have challenged this paradigm of the recent drug guideline regulation systems. Hence, CU must be conduct only in critically ill cases; specific situations and criteria are hold in appropriate legal rules and regulations. A major issue indicating the described conflict is a relation between CU and clinical trials. CU is mainly done for the benefit of critically ill individual patients [76]. Above all the main motto of the clinical trials is to collect the safety data of the investigating drug that is significant for future use [77]. The progress of the clinical trial is hampered because of too many participation of patients in CUPs [78]. Thus the guidelines stated that only critically ill patients who cannot be enrolled in a clinical trial or already have tried other approved options only they can took part in this program. Physicians must consult with the clinical ethics committees (known as hospital ethics committees). Basically these committees are present in many European countries, the USA, Canada, and Australia, and the major function is to advise clinicians about several ethical challenges appeared during the program [79,80].

Ethical regulations relevant for using unapproved treatment strategy

Significant ethical guidelines about the utilization of unapproved bio actives are described in Declaration of Helsinki. Before utilizing any investigational drug, the doctor must consult with the health expert and should sign the informed consent from the patient. Such interference may be utilized while they, in the doctor's judgment, may bring some positive therapeutic response among the infected patients. Declaration indicates the significance of measuring the safety and the efficacy of the bio actives and to spread new data which have been collected at the time of treatment [81]. In the guidelines several national codes of medical ethics have been declared properly. These can also be used by the physicians who consider the application of unapproved drugs. However, detailed description of these guidelines is out of scope of this article.

HAS CU EVER FAILED A DRUG?

New treatment strategy for serious disorder generates comprehensible exhilaration among sufferers with life-threatening conditions. As pharmaceutical agencies keep in mind CU of investigational drugs, one component is normally referred to as a barrier to such use: worry that unfavorable occasions incurred through sufferers all through CU/EA

will hinder regulatory approval of the drug. Such issues stem from the responsibility to file unfavorable occasions – which might be serious, unexpected, and suspected to be associated with the investigational drug experienced through sufferers at the time remedy by CUPs/EAPs. Such reports, it is feared, will harm the future of the therapeutics, especially because unfavorable activities might not be associated with the experimental drug and sufferers taking such bio-actives are critically sicker than the common patient [82]. Existing proof, though, does now no longer help the perception that such occasions jeopardize regulatory approval. A determined potential safety sign can also additionally result in a keep on use of an investigational new drug (IND), permitting examination of extra records or modifications in trial or get entry to protocols. In spite of, between 2005 and 2014, 1033 unique, commercial, active EA INDs have been authorized with the aid of using the USFDA; in mostly two instances (0.19%) made a critical unfavorable condition made to keep on use of the therapeutics. Both holds have been lifted inside a matter of months, and each drug improvement programs continued [83]. These information contradict the industry's declaration that CU/EA influences the approval process. An FDA deputy defined this declaration as "something of an urban legend, and (FDA is) uninformed about the fact [84]. It is noteworthy that medicines in CU/EA applications have already confirmed the efficacy of clinical trials even when it was not approved by FDA for marketed use, and sufferers receive them due to having no other treatment options [85]. Granting permission for CU/EA of medications for the remedy of the HIV verified key in stemming the AIDS (acquired immune-deficiency syndrome) crisis [86]; however, such significant implementation has not been made available for TB infected patients [87]. As no proof supports the declaration that unfavorable activities happening in patients going under CU/EA remedy bring about denial of approval, mechanisms which must be evolved to inspire the establishment of early, recurring CU and EA for bio actives being advanced for indicators inclusive of MDR-TB. These may want to consist of modifications to the US FDA Neglected Tropical Disease Priority Review Voucher System or the EMA Orphan Designation incentives, and improved sharing of economic and legal burden for imparting the access [88,89]. In France, Italy, and some Nordic countries, the costs for this treatment are deceived by the health-care system, not by the pharmaceutical industry or the patient [90].

CONVENIENCE OF INVESTIGATIONAL DRUGS MEDICINES VIA US FDA'S CU PROGRAMME

Through ClinicalTrials.gov, 92 FDA-accepted bio actives and biologics with linked EAPs started before FDA approval were clarified. These programs were conducted in between September 1996 and June 2017 for the medications that were mainly used for the treatment of cancer, metabolic, endocrine, and genetic diseases and infectious diseases. Among 92 EAPs, 64 (69.6%) were started just before or after new drug application submission, 24 (26.1%) were started during the 6-month period before, and rest 40 (43.5%) in the 6 months after. Skeptics insist that patients can already achieve access for investigational drugs with the help of FDA's existing EAP that allows >99% of the patient requests got for investigational therapeutics. In case of emergency situation a single-patient request, the agency typically responds just within hours. The main motto of FDA's EAP was to give approval for investigational therapeutics where adequate clinical safety and effectiveness data are present and with authorization from the commercial sponsors basically from pharmaceutical industries [91]. Therefore, the FDA is maintaining two competing priorities first one is IND access and second one is defending of patients from therapies without safety and efficacy data. Legislative efforts focusing to safely verified drug availability must work to involve both investigational drugs producers and the FDA. This type of legislation can help patients with life threatening situations achieved access to investigational bio actives without compromising patient safety profile or the procedures to measure drug efficacy and safety data by FDA [77]. A more proactive system can be initiated by developing an independent service system which would help the patients to find protocols for the EAP and clinical trials, like a service granted in Europe. A public-private partnership could be established to do this in the US [92]. This system could upgrade the enrollment procedure in both EAP protocols and RCTs. The result would be both single fairness and quicker accessible for all by marketing approval, a result largely inscribed [93].

CONCLUSION

Overall, it may be acceptable for CU of the investigational drug during emergency cases to save life immediately. For that robust responsibility must have to control CU. This may consist of clear regulatory guidance, mandatory conflict of interest declarations, adequate information about safety, and adverse effects of the program and must be a rule for healthcare workers or other front line employees must be given priority to receive the treatment if they want it with the proper declaration. There is a huge expectation for it to be useful by providing a pathway to patients having a seriously debilitating disease or a life-threatening disease to receive unproven interventions in anticipation of health benefits, even when the benefit-risk ratio is unknown given limited safety or efficacy data. A compassionate drug use program must be strictly monitored and implemented and never be considered as an alternate for a clinical trial or biomedical research. To control this investigational drug use properly a regulatory body must be available to provide information about ethical aspects to the needy patients. This CU would also smooth the progress of the collection of *in-vivo* data, which may help in further future clinical trials. Although there are various ethical challenges because of limited sound scientific evidence, the possibility of therapeutic misunderstanding, limitations related to autonomy and that of equality, misinformation about the program, etc., this CU can save the dying patients from death. Now times have changed, and various pharmaceutical companies are accepting it as a marketing prospect to collect added clinical data from the CU of drug programs, for example, the biotechnology company, "Genentech" motivates the dying patients to take investigational drugs.

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Sumel Ashique has conceptualized, reviewed, and Tahamina has edited.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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