Understanding the challenges and ethical aspects of compassionate use of drugs in emergency situations

Introduction

Therapeutic use of unapproved drugs/interventions for the treatment of serious life-threatening conditions/infections in situation of unavailability of any authorized drug is called as compassionate use, and it has been proposed to be defined as “compassionate use for treatment of patients suffering from life threatening disease or disease causing serious permanent disability or disease requiring therapy for unmet medical need, which has not been permitted in the country but is under Phase III clinical trial in the country or in any other country.”[1,2]

Ministry of Health and Family Welfare in India notified the draft for the amendment to the New Drugs and Clinical Trial Rules, 2019 inviting public comments and have introduced the regulatory framework for import or manufacture of unapproved new drugs for compassionate use.[2] This is very much needed step in coronavirus disease 2019 (COVID-19) crisis to have access to experimental drugs as no approved therapies are available for the management of this pandemic.

At present, in India, the term “compassionate use” or expanded access or preapproval access or special access or early access may be understood and used interchangeably.[3] Compassionate use broadly refers to use of drugs that are unapproved but still in clinical development; use of drugs that are approved in one country but not available globally; use of drugs that are approved but not commercially available; use of drugs that may never be approved but has important medicinal value for a small patient population; and use of drugs that had been withdrawn from market but can still benefit patients.[4] The World Health Organization (WHO) Ebola ethical panel has also justified the compassionate use of the drug, provided it should not delay the initiation of properly designed clinical research to reach the more conclusive results.[5] “Expanded access” is another process regulated by the United States Food and Drug Administration (FDA) pathway that permits patient to gain access to an investigational drug outside a clinical trial. As per the FDA, following conditions will justify expanded or compassionate use of the drug:[4]

- “Patient suffering from serious disease or life-threatening condition and nonavailability of any satisfactory alternative therapy to diagnose, monitor, or treat the disease
- Enrolment of patient is not possible in a clinical trial
- Benefit with expanded use of drug justifies the potential risks of treatment
- Using the investigational drug will not interfere with clinical trials that were conducted for marketing approval of drug for the treatment indication.”

The request for preapproval treatments outside of clinical trials usually requires an entirely distinct proficiency, skills, capabilities, and legal regulations. It is very difficult to generalize guidelines regarding compassionate use in the whole world because of difference in country-specific drug access regulations and legal pathways.[6] Moreover, the scope of compassionate use in any country will depend on many factors, such as anticipated demand, regulations, status of the drug license, drug costing structure, as well as company strategy, costs, and product supply. Compassionate use is not possible in countries where policies are unclear or nonexistent.[7] There is a need for harmonization on global level to frame guidelines or definitions as there is lack of single definition of compassionate/expanded use programs all over the world with different nomenclature for such concerned programs in different countries, for instance, Expanded Access Program (USA), Special Access Scheme (Australia), Temporary use authorization (France), Hardship Case Program (Germany), Uso Compassionevole (Italy), Temporary Use Authorization (Spain), Earlier Access to Medical Scheme (UK), Special Access Programme (Canada), Compassionate care (Israel), Compassionate use (Turkey), Clinical Access Programme (South Africa), and Conditional Approval for Regenerative Medicines (Japan).[8,9]

Compassionate Use versus Clinical Trials versus Off-Label Use

Compassionate use is different from term off-label use and clinical trial in many aspects. Compassionate use of unlicensed drug serves the need of patients with serious debilitating disease in the absence of alternative approved therapies, whereas off-label drug use refers to
the use of drugs outside the indications of the licensed product or under different conditions in terms of dose, route of drug administration, and contraindications, and clinical trial is a study that prospectively allocates human participants to different interventions to estimate the effects on health outcomes.\(^{[10-12]}\) Table 1 shows some key differences between these three terms.\(^{[12-18]}\)

**Compassionate Use Programs in Different Countries**

**US Food and Drug Administration**

Requirements for expanded use of drug are explained under subpart 1 of part 312 in Code of Federal Regulations. There are three major categories under which the FDA accepts requests for compassionate use: Expanded access for widespread use, Expanded access for intermediate size populations, Expanded access for individual patients.\(^{[19]}\) The success of expanded access approach is only possible with support from doctors, FDA, and institutional review board (IRB). Physicians can fill form issued by the FDA to request for compassionate use of the drugs. It is the responsibility of a physician/investigator treating the patient to obtain the IRB approval (consistent with 21 CFR part 56), but such approval is not required in case of emergency expanded access use where only requirement is to notify IRB within 5 working days of emergency use.\(^{[19]}\) The federal right to try law was enacted in 2018 and created second alternative pathway for access to drugs which have completed Phase I clinical trial. This has similarity to expanded access program with the exception that no approval or permission is required from the FDA and an IRB for access to new investigational drug. Patient needs to give direct costs for investigational products to companies.\(^{[20]}\)

**European Union**

The word “compassionate use” is mentioned in Article 83 No. 2 of the Regulation (EC) No. 726/2004 of the European Parliament and of the European Council. EMA is responsible for providing recommendations for compassionate use through the Committee for Medicinal Products for Human Use (CHMP) which are nonbinding as member states can establish their own rules and procedures. Member States should notify the EMA about compassionate drug use. Germany, Netherlands, Norway, and Spain have already established their own national guidelines.\(^{[21]}\)

**World Health Organization**

A new term was coined by the WHO during the Ebola outbreak, namely, Monitored Emergency Use of Unregistered and Experimental Interventions (MEURI), for experimental interventions carried outside of clinical trials during an emergency and to be guided by specific ethical and scientific criteria, as the expert group felt that the term compassionate use has other meanings.\(^{[22,23]}\) It was suggested that these interventions must be scientifically reviewed and approved by regulatory agencies, including an ethics committee, and informed consent be recorded while acknowledging uncertainty about safety/efficacy, avoiding unfounded expectations, and appropriate monitoring of the outcomes. The WHO laid down seen requirements such as no possibility of clinical trials, no proven intervention, preliminary evidence of efficacy, as well as safety, approvals from relevant authorities, e.g., ethics committees, adequate resources for risk minimization, informed consent, and monitoring with documentation.\(^{[22,23]}\) Recently, the WHO has also come up with a brief guide on off-label use of medicines for COVID-19 as no pharmaceutical product was shown

| Objective | To give access to patients in the absence of any satisfactory alternative therapy | To treat diseases with products approved for other disease indications | Demonstration of efficacy and safety of investigational product for prevention, prophylaxis, or treatment |
| Disease | Serious debilitating or life-threatening or rare disease | Any disease for which drug is not approved | Any disease |
| EC approval | May be required as per country compassionate use regulations | Not required, therapeutic privilege on case-to-case basis unless conducted as a planned study | Required |
| Informed consent | May be required as per country compassionate use regulations | Not required | Required |
| Examples of drug use in COVID-19 | Remdesivir Convalescent plasma | Hydroxychloroquine Azithromycin Lopinavir/ritonavir Some IL-6 inhibitors Dexamethasone | Most of drugs in clinical trial. In India, as per the CTRI following drugs in clinical trial: Hydroxychloroquine Remdesivir Convalescent plasma BCG (for prevention) Ivermectin (prophylaxis) |

CTRI=Clinical Trial Registry of India, IL-6=Interleukin-6, COVID-19=Coronavirus disease 2019

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**Table 1: Drug access via different pathways**

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to be safe and efficacious, and thus, prescription of off-label use by doctors for licensed medicines was suggested in compliance with national laws on an emergency basis outside of clinical trials. It also suggested the need to document results and share them in a timely manner.[24]

**India**

As per the notification to the Draft Amendments in the New Drug and Clinical Trial Rules, 2019, compassionate drug use can be permitted in some special situations for both import and manufacture of limited doses for the management of patients diagnosed with life-threatening disease or disease leading to serious permanent disability in the absence of any satisfactory alternative drug treatment in the country.[2] Any medical officer of a government medical institution can prescribe or import any new unapproved drug for compassionate use, and such drug must be under Phase III clinical trial in India or outside the country. Manufacturer should make an application for the issue of license to manufacture the new drug after getting permission under the rule 96E.[2] The Central Licensing Authority (CLA) has made some changes in new draft to ensure closer monitoring requirements, such as the inspection of manufacturing site of new drug by persons authorized by CLA, requirement to submit quarterly reports on status and stock of unapproved new drugs imported, utilized, destroyed, or supplied to authorized patient from hospitals as well as manufacturers, and extended the eligibility to all hospitals whether in government or private.[5] The National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017 issued by the Indian Council of Medical Research (ICMR) does not have any mention of compassionate use; however, under the section on research during humanitarian emergencies and disasters, certain requirements adopted from the WHO Guidance on MEURI to address the conditions for using unregistered and experimental interventions in emergency with precautions have been stated.[25] It highlights the need for thorough scientific review and ethics review at the national level, oversight by local ethics committee, GMP compliance, rescue medications and supportive treatments, provisions for data sharing, informed consent processes, community engagement, and fair distribution.[25] Important features of compassionate use in different countries are provided in Table 2.[2,4,19,20,21,36,27]

**Examples of Compassionate Drug Use**

The FDA has simplified process by the introduction of an application form that enables physicians to request for drugs for compassionate use.

**Coronavirus disease 2019**

On the basis of preliminary clinical trial findings, the FDA has been given emergency use authorization for remdesivir for the management of patients with severe COVID-19 in adults and children.[28] Remdesivir is a nucleotide analog prodrug which causes the inhibition of viral RNA polymerases and also shows *in vitro* activity against SARS-CoV-2.[15] Recent study showed that there was clinical improvement in 68% of the patients with the administration of remdesivir for 10 days.[15] Recently, the Central Drugs Standard Control Organization also approved remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe COVID disease.[24]

**Ebola virus**

Unapproved drugs such as GS-5734, REGN monoclonal antibody combination Zmapp and mAb114, had been allowed for compassionate use by the Ethics Committee in Africa during Ebola outbreak. Informed consent was obtained from patients with close monitoring of any adverse events.[10,31] Postexposure prophylaxis with rVSV-ZEBOV vaccine was also allowed on a compassionate use basis to persons who come in close contacts with infected patients.[32]

**Henipavirus**

m102.4 (human monoclonal antibody) was allowed for compassionate drug use after it showed protection against virus in animal models.[33] It was given to a small number of individuals exposed to either Hendra virus or Nipah virus.[34] During outbreak of Nipah virus in Kerala, government imported limited m102.4 from the Queensland Department of Health in Australia for the management and postexposure prophylaxis of additional cases with Nipah virus.[35] Results of recent clinical trial showed efficacy with m102.4 in neutralizing virus infection which further supported the decision of administration of m102.4 under compassionate use program.[36]

**Swine flu**

In 2009–2010 “swine flu” outbreak, the FDA allowed use of peramivir in severely ill hospitalized patients with H1N1 influenza.[37,38] In 2010, the CHMP provided opinion on compassionate use of tamiflu and intravenous zanamivir for the treatment of critically ill patients with H1N1 influenza.[39]

**Benefits and Challenges with Compassionate Use**

The most important benefit of compassionate drug use is for the patient to get a chance to receive potentially useful investigational drugs in an emergency situation.
Expanded access to an investigational product provides a treatment alternative to a patient with unmet needs. Compassionate drug use may bridge the time gap between the developmental phase and the final approval of a drug since the data from compassionate use programs demonstrating benefit with investigational drug may lead to increased expanded use of the drug. Efficacy and safety data can be collected from patients treated with compassionate use which may aid the manufacturer by accelerating approval of treatment drug.

The chances of therapeutic advantage from early-stage experimental trials may be <10%, and informational dissymmetry can make the patients vulnerable. Unknown safety profile for the drug, financial limitations in manufacturing as well as providing the drug precommercially, drug availability, and administrative burdens are some of challenges with compassionate use of drug. Allocation of scarce resources may further involve ethical challenges in ensuring fair access to such compassionate use programs.

Since compassionate use would usually be only permitted in patients suffering from advanced or life-threatening disease, evaluation of drug in terms of efficacy and safety may be doubtful. It may also be argued whether not giving compassionate drug/product would itself be called unethical and would be depriving a chance to save the life. Compassionate use can however lead to difficulty in conducting clinical trials in the future for said drug as facilitation of expanded use of drug to large patients making requests can deplete supply of drugs for clinical research. Moreover, this may also discourage physicians as well as patients to participate in clinical research, thereby slowing the clinical trial process. Very few patients may want to opt to be placed in the placebo arm in a randomized controlled trial, and it further becomes very difficult to study the efficacy and safety of experimental arm without placebo group. The following examples can illustrate drawbacks with compassionate use drugs as follows:

a. Benefits with compassionate drug use are unknown and may be negligible, for instance, compassionate use was approved with peramivir in H1N1 patients, but results of the clinical trial showed disappointing results
b. Although compassionate use of ganciclovir was successful in many patients, yet the FDA rejected application for the approval of ganciclovir because of scarcity of data from clinical trials. It was also difficult to conduct placebo controlled clinical trial in such cases where compassionate use of ganciclovir is already showing benefit in many patients during compassionate use
c. Cost of drug for compassionate use may be a concern, for instance, the high production costs of few drugs (particularly biologic drugs). The FDA permits

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**Table 2: Characteristics of compassionate drug use in India, USA and EU**

| Requirement | India | USA | EU |
|-------------|-------|-----|----|
| Regulation and safety reporting | Draft Amendments to New Drug and Clinical Trial Rules, 2020. (Chapter XI) | Code of federal regulations: 21 CFR 312.305 | Regulation: (EC No. 726/2004 Article 83) for a group of patients and a common EU directive (Directive 2001/83/EC Article 5) for individual patients |
| Drug eligibility | Drug in Phase III Clinical Trials | Expanded use program: No restrictions RTT: Drug must have completed Phase 1 clinical trial | No restrictions |
| Authorization | Drug Controller General of India | Expanded access program: FDA | Individual member states |
| Informed consent | Required | Required | Required in some member states |

RTT=Right to Try, FDA=Food and Drug Administration

**Table 3: Arguments for and against compassionate drug use**

| Arguments in favor of compassionate drug use | Arguments against compassionate drug use |
|---------------------------------------------|------------------------------------------|
| **Principle of autonomy** | **Patients with serious illness, being autonomous, capable to give voluntary informed consent, also have a right to self-preservation of life and health** | **Therapeutic misconception and therapeutic optimism may often compromise clear understanding of risks involved related to unapproved interventions and may compromise the informed consent process** |
| **Principle of beneficence and nonmaleficence** | **Patients with terminal illness are usually expected to health benefits and may have limited relative risk (since the patient is already at risk of death)** | **Can lead to unexpected serious adverse events which can harm patient either physically as well as financially** |
| **Principle of justice** | **Impractical to include all eligible in CT (e.g., long travel distance or strict inclusion criteria). Compassionate drug use can be option for such patients and suitable pathway to get access to investigational products** | **There may be selective preference to request for compassionate drug use, issues related to fairness, very few to get access to compassionate drugs leading to bias** |

CT=Computed tomography
pharmaceutical companies to charge the prices of manufacturing, shipping, monitoring, and reporting to patients who requested for compassionate use. Charging direct costs can cause negative publicity because these pricing structure will be far less when it will be approved by the FDA.\(^{[41]}\)

**Ethical Aspects**

Compassionate use of the drug is often seen as a therapeutic process, not planned appropriately, and to be administered to patients for the treatment purpose without adequate informed consent or without plan to monitoring adverse events and outcomes. However, any compassionate use may also involve data collection to evaluate the available evidence/justification of drug efficacy as well as safety, risk–benefit ratio, patient selection criteria, physicians’ qualifications, etc., and other aspects as applicable for research.\(^{[45]}\)

**General principles**

Ethics revolves around the principles of autonomy, justice, beneficence, and nonmaleficence and needs to be applied for any use of compassionate products. The principle of autonomy or respect for persons requires one to adequately inform the patient regarding the possibility of little or no benefit and the high probability of harm before seeking voluntary agreement. 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 compassionate use. The principle of nonmaleficence and beneficence ensures best procedures for adequate safety, monitoring, and protection from harm.\(^{[25]}\) Though the right to alleviate intense suffering and right to increase self-preservation would justify the compassionate or expanded use of drug but the chances of success may be small due to inadequate safety as well as efficacy data and therefore, in such situation, the use of compassionate drug may not be justified.\(^{[46,47]}\) Moreover, patients are more vulnerable to significant abuse in the context of compassionate use in some circumstances as there can be conflict of interest of physician to prioritize research of compassionate drug use over clinical care, or there may be commercial interests of drug manufacturers to promote its investigational drug for fast-track approvals which may influence decisions in patient selection.\(^{[41]}\)

Table 3 depicts the main arguments for and against compassionate drug use.\(^{[47]}\)

**Ethics committee review**

Ethics committee review is an oversight mechanism to safeguard and protect interests of participants involved in biomedical health or clinical research. However, the role of ethics committee in reviewing protocols regarding compassionate use is variable and a requirement in only few countries including USA, Spain, and Italy.\(^{[45]}\) Informed consent for compassionate drug use is listed in the regulations drafted in the USA, Canada, and Australia.\(^{[46,48-50]}\) An ethics review at the local level can help safeguard patient rights and minimize risks by suggesting safety precaution, access to emergency supportive treatment, etc. The ICMR recently released National Guidelines for Ethics Committee reviewing biomedical and health research during COVID-19 pandemic.\(^{[51]}\) As per the guidelines, ethics review is required for research in following cases: new study directly related to COVID, ongoing, or new non-COVID research; however, the guidelines do not apply to clinical therapeutic or nonresearch settings. Central regulatory authority will be responsible for conducting the expeditious review process for compassionate use and also ensuring efficacy/safety monitoring processes. Research during emergencies can be reviewed through expedited review/unscheduled full committee virtual or tele/web meetings to observe social distancing norms.\(^{[51]}\)

**Informed consent**

Protection of the patient’s autonomy is an important safeguard against potential abuse of rights, and informed consent helps ensure their right to information, opportunities to discuss, and voluntary decision-making. This is especially important when there is possibility of little or no benefit but high probable harm due to implementation of unapproved interventions on compassionate grounds. Informed consent should be carried out in a manner that is culturally sensitive, in local language and with a focus on ascertaining voluntariness without imparting any undue influence of decision-making.

ICMR guidelines have highlighted the need for utilization of technology to narrate the information associated with a study and to obtain e-informed consent.\(^{[25,51]}\) There may be need to take consent from appropriate legally acceptable/authorized representatives as per need. In cases where such proxy consenting is planned, safeguards are important so that patient wishes are respected and there is adequate documentation of the same. Additional safeguards are needed to protect persons with enhanced vulnerabilities or where voluntary decision-making is doubtful, for example, persons in senior age group, or those with other comorbid conditions, or those in a state of panic or under therapeutic influence or misconception.\(^{[25,51]}\)
Stakeholders
Compassionate use of the drugs involves a number of stakeholders to play their part with defined roles and responsibilities. Not only regulators but also the clinicians, sponsors, ethics committees, involved hospitals/institutions, patient advocacy groups, and others must work together for ensuring that the safety and well-being of the patients receiving compassionate drugs. Adequate attention is needed for upholding their interest, ensuring appropriate monitoring and oversight. The patients need to be protected from any personal or business interests of sponsors or clinicians and receive adequate information for clear understanding and decision-making without any undue pressure. The stakeholders must have in place adequate implementation and monitoring plan for accountability and transparency in procedures.\cite{25,51}

Community engagement and trust
Any plans to implement compassionate use of drugs should be tailored to be sensitive to the needs in the local context. Efforts to be made to adopt methods that can efficiently inform, promote healthy dialog, and improve clear understanding. This requires good communication, using appropriate advocacy tools, and making sure that the relevant decisions are taken in consultation with all, including public at large, and there is timely dissemination of information to the public. These measures are critical in ensuring transparency and thereby building trust and stakeholdership which are important for public acceptability and support. This is especially true for compassionate use as there is higher probability of harm in view of limited scientific evidence, and the use is encouraged through expedited regulatory pathways to save lives in emergency circumstances. In recent times, there is an infodemic related to COVID-19, and it is important to not oversensationalize or make claims regarding unproven benefits of compassionate products but rather to present a balanced perspective without false promises of unknown.\cite{52,53} The role of responsible media to undertake ethical, balanced, and unbiased reporting of facts cannot also be undermined. Further, like any other research study, it would be a good practice to register the compassionate use protocols on a public platform such as the CTRI.\cite{18,51}

Monitoring and collection of data
It is an important obligation to have a robust regulatory framework to guide compassionate use. This may include clear regulatory guidance, defined timelines, mandatory conflict of interest declarations, and processes for adequate oversight to ensure safety and adverse event reporting and its management. There are concerns as accurate recording of data in actual practice may be quite challenging unless the compassionate use is not planned well like a clinical study. There are additional obligations related to maintaining the right balance in collection and sharing of confidential information with authorities, while ensuring transparency, accuracy, safeguarding against unauthorized access, protecting patient identity, and doing all this fairly in a defined timeframe.\cite{52,53}

Payment of compensation, funding, and insurance
Clinical trials governed under the New Drugs and Clinical Trial Rules 2019 have mandates and described the requirements for having insurance policies, reporting of adverse events, medical management, and payment of compensation for related injuries. The role of sponsors and/or the investigators and ethics committee is clearly stated to ascertain the same. For compassionate use of drugs, these requirements are not clear. While there is no proven benefit and it is outside the umbrella of a clinical trial, and the probability of harm to patient is high, ensuring an insurance cover for management of injuries and payments of compensation, though ethically required, would be quite challenging. More clarity is needed on who would bear the cost of interventions/follow-up/costs regarding medical management and compensation as the sponsor may claim inability citing compassionate use on humanitarian grounds. Since compassionate use of the drug may also involve collection of data, like a research study, which would be of use in planning for future clinical trials, there is need for wider discussion with relevant stakeholders to create a framework that would protect the best interests of the patient.\cite{2,10}

Fair allocation, distribution, and priority setting
Mechanisms may be established under guidance of the scientific/regulatory authorities to decide eligibility and fair access.\cite{54} It is widely accepted that healthcare workers or other frontline workers should be given priority to receive treatment or enrolment in research, as they are putting themselves at risk for saving others. This includes not only doctors and nurses but also other frontline workers such as sanitation workers, caregivers, police, or other personnel involved in the delivery of essential services. Many a times, the requests for compassionate use by patients cannot be entertained as there is limited supply of unproven interventions outside of clinical trials. There is need for proper strategy in response to requests for compassionate use; for instance, multicenter committees can be established to take decision of compassionate requests in some countries. In 2015, Compassionate Use Advisory Committee (CompAC) was established to provide recommendations to pharmaceutical companies to provide or not to provide access to drugs. For example, CompAC advised Janssen on requests for compassionate use for daratumumab in the patients with multiple myeloma.\cite{55}
Conclusion

Compassionate drug use is an important regulatory provision that is being proposed as an amendment to the New Drugs and Clinical Trial Rules, 2019 and will facilitate making provisions for unapproved interventions to needy patients in emergency situations and is a welcome step proposed by the drug regulator. There is a huge expectation for it to be useful by providing a pathway to patients having 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 in view of limited safety or efficacy data. Compassionate drug use provisions should be carefully prepared and implemented and never be equated to or considered as a substitute for clinical trial or biomedical research. Creating a regulatory framework to facilitate access of unapproved interventions to the needy patients under a close ethical oversight and monitoring would help ensure safety and well-being of the patients. Having such a system in place would also facilitate collection of required data, which may facilitate future clinical trials. However, there are challenges in ethically implementing compassionate use of the drugs due to limited sound scientific evidence, probability of therapeutic misconception, challenges related to autonomy and that of fairness, possibility of misuse for commercial gains, or being a substitute for clinical trials. In view of this, a clear and robust guidance and regulatory policy on compassionate use of drugs are much needed in India.

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