Compassionate Use

Overview

This module encourages students to think through ethical and social issues surrounding compassionate use of experimental drugs and devices. Although access to drugs before they’re approved by the United States Food and Drug Administration (FDA) is officially called “expanded access,” the more term is “compassionate use.” Students will be exposed to the process of testing and licensing new drugs with the FDA in an effort to understand the motivations for compassionate use and the ethical issues it raises. The module relies on a case-based approach to learning. Three cases are presented, and students will be led in an analysis of the issues presented in the cases.

Contents

1. Introduction to Topic
2. Definitions
3. Case Study: The Effects of Social Media
4. Case Study: When the Drug Fails
5. Case Study: Unequal Access
6. Conclusion
7. References and Additional Resources

Learning Outcomes

1. Learn the basics of compassionate use
2. Understand the motivations and ethical dilemmas behind the development of compassionate use
3. Examine case studies and formulate opinions about the current state of compassionate use
4. Brainstorm possible solutions for the future of compassionate use

Procedures and Activities

This unit uses a student-centered and interactive approach to teaching. Activities are designed to allow for a maximum degree of student participation and collaboration. Each activity is marked as an individual, partner, or group activity, or as a teacher-directed class discussion.

The following terms are used to designate the different types of activities:

- Individual Activity
- Partner Activity
- Group Activity
- Teacher-Directed Class Discussion

1. Introduction to Topic

Teacher-Directed Class Discussion

Suppose you have a disease or illness that can’t be treated. You’re going to get worse. Perhaps you’re even dying. There is no drug available in a pharmacy that can help. Maybe your doctor has already prescribed many medications, and nothing has worked. What’s left to do?

Some patients in this position might learn about a new medication that might help. It’s still being developed, so your doctor can’t just prescribe it to you. But you still may be able to get to try it.

Maybe the drug is being tested on volunteers who are healthy or in patients who have the condition or disease or in animals. These tests are known as “clinical
trials,” a series of studies done to make sure that a new drug is safe, effective, and either equivalent to or better than other already available options. In this case, you might decide to volunteer for one of the clinical trials to try to get the new drug.

If you are unable to enroll in the clinical trial—perhaps you live too far away from where it is being conducted, or the company running the trial doesn’t think you’re suitable for it—you may choose to ask the company to let you use it outside of the clinical trial. This is called “compassionate use” of an investigational—unapproved, experimental, under investigation—medication or treatment. However, the company is not required to say yes to requests for compassionate use. Many drug companies have laid out procedures for compassionate use requests on their websites, and more and more are doing so.

Compassionate use is for patients with serious or life-threatening diseases or conditions who cannot enroll in a trial and have no other treatment options. If you’re sick or dying from an untreatable disease, you could imagine how badly you’d want access to a new drug. But drug companies can say no to requests, and there are many reasons why they may do so. They may not have enough of the drug to spare outside of trials, or they may not have the financial or human resources to run a compassionate use program. Patients who are denied access have turned to social media outlets to find support from well-connected friends who might be able to help by intervening with executives at a company. Sometimes, patients will use social media and news outlets to publicly pressure drug companies into providing the unapproved medication.

In general, the public is in favor of patients who are out of other options gaining access to experimental drugs. However, this method of obtaining unapproved medication often works better for patients who are wealthy, connected, and socially savvy, because they are more likely to have access to better healthcare. The best medical professionals are more likely to be aware of compassionate use and ongoing drug development. For patients to find out about compassionate use, they must have access to someone in the know about what’s in the drug development pipeline or being tested in clinical trials.

Inequitable access is not the only ethical problem raised by compassionate use. Without patients participating in clinical trials, we won’t get the data needed to prove that a new drug is safe and effective. In fact, without people participating in
clinical trials, the FDA won’t have enough data to decide whether to approve a new drug, and unless it’s approved, a drug can’t be sold or prescribed in the US. If fewer people participate in clinical trials, that means it will take longer to conduct those studies, which means it will take longer for the FDA to make a decision. This could cause a delay for future patients to have access to new, potentially lifesaving drugs.

So, what will happen when it becomes easier for patients who otherwise would be enrolling in clinical trials to access the drug in development outside of clinical trials, through compassionate use?

An unapproved drug, device, or treatment can potentially cause more harm than good. It is even possible that you could die prematurely from using an unapproved drug. Even a drug that seems promising in early clinical trials can act differently in sicker patients, which could be the case for many people requesting compassionate use. Perhaps if you are getting sicker every day, and you know that you will probably die anyway, you’d be willing to take the risk. Still, compassionate use is a complex issue that affects not only the patient but also drug companies, the drug development process, and the entire healthcare system. In fact, because nobody knows what diseases or conditions they may someday develop, compassionate use affects us all.

Even if you are healthy now, you may someday need a drug that is still in development.

However, drug development is a long and complex process without a guaranteed positive outcome. As you can see from the chart below, the entire process of drug development—from discovering a medicine to finishing late stage clinical trials—can span many years on average. In some rare cases, the process can last 20 years or more. What’s even more alarming is how unlikely it is that a drug in development will even make it to the market. On average, only 1 in 5,000 new early stage potential drugs successfully make it to pharmacy shelves.
2. Definitions

Teacher-Directed Class Discussion

Compassionate Use
Compassionate use describes the treatment of a seriously ill or terminal patient who has exhausted all possible approved drugs and therapies. These patients seek access to unapproved investigational drugs as a last resort, often accepting the risk that the treatment may not work, or that it may even do more harm than good.

The term compassionate use was designed to make clear that the drug was being administered primarily to help the patient, not to gain data, as in formal clinical trials. However, sometimes data are collected from people who get drugs through compassionate use. Also, drug companies and others do not like the term
compassionate use. After all, if they decline a patient’s request, that makes them seem automatically uncompassionate! However, there may be very good reasons to decline a request. For example, the supply of the drug in development may be so limited that there is already barely enough to go around.

So, there are a variety of other terms for compassionate use. The FDA calls it “expanded access.” Other terms include “early access cohort programs,” “single patient IND,” “single patient requests,” and “emergency IND.” Internationally, compassionate use might be referred to as “named patient program,” “temporary authorization for use,” “special access program/scheme,” and others. A term that is increasingly preferred is “preapproval access,” as it refers to all types of access to an investigational (unapproved) drug outside of a clinical trial.

**FDA Regulations for Compassionate Use**

A patient may seek individual patient expanded access (sometimes called single patient access) to investigational products for the diagnosis, monitoring, or treatment of a serious disease or condition if the following conditions are met.

1. The person’s physician determines that there is no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat the person’s disease or condition, and that the probable risk to the person from the investigational product is not greater than the probable risk from the disease or condition.
2. The FDA determines that there is sufficient evidence of the safety and efficacy of the investigational product to support its use in the particular circumstance.
3. The patient is ineligible for or is otherwise unable to participate in a clinical trial.
4. The FDA determines that providing the investigational product will not interfere with the initiation, conduct, or completion of the clinical investigation to support marketing approval.
5. The sponsor (generally the company developing the investigational product for commercial use) or the clinical investigator submits a clinical protocol (a document that describes the treatment plan for the patient) that is consistent with the FDA’s applicable regulations for INDs or investigational device exemption applications (IDEs), describing the use of the investigational product.
Also under FDA regulations, a sponsor or a physician may submit a protocol intended to provide widespread access to an investigational product. In this scenario, FDA will permit the investigational product to be made available under a “treatment” IND or treatment IDE if certain criteria are met.

**The 21st Century Cures Act**

In 2016, the 21st Century Cures Act, legislation designed to spur innovation in and increase the speed of drug development, was enacted. It requires companies to make public their compassionate use policies and list whom to contact about requests, how long it will take to hear back, and more. Not every company has complied with this requirement, but more and more companies are posting information about their compassionate use policies.

**Project Facilitate**

Project Facilitate is a “concierge” service created by the FDA to help guide oncologists wishing to make expanded access/compassionate use requests for their patients. The program, launched in 2019, includes a call center with staff available to help physicians through every step of the expanded access process.

**Right to Try Laws**

The Right to Try movement began in 2014 as a way to let patients ask a pharmaceutical company for access to an unapproved treatment without FDA approval. The organization that began it believed that the FDA was an obstacle for patients to receive investigational drugs. To be eligible for Right to Try, a person must have a life-threatening disease or condition, a doctor’s prescription, and the treatment requested must have passed Phase 1 safety trials, among other conditions.

In Phase 1 trials, new treatments are first tested on people. In a drug trial, the drug is given to healthy volunteers—not patients—to see how much of the drug can be given before there are unacceptable side effects. So, the point of a Phase 1 Trial is to determine a safe dosage, and this dosage is used in later trials on patients to determine whether a drug is effective at a safe dose. This means that with Right to Try, people may request access to drugs that have not yet been tested to see if they work on the disease. (Some medications, like cancer drugs, are only administered to patients with cancer in Phase 1 trials, as it would be too dangerous to use these treatments on healthy volunteers.)
Right to Try laws were designed to limit the role of the FDA, suggesting that the agency approval process is restrictive and has slowed the process of drug development. However, the track record of the FDA has been to approve over 99% of applications, and in recent years the agency has developed new guidelines and procedures to streamline the process, speed up decisions, and improve potential access.

Right to Try laws may sound like the patient has a right to get access to the desired drug or device in development. However, they do not obligate anyone to provide treatment, provide any payment for treatment, or require a patient’s insurer to pay for/provide any resources for travel, lodging, or other logistics necessary for treatment. Even the term “Right to Try” may be misleading, since there is no “right” associated with these laws to guarantee access, without the approval of the drug company.

The first Right to Try law was passed in Colorado in May of 2014, and, as of November 2021, 41 states have enacted laws. These laws are sometimes called “Dallas Buyers Club” laws, after a movie with that name. (The movie was based on real, historical events related to a case on AIDS drugs, but is not entirely factual.)

In May 2018, the federal Right to Try Act of 2017 was enacted, making Right to Try the law of the land. Still, only a handful of patients are known to have received drugs through Right to Try, as companies still appear to prefer the FDA’s programs.

Opening Discussion Questions
1. In compassionate use cases, what role should the FDA play? What about patients and families? Physicians and medical professionals? Drug companies?
2. Who should decide what wins the balance between the risks and benefits of a medicine? Why?
3. What is more important: giving compassionate Use to a sick or dying individual, or streamlining drug development for every patient to have access? Can we find the balance between individual and societal rights?

3. Case Study: The Effects of Social Media
Teacher-Directed Class Discussion

1. How do you think social media affects compassionate use cases?
2. If you were seeking compassionate use, would you utilize social media? If so, why and how? If not, why would you refrain?

Case Study: Josh Hardy
Josh Hardy was a 7-year-old boy who suffered from a life-threatening virus in 2014. His virus was an adenovirus, a common virus that is not very harmful to healthy people but can be fatal to those who are sick. Josh was quite sick; because he had been diagnosed with cancer as a young child, he’d been exposed to many powerful drugs and treatments, which caused their own problems for his body.

Josh had been treated with an antiviral agent called Vistide but, unfortunately, had to stop treatment because the medication was destroying his kidneys.

His physicians had heard of an experimental antiviral drug called brincidofovir, being developed by a company called Chimerix for the treatment of several different viral infections. Josh’s physicians requested that Chimerix provide Josh with access to brincidofovir, but the company had planned to focus solely on the completion of the drug’s Phase 3 clinical trials. These are the trials in which a drug’s safety and efficacy is more formally proven in larger clinical trials, providing data that the FDA can use to decide whether to approve a drug for marketing.

Chimerix was a small company without a lot of people or money, and it had decided earlier that it didn’t have the capability to run Phase 3 trials (which are expensive and involve a lot of work) and provide compassionate use at the same time. For compassionate use, there is paperwork to be filled out and the company not only has to provide the drug, but possibly teach the doctors how to use it. Also, the company needs to stay in touch to see if there are side effects, which must be recorded and reported to the FDA.

Here, we arrive at a moral dilemma: Should Chimerix endanger its ongoing clinical trials and drug development stages for brincidofovir to make an exception for the life of a 7-year-old?
When Chimerix decided to protect the process of drug development for brincidofovir, denying Josh access to the treatment, his mother took to social media, posting a letter to her Facebook page. She asked if anybody had connections to Chimerix and could possibly help in persuading the company to give the drug to Josh.

Seemingly overnight, Josh Hardy’s story blew up on social media and in the news. There was a massive public outcry against Chimerix. The CEO was contacted by state and national politicians, and even received some death threats.

The company tried to explain the grounds for its decision. It also pointed to another ethical problem: Before Josh, some 300 patients had requested access to brincidofovir and been denied. Was Josh different from all these other people, or, if Chimerix gave Josh the drug, would they also have to give it to everyone else who had asked? If so, who would pay for this expensive program? (The company normally can’t charge patients, because it’s illegal to sell a drug before FDA approval; however, some compassionate use programs make the drugs available at the company’s costs without any profit.)

On March 11, 2014, Chimerix worked with the FDA to open a 20 patient clinical trial that would include Josh Hardy. Josh received brincidofovir on March 12, and left the hospital on March 25, nearly virus-free. Sadly, Josh died from cancer a couple of years later.

The following discussion questions are appropriate for a teacher-directed classroom activity, or as group activity. Students could also be asked to write a response or argumentative essay in response to any one of these questions. Why do you think Chimerix initially denied Josh Hardy’s request for brincidofovir? Was it wrong for the company to want to focus on getting the drug approved for everyone? How could Chimerix have better handled the situation?

1. Was it wrong for Josh Hardy’s mother to take to social media? Why do you think her efforts were so effective? Do you think anyone could have solicited such a public outcry in an effort to receive compassionate use?
2. It is clear that the general public wants to rescue patients like Josh Hardy from their afflictions and help them circumvent the strict regulations of drug companies like Chimerix. Is there a better way to help patients like Josh,
while allowing pharmaceutical companies to focus on important clinical trials?

3. What do you need to launch a successful social media campaign for compassionate use? What kinds of people wouldn’t be able to do this?

4. Case Study: When the Drug Fails

Teacher-Directed Class Discussion

1. How could a compassionate use treatment impact ongoing clinical trials and drug development?

Case Study: Thomas Eric Duncan
In September 2014, Chimerix provided a man named Thomas Eric Duncan with the same experimental antiviral drug that had successfully treated Josh Hardy. Duncan was suffering from a viral infection with no known cure. This particular viral infection gained an immense amount of media attention: Duncan had contracted Ebola.

Because there were no standard treatments for patients with Ebola, Duncan gained access to brincidofovir through compassionate use. Unfortunately, Duncan did not survive. He was the first person to die in the United States from Ebola.

It is unclear whether Duncan was too ill to have benefited from the drug, or if brincidofovir had contributed to Duncan’s death in any way. Regardless, the story of Duncan’s death circulated rapidly across the country, and the public responded. Chimerix’s stock price increased after the announcement that Duncan would receive brincidofovir and decreased after the announcement of his death.

Compassionate use is often potentially problematic for companies; a bad result in the area for which the company is seeking approval would have to be reported and explained to the FDA, which could make the FDA less willing to approve the drug. For example, if Josh Hardy had died, Chimerix would have had to explain why its drug for adenovirus didn’t work on a patient with adenovirus. However, Chimerix had not been looking to develop brincidofovir for Ebola. Because adenovirus and Ebola have some similarities, it seemed to doctors that
brincidofovir might work on Ebola as it worked for adenovirus. However, if the drug did not work on Ebola, this negative finding would not be a problem when Chimerix went to the FDA to try to get brincidofovir approved, as it was seeking approval for brincidofovir as a treatment for adenovirus, not for Ebola. So, in this case, the stakes were lower for Chimerix than for many companies grappling with compassionate use requests. (Remember, those seeking compassionate use are usually quite sick, and thus more likely to have bad outcomes.)

Group Activity

1. What are the risks of a small biotech company providing an experimental treatment through compassionate use? Conversely, what could biotech companies gain in providing experimental treatment through compassionate use?
2. Should Thomas Eric Duncan have received brincidofovir, even though he may have already been too ill to survive? Why or why not?
3. How can we alter our expectations for experimental treatments through compassionate use, so as to protect ongoing drug development?
4. Why was Chimerix initially unwilling to give brincidofovir to Josh for his adenovirus, but surrendered the drug to Thomas Eric Duncan? (Answer: Ebola is a highly contagious virus that had no known treatment and frequently caused death. So, Thomas Eric Duncan’s situation was a public health emergency while Josh’s was simply a personal tragedy. If adenovirus had spread from Josh, it likely would not have made anyone very ill, unless they were already quite sick.)

5. Case Study: Unequal Access

Teacher-Directed Class Discussion

1. What are some factors that could prevent equal access to compassionate use?

Case Study: The Ebola Epidemic
Although it originated in West Africa, the 2014 Ebola epidemic ignited a climate of global panic. There are no approved treatments for the contagious virus. Ebola spread like wildfire throughout West African countries, killing more than 11,000 people.
Meanwhile, Mapp Biopharmaceutical Inc. was in the process of developing a possible treatment for Ebola called ZMapp. ZMapp had never been tested in humans and was not a promising solution for ending the Ebola epidemic. It could not have been produced and distributed in large quantities within the time constraints dictated by such a global emergency. However, ZMapp had been administered to two American aid workers and a 75-year-old Roman Catholic priest from Spain before the supply ran out.

Unfortunately, five days after he was evacuated from Liberia, the priest, Miguel Pajares, died. However, his death cannot be attributed to his treatment with ZMapp, because he was already terminally ill with Ebola when he received the medication.

The fact that this experimental drug was administered to non-Africans was widely perceived as racist and unjust. In response, others pointed out that if the drug was given to Africans and not to Americans or Europeans, it may have been seen as experimenting upon Africans, a troubling situation that has happened in the past, such as in the case of the early history of HIV/AIDS drug development.

The Americans had requested access to ZMapp before West African nations, which could have explained why they were initially the sole recipients of this experimental treatment. However, it is puzzling that a 75-year-old would be granted this extremely rare treatment; elderly immune systems are much less likely to have the capacity to fight such an aggressive viral infection, with or without medication. Furthermore, it is difficult to monitor the effects of an experimental drug when the patient has an already weak immune system and may not be alive for long enough to track the drug’s long-term impact.

**Group Activity**

1. Why do you think West African countries were less aware of ZMapp as a possible treatment? Why do you think a 75-year-old Roman Catholic priest had precedence in receiving ZMapp? Should the elderly be discriminated against in the case of compassionate use?
2. ZMapp did not have the potential to end the Ebola epidemic; does this justify
the fact that no West African nations received ZMapp?
3. How can pharmaceutical companies, government officials, and relief organizations work together to create more equity for compassionate use cases?
4. If quantities of a compassionate use drug are extremely limited, what should be done?

6. Conclusion

Individual Activity

1. List the benefits of compassionate use.
2. List the drawbacks of compassionate use.
3. Discuss the costs and benefits of the current state of compassionate use, drawing from the definitions and case studies.

Teacher-Directed Class Discussion

1. Should there be compassionate use? Why or why not?
2. In what ways can we improve compassionate use? Are there underlying ethical issues that cannot be solved?

7. References and Additional Resources


Caplan Arthur, Moch K. Rescue me: the challenge of compassionate use in the


U.S. Food and Drug Administration. Learn about Expanded Access and Other Treatment Options. [http://www.fda.gov/ForPatients/Other/](http://www.fda.gov/ForPatients/Other/). Accessed 8 Dec 2021

Acknowledgments
This module was prepared by Samantha Scheer with support from Arthur Caplan and Alison Bateman-House of the Division of Medical Ethics, and Carolyn Neuhaus, formerly of the Division of Medical Ethics and currently at the Hastings Center. Maya Grunschlag and Lisa Kearns updated the content in July 2021.