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POINT OF VIEW

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Ethical crossroads: expanded access, patient advocacy, and the #SaveJosh social media campaign

Kenneth I. Moch

Cognition Therapeutics, Inc., Pittsburgh, Pennsylvania - USA

ABSTRACT

Expanded access programs raise complex ethical dilemmas regarding the use of experimental medicines to treat life-threatening medical conditions – issues for which there are no simple, monolithic solutions. Beyond the risks to an individual, how does society or a company balance the immediate needs of a critically ill individual versus the potential needs of many future patients? This article offers insights into and learning experiences from the case of a 7-year-old boy whose family sought access to an experimental antiviral medicine being developed by Chimerix, where the author was Chief Executive Officer. The high-profile #SaveJosh social media campaign helped to catalyze and crystalize the international debate on issues of ethics and equity in expanded access, raising questions regarding the role of patient advocacy and the impact of social media on healthcare and the biopharmaceutical industry. Additionally, the #SaveJosh campaign demonstrated how easily thoughtful dialogue can be overwhelmed by a hyper-immediacy that increases the intensity and scrutiny under which these issues must be addressed. Given that the decision to grant an expanded access request lies solely with the leadership of the company developing the experimental medicine, management must evaluate and balance a request against what is known about the safety and efficacy of the compound, where it is in its testing pathway, and any other complexities or risks identified during the development process. Furthermore, companies must craft and be prepared to explain their rationale, including the right not to make an experimental medicine available, to regulators, legislators, patient advocates, and patients in need.

Keywords: #SaveJosh, Bioethics, Compassionate use, Expanded access, Social media, Patient advocacy

Introduction

The past 40 years have seen the creation of the modern "biotechnology industry," overwhelmingly comprised of fledgling companies that must navigate complex scientific, clinical, and financial challenges while maintaining their clarity of mission: developing new medicines to hopefully save lives and/or improve the quality of life of future patients in need (1). During this same period, there has been a revolution in patient awareness, education, and advocacy, clearly spurred on by the development of new communications technologies, which have given rise to immediate access to medical information as well as to large and active social media networks (2, 3).

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Corresponding author:
Kenneth I. Moch
President & CEO
Cognition Therapeutics, Inc.
2403 Sidney Street, Suite 261
Pittsburgh, 15203, PA, USA
kenneth.moch@gmail.com

Increasingly, the objectives and clinical trial practices of companies pursing the development of new medicines are intersecting and conflicting with the interests and activities of patient advocates and patients who are the potential beneficiaries of these experimental medicines – perhaps nowhere more clearly than in the issue of expanded access, often referred to as compassionate use (4, 5). This intersection sets the lengthy and complex process of developing new medicines for future patients in conflict with the immediate needs of current patients. For me and for others in leadership positions in biotechnology companies, the questions raised by this conflict can be trajectory altering for our experimental medicines: Whose life should we focus on saving? How should these decisions be made? Who should make these decisions?

In the era of social media, where people can express their opinions and interact with others in real-time, the ethical issues created by these situations are complicated by a hyper-immediacy that increases the intensity and scrutiny under which these issues must be addressed. Some will argue that the moment that you can save a life, no matter where your experimental medicine is in its development pathway, you must save that specific life. Others will argue that you must do whatever you can to secure regulatory approval for the new medicine in order to save the largest number of people.

This article is based on my experiences as the Chief Executive Officer (CEO) of a small biotechnology company, Chimerix,

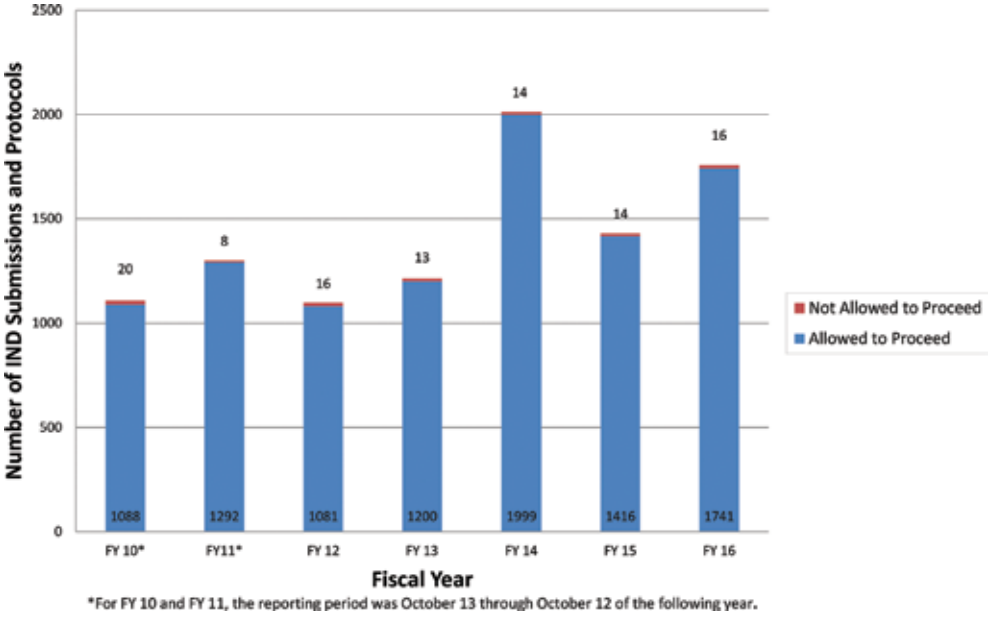

Fig. 1 - CBER and CDER Expanded Access IND Submissions and Protocols FY 2010-2016. https://www.fda.gov/downloads/News-Events/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm547754.pdf.

which was faced with a social media uproar arising from the desire of the family of a 7-year-old cancer patient, Josh Hardy, to receive an experimental medicine to treat his life-threatening viral infection. While there had been many other requests for experimental medicines in prior years (6), both by individuals and their families, and by activist groups as occurred during the early days of the AIDS epidemic, the social media efforts associated with the Hardy family's request exploded into a global campaign that has altered the way that biotechnology and pharmaceutical companies, as well as regulatory authorities, view "expanded access." Additionally, it has served as one of the underpinning arguments for the Right-to-Try laws that have been adopted throughout the USA and are currently under consideration by the U.S. Congress.

The framework: FDA and expanded access

Requests for compassionate use of unapproved drugs are not isolated events. This has been ongoing for many years, mostly through private medical channels, but increasingly it is being done in more public settings (7).

The U.S. Food and Drug Administration (FDA) has guidelines on its website for what it calls "expanded access," under which an unapproved medicine is made available to an individual with a serious or immediately life-threatening disease. In 2014, when the Hardy family sought expanded access for Josh, the FDA website stated that "Expanded access, sometimes called 'compassionate use,' is the use of an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options. … [T]he drug manufacturer and the patient's doctor must make special arrangements to obtain the drug for the patient. These arrangements must be authorized by the FDA. These safeguards are in place to avoid exposing patients to unnecessary risks (8)."

The FDA website at that time further stated that

"a patient may seek individual patient expanded access to investigational products for the diagnosis, monitoring, or treatment of a serious disease or condition if the following conditions are met.

- The patient and a licensed physician are both willing to participate.
- The patient's physician determines that there is no comparable or satisfactory therapy available to diagnose, monitor, or treat the patient's disease or condition.
- That the probable risk to the person from the investigational product is not greater than the probable risk from the disease or condition.
- FDA determines that there is sufficient evidence of the safety and effectiveness of the investigational product to support its use in the particular circumstance;
- FDA determines that providing the investigational product will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval;
- The sponsor (generally the company developing the investigational product for commercial use) or the clinical investigator (or the patient's physician in the case of a single patient expanded access request) submits a clinical protocol (a document that describes the treatment plan for the patient) that is consistent with FDA's statute and applicable regulations for investigational new drugs (IND) or investigational device exemption applications (IDEs), describing the use of the investigational product; and
- The patient is unable to obtain the investigational drug under another IND or to participate in a clinical trial (9)."

According to Richard Klein, formerly the Director of FDA's Patient Liaison Program, the FDA's role is to provide a "mechanism" for expanded access (10). Indeed, the FDA approves over 99% of the requests it receives for expanded access. From 2009 to 2013, prior to the Josh Hardy event, the FDA approved 4,017 expanded access requests, both individual

patients and larger expanded access protocols, and denied 24. In 2014, the FDA approved approximately 2,000 more requests. While the number of IND submissions and protocol requests declined in 2015 and 2016, the approval rate remained at a similar percentage (Fig. 1).

Given that the FDA only processes an expanded access request when it has been received from the drug's sponsor – almost always a company that is developing the experimental medicine – these approval percentages clearly illustrate that the decision as to whether or not to grant a compassionate use request falls to the leadership of the company developing the new medicine, not the FDA.

Chimerix, brincidofovir, and expanded access

Chimerix, Inc., was founded in 2000 to develop an oral form of a potent intravenously administered antiviral drug as a potential medical countermeasure against smallpox. The parent molecule, cidofovir, has a "black box" warning due to significant nephrotoxicity; the hope was that the lipid-modified version, ultimately called brincidofovir, would be equally as potent, but would avoid this dose-limiting side effect and, as an oral drug, would be more readily useable in the event of a smallpox emergency.

At the time that I joined Chimerix in June 2009, the company was beginning to expand its development program to look at the potential for brincidofovir to treat other viruses within the double-stranded DNA viral family, including herpes viruses, such as cytomegalovirus, papilloma viruses, polyoma viruses, and adenovirus. Soon thereafter, the decision was made to focus the company's clinical development efforts on the potential use of brincidofovir to prevent the reactivation of cytomegalovirus in stem cell transplant recipients, a pathological event that was known to significantly increase posttransplant mortality. While Chimerix continued to pursue brincidofovir as a potential medical countermeasure against smallpox, the intent was to do so only with government funding.

The first compassionate use of brincidofovir occurred in March 2009, when Chimerix provided brincidofovir to help save a soldier who, after receiving a smallpox vaccination, had a life-threatening breakout of the vaccinia pox virus. From this single event and the subsequent publication by the Center for Disease Control in May 2009, interest in and requests for brincidofovir grew through word of mouth within the medical community, and led to a significant expanded access program by Chimerix (11). Starting in September 2009, approximately 50 individual requests for brincidofovir were received over a 9-month period, increasing to approximately 50 requests over the next 3-month period. Because of this, the FDA asked Chimerix to establish a formal "intermediate size" expanded access program that would be listed on clinicaltrials.gov (12). The enrolment criteria included patients with serious or immediately life-threatening diseases or conditions caused by cytomegalovirus, adenovirus, herpes simplex virus, and 3 different pox viruses.

In February 2011, Chimerix received an $88.1 million contract from the Biomedical Advanced Research and Development Authority (BARDA) – a portion of which was designated to pay for the 200-patient clinicaltrials.gov expanded access protocol in order to gain insights into emergency situations that were closely analogous to a potential smallpox outbreak. In late 2012, when funding under the BARDA program ended, Chimerix notified the clinician/investigator community that it was ending this expanded access program in order to focus its resources on the formal regulatory approval process for brincidofovir. At this time, Chimerix was still a private company.

In total, brincidofovir was provided via expanded access to approximately 430 patients (215 individual patient requests plus 215 under the BARDA funded clinicaltrials.gov program) to treat many different dsDNA viruses. During 2013 and into 2014, after the cessation of the brincidofovir expanded access program, more than 300 additional requests were received, covering the spectrum of dsDNA viruses, except pox viruses, and including approximately 80 requests for individuals with adenovirus infections. Under the announced and stated response protocol, all of these requests were denied by the Chimerix Medical Department. There were a number of direct pleas to Chimerix leadership from friends, politicians, and other public figures to make exceptions and provide brincidofovir on a "one-off basis," but as a matter of policy, no exceptions were made to the expanded access program termination decision. The total number of denied requests was lower than the overall interest in brincidofovir because most major transplant centers ceased requesting brincidofovir when they accepted that the expanded access program was no longer open.

Chimerix completed its initial public stock offering in April 2013 – the proceeds of which were primarily used to initiate in September 2013 the Phase 3 SUPPRESS trial of brincidofovir for the prevention of cytomegalovirus reactivation in adult stem cell transplant recipients. Also in September 2013, Chimerix announced the results of a 48-subject study of brincidofovir to treat early adenovirus infections in stem cell transplant recipients, which provided initial insights into the use of brincidofovir for this patient population. Although statistical significance was not achieved, the study demonstrated numerical benefit of brincidofovir in virologic response, treatment failures, and mortality (13).

As of March 2014, Chimerix had 55 employees. At that time, the public filings by Chimerix stated that "Brincidofovir is a new investigational medicine currently being studied in the US in a Phase 3 clinical trial. The ongoing Phase 3 trial, called SUPPRESS, is being performed to evaluate the safety and efficacy of brincidofovir for the prevention of cytomegalovirus in adult patients undergoing allogeneic stem cell transplant. Brincidofovir has the potential to be the first broad-spectrum antiviral for the prevention and treatment of clinically significant infections and diseases caused by DNA viruses. It has shown broad-spectrum antiviral activity against all 5 families of DNA viruses that affect humans, including cytomegalovirus, adenovirus, BK virus and herpes simplex viruses. Brincidofovir has shown a favorable safety and tolerability profile, with no evidence of kidney or bone marrow toxicity in nearly 900 patients dosed to date, including the compassionate use of brincidofovir in over 400 patients with a range of DNA viral infections" (14).

The child in need: Josh Hardy

Seven-year-old Josh Hardy was diagnosed at the age of 9 months with a malignant, highly aggressive, and rare form

of kidney cancer (15). He subsequently survived 3 other bouts of cancer but, as a result of the treatments he had earlier in his life, in November 2013 a bone marrow biopsy revealed that he had bone marrow failure. On January 10, 2014, he received a bone marrow transplant at St. Jude Children's Hospital in Memphis, Tennessee. While he'd had heart and kidney issues before, the transplant caused further complications. Several days after the bone marrow transplant, he was moved to the intensive care unit (ICU) for heart failure, and 5 days later he was put on a ventilator. He then developed an adenovirus infection as a result of his compromised immune system. In healthy adults an adenovirus infection may be as simple as a common cold, but it can be life-threatening in immunocompromised children. As a result, Josh's doctors, who had previously participated in the Phase 2 clinical trial exploring the activity of brincidofovir against adenovirus, recommended that he receive brincidofovir under expanded access.

On February 12, 2014, doctors at St. Jude requested that Chimerix provide brincidofovir for Josh Hardy. Consistent with Chimerix's decision to focus its full resources on enrolling patients in, and as rapidly as possible completing, the ongoing Phase 3 SUPPRESS clinical trial, this request, like the hundreds before it, was denied by the Chimerix Medical Department.

On March 5, 2014, after Josh developed renal failure, the St. Jude Vice President of Clinical Trials Administration sent a letter to Chimerix containing a second request for brincidofovir, stating that "it is likely that after having fought against childhood cancer for so long, he may succumb to this infection without a non-nephrotoxic medication with superior efficacy proven in clinical trials." In line with the stated policy, this second request was also denied (16, 17).

The ethical crossroads in expanded access

It is at this moment that the process of developing new medicines intersects with the expanding world of patient advocacy and social media. The overarching and very personal question is: if Josh Hardy were your child, what would you do? And if you were CEO of the company involved, how would you respond?

Reflecting back a year after the events that occurred over the subsequent 5 days, from March 6 to March 11, 2014, I asked the following questions in an article that I wrote for The Wall Street Journal (18):

- "Should pressure from social media or special connections play a role in whether a patient receives an experimental medicine?
- Should a company avoid any risks to a development program in order to help a larger number of patients in future years?
- If there are a limited number of doses available, how should a company choose which patients receive the medication?
- What if a critically ill patient gets worse or dies for reasons unrelated to the experimental drug, but because of an ensuing uproar other patients decline to participate in clinical trials?
- Who is advocating for future patients who, because of slower clinical-trial enrollment or unexpected events, might not receive a needed medicine because FDA approval is derailed or delayed by even a month?"

At the time that Chimerix was faced with these questions, very little had been written and was easily accessible to provide support and guidance to corporate leaders who were trying to make decisions about expanded access, especially with immediacy and under intense external pressure. Thus, I relied on my own expanded access experiences from prior companies, on several Chimerix colleagues, and on a number of industry leaders who had relevant experience in expanded access and crisis management. Additionally, I consulted the "Statement of Ethical Principles on Early Access Programs" that had been published in 2010 by the Biotechnology Innovation Organization's (BIO) Standing Committee on Bioethics (19). There are four principles in BIO's "Statement on Ethical Principles," and portions of two of these principles provided the most significant guidance during the social media campaign:

- "A patient's right to treatment based on his or her autonomous decision-making ability does not supersede a company's ethical responsibility to develop and market safe and effective products as fast as possible. From this perspective, the question often confronting companies is whether to put an entire project at risk and therefore jeopardize availability of a drug for a larger patient population – in order to provide early access to a product for an individual or small group of patients."
- "If a company makes unapproved products available outside of a clinical trial, it must ensure equity in distribution. If a company decides to make an unapproved product available, it must consider the process for determining which patients should have access to it. For example, certain patients may have an advantage over others because they know about early access programs, have hired outside counsel, or are particularly knowledgeable about research activities for a particular disease. None of these establish that patient as 'more deserving' of early access to a product than others. Therefore, a company needs to create appropriate inclusion/exclusion criteria for its early access program. These criteria should, to the greatest extent possible, ensure equity in availability and distribution of the product available under the early access program. If no such criteria can be developed, the company should reconsider whether to establish the program."

I believe that these are all thoughtful questions and positions, worthy of significant and lengthy debate. However, in the era of social media, such ethical questions can be swamped by the immediate statements and demands of a social media "whirlwind." So it was with the #SaveJosh social media campaign.

The social media campaign begins

On Thursday night, March 6, Josh's mother Aimee Hardy wrote the following post on her Facebook page:

"Our son, Josh Hardy, who recently had a bone marrow transplant has developed the adenovirus. This [is] a deadly

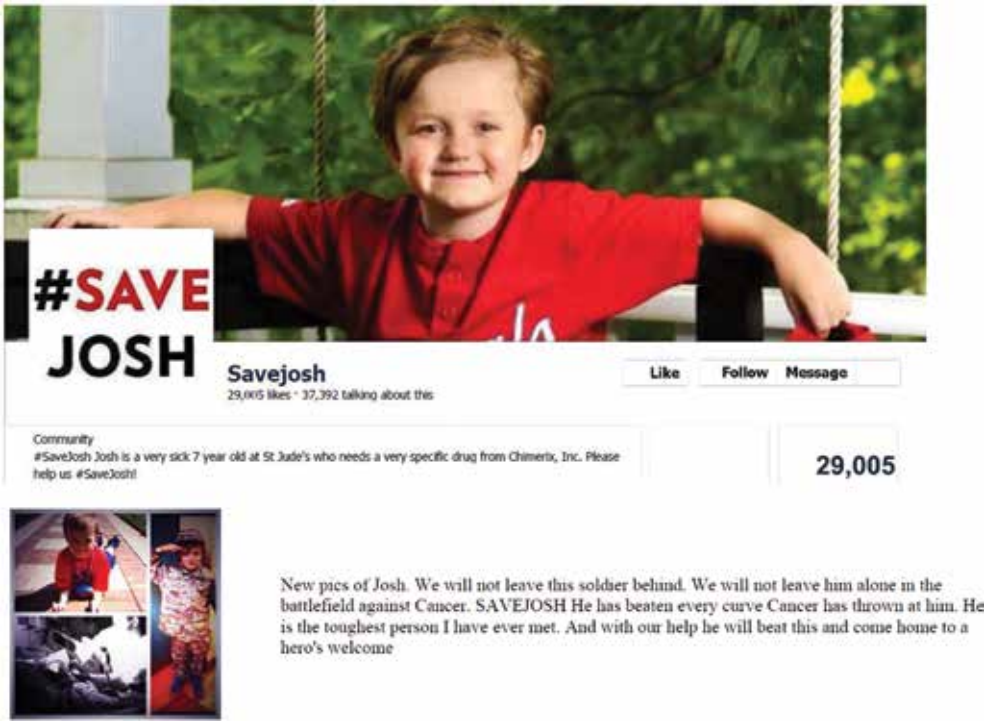

Fig. 2 - Excerpt from the #SaveJosh Campaign.

virus for people who have weak immune system[s]. There is a drug called brincidofovir that has been proven to treat the adenovirus effectively. Our doctor at St. Jude told us they ran the study for the drug company and he knows it will work. However, the drug company has refused to release the drug for compassionate care because they are trying to take it to market. Basically they are not going to save a child's life for money. The company is Chimerix Inc. out of Durham, NC. And the main contact is Dr. Herve Mommeja-Marin. And the drug is called brincidofovir. The child that absolutely needs it to save his life is Josh Hardy. He is currently in the ICU at St. Jude Children's Research Hospital. If anyone with influence can help us convince the Chimerix Inc. to release the drug for compassionate care for our son, we would be forever grateful. The phone # of Chimerix Inc. is 919-806-1074 and the email is compassionateuserequest@chimerix.com" (20).

Mrs. Hardy also posted her plea for help on Caringbridge, a website designed to allow people to share health issues and "to rally support for a loved one during a health journey":

"We are asking everyone to think of any U.S. representatives they might know or pharmaceutical connections that might help us. If anything, if 500 people or so just called Chimerix and told them they should send the brincidofovir to Josh Hardy at St. Jude's, it might be helpful" (21).

Overnight, and into the morning of March 7, Josh Hardy's uncle created a Facebook page and Twitter campaign called "#SaveJosh" (Fig. 2). His first post on the Facebook page was the letter from the St. Jude Vice President to Chimerix containing the second request for brincidofovir.

By midday on Friday, March 7, Chimerix employees and Board members had already received hundreds of phone calls and emails in support of Josh (15). This included emails from friends of Chimerix employees and Chimerix investors, as well as calls from politicians including a United States Congressman and the Speaker of the Virginia House of Delegates. During the day, Chimerix released a statement to all interested parties that stated, in part, the following:

"It is situations like these that drive all of us at Chimerix to move as quickly as we can to complete the development of brincidofovir. Chimerix is a small biopharmaceutical company founded 14 years ago specifically to develop brincidofovir. This is our only potential product. We now have just over 50 employees, and we are committed to the discovery and development of new, oral, antiviral therapies in areas of high unmet medical need.

Five years ago, early in brincidofovir's clinical development pathway, Chimerix began receiving requests from physicians for the emergency use of brincidofovir, in patients with many different viral infections, and we were able to supply brincidofovir for relatively small numbers of these requests.

As our small company progressed to larger and more complex efficacy and safety trials designed to gain FDA approval of brincidofovir, we made the difficult decision two years ago to cease our Compassionate Use program and focus on earning FDA approval. This is the only path to making brincidofovir widely available to those who need it in the fastest manner allowed.

Our limited resources are dedicated to successfully completing the SUPPRESS trial and submitting the safety and

> efficacy data that would allow for brincidofovir to become available to physicians and patients in the USA and, ultimately, around the globe. Each one of us at Chimerix is committed to achieving this goal and thereby enabling access to this potentially life-saving drug" (22).

On March 8, based on the efforts of a number of pediatric cancer advocates, including Richard Plotkin, the chairman of the MaxCure Foundation, Chimerix was contacted by local and national network television reporters who stated an intention to cover the story. Mr. Plotkin would later state that "I decided I was going to get this kid the drug or I'd destroy Chimerix and Ken Moch" (23).

On Sunday night, March 9, CNN ran an 8-minute segment on Josh Hardy and the family's request for brincidofovir (24). As part of her introduction, CNN Anchor Deborah Feyerick stated,

> "The company that manufactures this drug is expressing regret, but it says because of limited resources and a push to get FDA approval, it cannot provide the drug to Josh. His parents say this drug is the only thing that will save their son's life. They are begging the company to reconsider. […] incredible to think that a drug company has something to help and won't give it out."

During the segment itself, Elizabeth Cohen, CNN Senior Medical Correspondent added,

> "It just breaks your heart to say he is in heart failure and he is in kidney failure. Now, I know you think – all of us think, why can't they just give this little boy this drug? It's something called compassionate use. When a drug is being studied, a company can give it out."

Mrs. Hardy was interviewed during the Sunday night CNN segment during which she stated that, "It's unimaginable that they have what we need and they won't give it to us." After being read an excerpt of the Chimerix statement above, she stated the following: "There is no good excuse for us. There is nothing that they can say that will keep us from asking…none of that matters to me, what their excuses are."

Further inciting the social media community was the on-air statement by CNN reporter Elizabeth Cohen that the cost of a compassionate use patient was $50,000, derived by dividing the amount of BARDA funding by the number of patients treated. This was in response to the statement that Chimerix did not have the "human and financial resources" to focus on compassionate use and was instead focusing on the SUPPRESS clinical development program. When Chimerix responded that the monetary consideration was not the issue, Fox carried the headline: "Charity offers to pay for 7-year-old's lifesaving treatment; drug maker still refuses," ignoring the ethical considerations raised by the Company.

In an interview on Fox & Friends on Monday, March 10, Mrs. Hardy stated "To me it's almost a crime not to make it available to everyone who needs it and I definitely am going to keep fighting for my son until they give it" (25). Additionally, print media around the world covered the story of Josh Hardy (Fig. 3A). CNN's print headline was "Company denies drug to dying child." Fox News carried the headline "Company Denies Drug to 7-Year-Old Boy Struggling Against Curable Virus," (25) ignoring the fact that brincidofovir was still in the experimental phase and thus the ability to "cure" an adenovirus infection was unproven. In response to the statement that, based on having turned down hundreds of prior requests, the complexities of the situation were such that Chimerix considered the ethical dilemma to be "yes to all or no to all" expanded access requests, Mr. Plotkin went on Fox & Friends to implore the Board of Chimerix to order management to provide brincidofovir to Josh (26).

On Monday March 10, the #SaveJosh campaign trended in the top 5 on Twitter, based in part on the participation of social media "amplifiers," – individuals with large followings who retweeted the #SaveJosh message. By March 13, over 25,000 people had "liked" the Facebook page, which had been viewed by over 1.3 million people (27). The social media campaign was not only targeted at Chimerix's employees and Board, but also at politicians and the FDA. Within these messages, a darker side of social media was exposed, one based on threats of violence (Fig. 3B). Death threats against me and my family were received that were deemed sufficiently credible to require the use of around-the-clock armed guards.

In the face of this media storm (Fig. 3A, B), I tried to explain the ethical dilemma that Chimerix was facing, pointing to BIO's expanded access principles and stating that "this is not only about Josh, it is about the many Joshes" (28). This approach did not quell the uproar. Darshak Sanghavi, M.D., a former Brookings expert and Managing Director of the Engelberg Center for Health Care Reform, described this intensity as follows: "I think that whenever you have 140 characters to describe a complicated medical decision, it's going to be oversimplified – 'there's a dying child, why won't the drug company give the drug?' It's so easily amplified, and any nuance, even if it was present early on, rapidly gets rubbed out" (29).

The healthcare and medical ethics profession remains silent, except for one

During this intense period of media scrutiny, no one from the biopharmaceutical industry, any trade organizations, physician or hospital group, or related medical or ethics entity chose to comment "on the record," either proactively or in response to media inquiries. The only person to respond to media inquiries was Arthur Caplan, Ph.D., a professor of bioethics at the New York University School of Medicine. In an article on Tuesday, March 11 entitled, "#SaveJosh? Maybe, but What About the Rest?" Dr. Caplan wrote:

> "Josh is cute as can be. He owns a puppy. He is getting his care at a famous hospital, St. Jude's Children's, where the doctors know all about what is in the drug pipeline. His parents are young, vocal, and good on television. Already many news outlets have reported on the case of this poor little boy and the nay-saying drug company.
>
> Josh Hardy's family is pleading with the makers of an experimental drug to get him access.
>
> If Josh were 67 instead of 7, he would already be out of luck. Those who are not very cute get less attention in their pursuit of unproven drugs. If Josh had parents who did not understand how to use social media, he would already be

out of luck. If Josh did not have sharp, well-connected doctors, he would already be out of luck. But he is not in any of these categories, so he may yet get the drug" (30).

Dr. Caplan's article foreshadowed the broad ethical discussion that arose subsequent to the social media campaign, but it was the only evidence of such concerns being raised by someone other than Chimerix while the event was ongoing.

FDA and Chimerix craft a solution

While the very public and highly negative social and traditional media frenzy pleading for access for Josh was intensifying, behind the scenes there were active conversations between Chimerix and the FDA. Reflecting back on these discussions, Debra Birnkrant, M.D., of the FDA's Division of Antiviral Products stated that she first learned of the Josh Hardy situation through the media, and she described the media coverage as "something I have never seen, and I've been in this division for 26 years" (31).

During the discussions with the FDA, Chimerix maintained its position that for a multitude of reasons it did not have a clear path to make brincidofovir available to Josh Hardy under a single patient expanded access protocol. In response, the FDA proposed a novel solution. On Tuesday evening, March 11, 120 hours after the first Facebook post by Mrs. Hardy, Chimerix announced in a press release that "it has reached agreement with the FDA for the immediate initiation of a pilot trial of open-label brincidofovir for the treatment of adenovirus infections in immunocompromised patients…This study is expected to begin with Josh Hardy as the first patient enrolled on Wednesday, March 12, 2014" (14).

In the same press release, I stated the following:

> "This 20-patient open-label study underscores Chimerix's mission to develop innovative antiviral therapies in areas of high unmet need – for everyone. […] Being unable to fulfill requests for compassionate use is excruciating, and not a decision any one of us ever wants to have to make. It is essential that each individual in a health crisis be treated with equal gravity and value, a principle we have upheld by pursuing further clinical study of brincidofovir that will inform its use in adenovirus and other serious DNA viral infections" (14).

This novel solution to an extremely complex situation could not have happened in only 2 days without the expertise, advice, and guidance that the FDA provided through the specific involvement of senior level FDA personnel (32). As opposed to "conceding" in the face of social media pressure, the solution reached was the initiation of a new Phase 3 clinical trial that, in addition to treating Josh, had the potential to provide data that could be used for the benefit of future patients who were faced with life-threatening adenovirus infections – "the many future Joshes."

The aftermath of the social media wave

With the March 11 announcement of the new adenovirus clinical study and the treatment of Josh Hardy, the tone and

Fig. 3 - (**A**) Media headlines soon after the social media campaigns started. (**B**) Examples of Facebook messages. (**C**) Media headlines after an agreement with FDA had been reached.

texture of the social media changed from criticism to praise (Fig. 3C). Comments on Twitter immediately turned positive, and news headlines reveled in the success of the social media campaign. People Magazine declared "Dying Boy's Family Wins Battle for Experimental Drug" (33), and a Reuters article, which was published globally, declared that "US drugmaker to give unapproved medicine to dying Virginia boy" (34).

Josh Hardy received his first dose of brincidofovir on Wednesday night March 12. His progress and response were reported by his mother through multiple Facebook posts and by March 31, when Josh turned 8, the adenovirus was undetectable (20, 35). On April 10, after fewer than 10 doses of brincidofovir and a month after his first dose, Josh was released from St. Jude, although he was required to remain in

Memphis to be near his physicians (36). On July 17, he was allowed to return to his home in Virginia.

By March 14, just 3 days after the announcement of the new clinical trial, there were 6 additional physician requests for brincidofovir, emblematic of the concern that a unilateral decision for 1 patient would potentially open a floodgate of expanded access requests (37). Six months after the initiation of the 20-patient pilot portion of the new Phase 3 adenovirus trial, Chimerix reported that 80 individuals had been enrolled in the study.

The social media uproar regarding Josh Hardy exploded and reached a conclusion over the course of 5 days, just 120 hours, and in doing so highlighted a key societal question: What power (if any) should social media have to influence the decision-making process regarding access to health care?

Within a few weeks of the media firestorm, articles analyzing the ethical dilemma and the role of social media began to appear. On March 23, The Washington Post published an article entitled, "Crowdsourcing medical decisions: Ethicists worry Josh Hardy case may set bad precedent" in which the author noted that "critics of the strategy say they sympathize with Josh's parents and admire them for being willing to do anything to save their child, but they decry the crowdsourcing of medical decisions and warn that the case may set a dangerous precedent" (38).

This collective public opinion marshalled by social media can create immediate pressure, which is difficult – if not impossible – to ignore, and can easily spur further action, outside of the realm of social media, for or against a specific target or interest. BioCentury, a key weekly report for the life-sciences industry, published a 10-page analysis in which the author noted that "lawmakers, industry, and patients still are grappling with the fundamental inequities and flaws of the U.S. system for granting compassionate access to investigational therapies. There can be little doubt that the fact that individual companies have been left to make these decisions on an ad hoc basis inevitably fuels suspicions among patients, family members, and the public about the motives for denying access" (39).

The article went on to say that "The rise of social media as an advocacy tool now raises the prospect that medical and regulatory decisions will be tipped by a public outcry. As the Hardy case illustrates, patients or their relatives can generate hundreds of thousands of supporters virtually overnight, along with a wave of attention on television. In the heat of a media feeding frenzy, it is impossible for a CEO to communicate the complexities of drug development and why the integrity of the regulatory approval pathway must be protected to get a drug to as many patients as possible" (39).

In early 2016, an article in BMC Medicine further explored the use of social media as a tool for patient advocacy and the policy environment within which these events occur. The authors evaluated numerous social media campaigns which were focused on expanded access, and concluded that,

> "Social media is fundamentally altering how we access health information and make decisions about medical treatment, including for terminally ill patients. This specifically includes the growing phenomenon of patients who use online petitions and social media campaigns in an attempt to gain access to experimental drugs through expanded access pathways. Importantly, controversy surrounding expanded access and 'compassionate use' involves several disparate stakeholders, including patients, manufacturers, policymakers, and regulatory agencies – all with competing interests and priorities, leading to confusion, frustration, and ultimately advocacy" (7).

The authors noted that the lack of clear and consistent policies, as well as the lack of consensus across the varied interest groups, is at the center of the individual social media campaigns. "Importantly, this form of digital patient advocacy appears to be a symptom of current policy fragmentation between the FDA, individual states, industry, and patient advocacy groups, as well as the absence of reliable information sources needed for patients when assessing whether expanded access pathways are viable options in the face of often serious and terminal diseases" (7).

It is a truism that in the absence of clarity and consensus, individuals act to their own best possible advantage. This is not a criticism, but rather a recognition that it is the duty of those in positions of responsibility and authority to provide clear guidelines and clarify areas of confusion.

A growing area of confusion in the use of expanded access has been created by the Right-to-Try movement. As of this writing, Right-to-Try legislation has been signed into law in 38 states and is currently under consideration and active debate within the U.S. Congress (40). As a result of these laws, individuals are likely to be asking for experimental medicines earlier in the development process and for conditions that are further separated from the primary conditions for which the medicine is being developed. A number of interest groups, particularly individuals supporting Right-to-Try legislation, have written that expanded access poses few, if any, risks to patients in need, or to the development pathway for experimental medicines (41), and further state that the safety of an experimental medicine is known after Phase 1 testing. This is a statement that I am certain people with knowledge of the drug development process would resoundingly reject as untrue.

Additionally, proponents of Right-to-Try state that the FDA is the impediment to expanded access, ignoring the FDA's approval rate for expanded access requests, and thus one of the underlying principles of Right-to-Try legislation is to allow the distribution of an experimental medicine outside the FDA's purview. Such statements and proposed actions ignore the complexity and inherent risk of giving an unproven medicine to extremely sick individuals, many of whom are considered to be within weeks of dying. Additionally, such uncontrolled situations would eliminate any mechanism to see either evidence of efficacy or, potentially, signs of dose-limiting or development-ending toxicities that could provide meaningful information for the overall clinical development process or for other individuals interested in receiving the experimental compound under expanded access.

No ethical company that I know of would ever release an experimental medicine outside of the FDA's regulatory process. A basic mantra is that "all drugs have side effects." When considering the risk/benefit profile of a critically ill or terminally ill patient, decisions must be made on a case-by-case basis for each specific experimental medicine.

The ethical dilemma of conflicting moral imperatives

How then does a company, a doctor, a patient advocate, a political body, or society for that matter, decide between the immediate needs of a critically ill individual and the future needs of a larger patient population?

As a parent, one can clearly see the motivation to seek expanded access. Mrs. Hardy addressed this issue openly in a post on her Facebook page: "We were criticized in our quest for the Brincidofovir for Josh because it could delay the public getting access to the drug that could help so many more people than just our son. That reasoning meant nothing to me. As a mother, I must save my son! Few would truly argue with me and our intentions to save Josh. Wouldn't just about anybody try to save their loved one" (20).

And in describing Josh's case during the social media event, a pediatric cancer advocate wrote:

> "Knowing all sides of this case, and even as a biased parent whose daughter lost her life to cancer, when you have the ability to save a child's life, you do it, no matter what. To me, and many people out there, the answer is simple, if you can afford it or not, if you have to go against your principles or not, whether there are consequences to reputation or not, you do whatever is necessary to save the life of a child. Period" (42).

But is this a universally accepted position? Are the immediate needs of a person clearly and absolutely more important than the future needs of another person or a group of people? Could we or would we morally or ethically say yes to one person and no to others? Do we value of the life of a child more than someone of a different age, with a different background, with different parents, with any different characteristics? What if meeting the current needs creates an incremental albeit unquantifiable risk for future patients, because of the vagaries and complexities of the process of developing new medicines? And how would you make any of these distinctions absolute?

An equally important question is who makes the decision to allow an experimental medicine to be provided under expanded access, and how should such decisions be made? Said differently, who should be deciding, "who shall live?"

If you or a loved one were in need now, you might indeed take the position of a parent in seeking the experimental medicine. But what if you were not to get sick for several years and, because of something that happened during the expanded access process, the availability of a potentially lifesaving medicine was delayed for a week, or a month, or longer, into the time period when you were faced with the life-threatening disease? Who is looking out for your future needs?

As noted, with the FDA approving over 99% of the expanded access applications, the decision to grant an expanded access request lies solely with the leadership of the "drug sponsor" – the company developing the new medicine. The question that must then be addressed is how to evaluate and balance the current request against what is known about the safety and efficacy of the compound, where it is in its testing pathway, and any other complexities and risks identified during the development process.

While discussions focus on the risks to the drug recipients, the impact on the drug developer itself can be different and potentially broader. In October 2014, 7 months after the Josh Hardy social media campaign, Chimerix's brincidofovir was provided under expanded access to treat the first U.S. Ebola patient. When that individual died a few days after his first dose, Chimerix's stock immediately dropped by a meaningful percentage. Difficult as it is to consider, what would have happened if rather than a rapid and positive response after receiving brincidofovir, Josh Hardy had had a rapid and negative response? Might it have made it more difficult for the company to raise funds to support its clinical development efforts? Might it have discouraged patients from enrolling in the ongoing Phase 3 SUPPRESS trial, which, while it was for a different indication, was still an experimental protocol using brincidofovir, thus slowing down the approval timeline?

Questions such as these always seem hypothetical, up until the moment that they become a reality. And these questions about expanded access are not only being asked in the USA, but increasingly on the global stage, particularly relating to children in need, highlighting the fact that the challenge of individual versus societal need is worldwide and remains highly contentious. The cases of Charlie Gard in the UK and Klara Brenner in Germany illustrate this societal dilemma (43, 44).

A much more complex discussion regarding expanded access relates to the needs that arise during a global health emergency. It was the conclusion of a World Health Organization committee during the Ebola crisis that even in such situations, where the risk/benefit calculation moves from an individual being confronted with a life-threatening disease to a larger patient population that has an immediate, collective need, "these interventions should not be distributed for compassionate use outside clinical trials – which might also undermine the feasibility of trials. If compassionate use nonetheless occurs, transparency is key and data about patient outcomes should be collected and shared in full" (45).

This is not to say that there is a blanket reason not to make experimental medicines available. Rather, the decision to proceed with expanded access must be carefully considered within the overall parameters of the clinical development program. All interested parties must understand that there is no simple, monolithic solution – a "one-size-fits-all" answer – to the decision to provide a drug under expanded access. As I wrote in the Wall Street Journal, "Each drug is different, the testing and data required for FDA approval are different, and patient populations are different" (18).

Five months after the Josh Hardy social media situation, Dr. Caplan and I co-authored an article in Health Affairs in which we concluded that a new expanded access system was needed to bring fairness, equality, and appropriate oversight to the availability of experimental treatments (46). Our concern was that without a new system and without clarity within the regulatory process, medical decision making would be left to individuals and mechanisms – to social media, newscasters and print reporters, and politicians – who are least appropriate to decide complex medical issues and ethical dilemmas. Clearly, in the era of social media, the potential exists for demands and threats to supersede science and logic, giving rise to a system that promotes unfairness rather than equality, and potentially destructive logjams rather than speedy development.

One recommendation of the article was that consideration be given to the creation of an expanded access review mechanism that would assist companies in evaluating factors including the immediate needs of the few versus the future needs of the many; the supply availability and cost of the experimental medicine; and the risks and benefits to potential patients. In 2015, Janssen, a leading pharmaceutical company, contacted Dr. Caplan and the Division of Medical Ethics at NYU for assistance structuring an objective method for reviewing expanded access requests for one of its experimental oncology drugs. This led to the creation of an independent pilot program, the Compassionate Use Advisory Committee or CompAC, comprised of physicians, bioethicists, patients, and patient advocates (47). Based on its success, the CompAC pilot program has been expanded to other Janssen experimental compounds, and programs of a similar nature are under consideration by other companies.

A second recommendation from the Health Affairs article was that regulators needed to address sponsors' concerns regarding the potential for unintended consequences that could negatively impact a product's development program, pathway, or timeline, including the potential for unanticipated adverse events or the reluctance of patients to enter placebo-controlled trials. Over the past few years, the FDA has implemented a series of changes designed to streamline the expanded access process and to increase information transparency. Most recently, in October 2017, the Agency updated its expanded access guidance to better explain the expectations regarding adverse event reporting and to clarify the context in which the FDA reviews this information (48).

Progress has also been made in the legislative arena through the 21st Century Cures Act. Companies are now required to make public their policies for evaluating requests for expanded access, providing greater transparency and a point of contact for interested parties (49). With the growing body of writing about expanded access and a greater public understanding of the process, intense situations such as the #SaveJosh campaign seem less likely to occur.

Despite progress on many fronts, more needs to be done and many critical questions remain, which all parties will need to consider. The potential confusion and complexities caused by the passage of Right-to-Try laws will need to be addressed and corrected. At its essence, expanded access is not drug development, and neither can it – nor should it – be used as an alternative to fully demonstrating the efficacy and safety of experimental medicines.

Postscript

Sadly, on September 22, 2016, 2 1/2 years after receiving brincidofovir, Josh Hardy died of further complications of his underlying disease. He was 10 years old.

Complex situations are often best analyzed in hindsight. Now, more than 3 1/2 years after the Josh Hardy situation, it is clear to me that I would not change any of the key decisions I made in dealing with the external forces and interests.

There are three key learning experiences that stand out.

First, despite all of the hope and desire, not all experimental medicines succeed in clinical testing. Brincidofovir did not achieve the level of effectiveness required for FDA approval in either of its two Phase 3 clinical trials, and Chimerix has had to reposition its development efforts for the compound in order to progress towards regulatory approval. This highlights one of the underlying complexities of the use of experimental medicines, as stated above: expanded access is not drug development. The understanding of the safety and efficacy of experimental medicines is constantly evolving, and there are no guarantees that the drug will have the desired effect without undesired side effects. While one recent study utilizing data from clinicaltrials.gov suggested that close to 75% of the compounds provided under expanded access were ultimately approved by the FDA (50), an internal review by FDA officials found that only about 30% of drugs requested under individual patient expanded access requests ultimately received approval (51).

Second, being open and responsive, no matter how difficult the situation is, can lead to unexpectedly positive outcomes. As the CEO of a company developing a potentially life-saving medicine, I believed I had a responsibility to discuss my position not only with supporters but also with critics, even individuals with whom I had vastly different opinions. Richard Plotkin (the patient advocate who was the most vocal critic of me and of Chimerix) and I began our conversations under extremely intense and hostile conditions. However, over the course of 5 days our dialogue became a bridge, one through which we better understood each other's positions. We have talked openly and publicly about conversations in which we were completely opposed to one another, when, in his words, "I considered [Ken] to be my #1 enemy" (52). We are now friends, and have met each other's families; we have given seminars and taught classes together, and talk often about the complexities of expanded access.

Finally, it is critical to realize that the complex ethical issues raised by expanded access will not be easily addressed. As it relates to developing new medicines and the potential for expanded access, the current needs of an individual and the future needs of many potential patients will create dilemmas that do not have clear solutions. In an interview in the Boston Globe, Mrs. Hardy was asked what she would say to me if she met me today. "I would tell him that I hope and pray that his family and himself are doing very well, and again I am sorry the situation had to be so public and difficult. But I would do it all over again if I had to. Josh is not just any Josh. He is my Josh" (53).

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References

1. Ernst and Young. Beyond borders: Biotechnology Report 2017. http://www.ey.com/Publication/vwLUAssets/ey-biotechnology-report-2017-beyond-borders-staying-the-course/$FILE/ey-biotechnology-report-2017-beyond-borders-staying-the-course.pdf. Accessed November 8, 2017.

2. Tyrawski J, DeAndrea DC. Pharmaceutical companies and their drugs on social media: a content analysis of drug information on popular social media sites. J Med Internet Res. 2015;17(6):e130.
3. Liang BA, Mackey TK. Prevalence and Global Health implications of social media in direct-to-consumer drug advertising. J Med Internet Res. 2011;13(3):e64.
4. Darrow JJ, Sarpatwari A, Avorn J, Kesselheim AS. Practical, legal, and ethical issues in expanded access to investigational drugs. N Engl J Med. 2015;372(3):279-286.
5. Bunnik EM, Aarts N, van de Vathorst S. The changing landscape of expanded access to investigational drugs for patients with unmet medical needs: ethical implications. J Pharm Policy Pract. 2017;10(1):10.
6. Nichols E. Institute of Medicine (US) Roundtable for the Development of Drugs and Vaccines Against AIDS. Expanding Access to Investigational Therapies for HIV Infection and AIDS: March 12–13, 1990 Conference Summary. Washington (DC): National Academies Press (US); 1991. https://www.ncbi.nlm.nih.gov/books/NBK234129/. Accessed November 8, 2017.
7. Mackey TK, Schoenfeld VJ. Going social to access experimental and potentially life-saving treatment: an assessment of the policy and online patient advocacy environment for expanded access. BMC Med. 2016;14(1):17.
8. U.S. Food and Drug Administration. Access to investigational drugs outside of a clinical trial (expanded access). Accessed May 2014. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccesstoInvestigationalDrugs/ucm176098.htm. Accessed November 8, 2017.
9. U.S. Food and Drug Administration. Expanded access (compassionate use). Last updated 25th August 2017. https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm. Accessed November 8, 2017.
10. Klein R. Expanded Access Programs for Drugs and Biologics. Presentation to NORD Rare Disease Summit. Accessed October 2017. http://www.cbinet.com/sites/default/files/files/Track%201_Klein_pres.pdf. Accessed November 8, 2017.
11. Centers for Disease Control and Prevention. Progressive vaccinia in a military smallpox vaccinee – United States, 2009. Morbidity and Mortality Weekly Report. May 19, 2009 58(Early Release);1-4. Last updated 19/05/2009. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm58e0519a1.htm. Accessed November 8, 2017.
12. Chimerix. A multicenter, open-label study of CMX001 treatment of serious diseases or conditions caused by dsDNA viruses. ClinicalTrials.gov Identifier NCT01143181 posted June 14, 2010. https://clinicaltrials.gov/ct2/show/NCT01143181?term=chimerix&draw=2&rank=15. Accessed November 8, 2017.
13. Chimerix. Chimerix presents brincidofovir (CMX001) adenovirus Phase 2 results. Published September 11, 2013. http://ir.chimerix.com/news-releases/news-release-details/chimerix-presents-brincidofovir-cmx001-adenovirus-phase-2. Accessed November 8, 2017.
14. Chimerix. Chimerix to provide brincidofovir to Josh Hardy as first patient in new open-label study in patients with adenovirus infections. Published March 11, 2014. http://ir.chimerix.com/news-releases/news-release-details/chimerix-provide-brincidofovir-josh-hardy-first-patient-new-open. Accessed November 8, 2017.
15. Sidersky R. Fredericksburg first-grader fighting for his life. The Free Lance-Star. Published March 7, 2014. http://www.fredericksburg.com/news/fredericksburg-first-grader-fighting-for-his-life/article_7a475882-3f03-5b29-a14d-49848ad7c187.html. Accessed November 8, 2017.
16. Facebook. Savejosh photo album. March 7, 2014. https://www.facebook.com/SaveJoshHardy/photos/pcb.666481523393017/666481483393021/?type=1&theater. Accessed November 8, 2017.
17. Jaslow R. Young cancer survivor's family pleads with company for experimental drug. CBS News. Published March 11, 2014. http://www.cbsnews.com/news/young-cancer-survivors-family-pleads-with-drug-company-chimerix-for-experimental-drug/. Accessed November 8, 2017.
18. Moch KI. Wanted: guidelines for access to experimental drugs. The Wall Street Journal. Published March 16, 2015. https://www.wsj.com/articles/kenneth-i-moch-wanted-guidelines-for-access-to-experimental-drugs-1426547602. Accessed November 8, 2017.
19. Biotechnology Innovation Organization Board Standing Committee on Bioethics. Early access programs: points to consider. Published April 16, 2010. https://www.bio.org/sites/default/files/files/20100416.pdf. Accessed November 8, 2017.
20. Facebook. Aimee Hardy Profile. https://www.facebook.com/aimee.hardy.5?hc_location=timeline. Accessed November 8, 2017.
21. Caringbridge. Joshua's journal. Last updated March 7, 2014. http://www.caringbridge.org/visit/joshuahardy/journal/view/id/5319641ecb16b40c20fb0945. Accessed November 8, 2017.
22. Facebook. Savejosh shared William R. Burns's status update. Published March 8, 2014. https://www.facebook.com/SaveJoshHardy/posts/10203200745921081?stream_ref=10. Accessed November 8, 2017.
23. Hobson K. The accidental ethicist. Princeton Alumni Weekly. Published October 21, 2015. https://paw.princeton.edu/article/accidental-ethicist. Accessed November 8, 2017.
24. CNN. Segment on Josh Hardy [video] *CNN Newsroom*. Cable News Network. March 9, 2014. https://archive.org/details/CNNW_20140309_230000_CNN_Newsroom/start/2400/end/2460. Accessed November 8, 2017.
25. Fox News. Company denies drug to 7-year-old boy struggling against curable virus. Fox News Insider. Published March 3, 2014. http://foxnewsinsider.com/2014/03/10/drug-maker-chimerix-refuses-release-drug-7-year-old-josh-hardy-struggles-against-curable. Accessed November 8, 2017.
26. Gerasimov E. Saved Josh: The gears of a successful patient advocacy campaign. KidsvCancer.org. Published March 9, 2016. http://www.kidsvcancer.org/wp-content/uploads/2016/01/Hardy-Case-Study-final-March-9-2016.pdf. Accessed November 8, 2017.
27. Facebook. SaveJosh post. Published March 13, 2014. https://www.facebook.com/SaveJoshHardy/photos/a.666481530059683.1073741827.666476203393549/669181626456340/?type=1&theater. Accessed November 8, 2017.
28. Miller J. When unapproved drugs are the only help: A case for compassionate use. Bioethics International. Published August 18, 2014. http://www.bioethics.net/2014/08/when-unapproved-drugs-are-the-only-help-a-case-for-compassionate-use/. Accessed November 8, 2017.
29. Chen C. The CEO who saved a life and lost his job. Bloomberg Businessweek. Published January 22, 2015. https://www.bloomberg.com/news/articles/2015-01-22/biotech-drug-approvals-social-media-storm-hits-chimerix. Accessed November 8, 2017.
30. Caplan AL. Bioethicist: #SaveJosh? Maybe, but what about the rest? Published November 3, 2014. https://www.nbcnews.com/health/kids-health/bioethicist-savejosh-maybe-what-about-rest-n50051. Accessed November 8, 2017.
31. NYU School of Medicine and the New York Academy of Sciences. Pre-approval access: can compassion, business, and medicine coexist? October 28 and 29, 2015. https://www.nyas.org/events/2015/pre-approval-access-can-compassion-business-and-medicine-coexist/ [presentation]. Accessed November 8, 2017.

32. Chimerix. Chimerix issues statement thanking the FDA for collaboration in developing protocol to treat patients with life-threatening adenovirus infection. Published March 14, 2014. http://ir.chimerix.com/news-releases/news-release-details/chimerix-issues-statement-thanking-fda-collaboration-developing. Accessed November 8, 2017.
33. Breuer H. Dying boy's family wins battle for experimental drug. Published March 12, 2014. http://people.com/celebrity/josh-hardys-family-wins-battle-for-brincidofovir-drug-in-fight-to-save-his-life/. Accessed November 8, 2017.
34. Reuters. US drugmaker to give unapproved medicine to dying Virginia boy. Kuwait Times. Published March 13, 2014. http://www.pressreader.com/kuwait/kuwait-times/20140313/282570196045918. Accessed November 8, 2017.
35. Brown G. St. Jude patient celebrates birthday and improving health. News Channel 3 website. Published March 31, 2014. http://wreg.com/2014/03/31/st-jude-patient-celebrates-birthday-and-improving-health/. Accessed November 8, 2017.
36. Josh Hardy released from hospital. The Free Lance-Star. Published April 11, 2014. http://www.fredericksburg.com/news/josh-hardy-released-from-hospital/article_0bf22369-5c90-5ce6-b228-1e3658fd83b5.html. Accessed November 8, 2017.
37. Carroll J. Chimerix started the week as a punching bag, then pulls off a TKO. FierceBiotech. Published March 16, 2014. http://www.fiercebiotech.com/story/chimerix-started-week-punching-bag-then-pulls-tko/2014-03-16. Accessed November 8, 2017.
38. Cha AE. Crowdsourcing medical decisions: Ethicists worry Josh Hardy case may set bad precedent. The Washington Post. Published March 23, 2014. https://www.washingtonpost.com/national/health-science/crowdsourcing-medical-decisions-ethicists-worry-josh-hardy-case-may-set-bad-precedent/2014/03/23/f8591446-ab81-11e3-adbc-888c8010c799_story.html. Accessed November 8, 2017.
39. Usdin S. Viral crossroads. BioCentury. Published March 31, 2014. https://www.biocentury.com/biocentury/regulation/2014-03-31/hardy-case-shows-flaws-compassionate-use-system-provides-catalyst. Accessed November 8, 2017.
40. U.S. House Energy and Commerce Subcommittee on Health hearing. Examining patient access to investigational drugs. October 3, 2017. https://energycommerce.house.gov/hearings/examining-patient-access-investigational-drugs/. Accessed November 8, 2017.
41. Right to Try Letter of Support. Goldwater Institute. August 2, 2017. http://righttotry.org/right-to-try-letter-of-support/?utm_source=Goldwater+Institute+Newsletter&utm_campaign=78a34df861-Weekly+Email+%233+-+Liberty+Spreads+like+Wildfire&utm_medium=email&utm_term=0_17048f5b32-78a34df861-. Accessed November 8, 2017.
42. Scott JA. Cancer drug could save this 7-year-old. But the company behind it won't give him access. The Huffington Post. Published March 11, 2014, updated May 11, 2014. http://www.huffingtonpost.com/jay-scott/josh-hardy-cancer-medication_b_4942307.html. Accessed November 8, 2017.
43. Bilefsky D. Charlie Gard dies, leaving a legacy of thorny ethics questions. The New York Times. Published July 28, 2017. https://www.nytimes.com/2017/07/28/world/europe/charlie-gard-dead.html. Accessed November 8, 2017.
44. Meier N. Wer rettet Klara? (Who Saves Klara?). Die Zeit. Published September 15, 2016. http://www.zeit.de/2016/39/medikamenten-zulassung-heilung-ethikfrage/komplettansicht. Accessed November 8, 2017.
45. Rid A, Emanuel EJ. Ethical considerations of experimental interventions in the Ebola outbreak. Lancet. 2014;384(9957):1896-1899.
46. Caplan AL, Moch KI. Rescue me: The challenge of compassionate use in the social media era. Health Affairs Blog. Published August 27, 2014. http://healthaffairs.org/blog/2014/08/27/rescue-me-the-challenge-of-compassionate-use-in-the-social-media-era/. Accessed November 8, 2017.
47. Caplan AL, Ray A. The ethical challenges of compassionate use. JAMA. 2016;315(10):979-980.
48. Individual Patient Expanded Access Applications. Form FDA 3926, Guidance for Industry. U.S. Food and Drug Administration. June 2016, Updated October 2017. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM432717.pdf. Accessed November 8, 2017.
49. 21st Century Cures Act—February 11, 2017. Deadline for company disclosure of expanded access programs. Jones Day. Published January 2017. http://www.jonesday.com/21st-Century-Cures-ActFebruary-11-2017-Deadline-for-Company-Disclosure-of-Expanded-Access-Programs-01-17-2017/?RSS=true. Accessed November 8, 2017.
50. Miller JE, Ross JS, Moch KI, Caplan AL. Characterizing expanded access and compassionate use programs for experimental drugs. BMC Res Notes. 2017;10(1):350. https://www.ncbi.nlm.nih.gov/pubmed/28754150.
51. McKee AE, Markon AO, Chan-Tack KM, Lurie P. How Often Are Drugs Made Available Under the Food and Drug Administrations Expanded Access Process Approved? J Clin Pharmacology. 2017;57(Suppl 10):S136-S142.
52. Plotkin R. To live or let die: Trying experimental treatments for the terminally and seriously ill. The Max Cure Foundation Blog. Published September 2, 2014. https://maxcurefoundation.org/liveorletdie/. Accessed November 8, 2017.
53. Westphal SP. Sick kids, desperate parents, and the battle for experimental drugs: The complex world of compassionate use drugs and who gets access to them. Boston Globe. Published July 15, 2015. https://www.bostonglobe.com/magazine/2015/07/15/sick-kids-desperate-parents-and-battle-for-experimental-drugs/Hle3CTwriFfTXoOvQ7TbZP/story.html. Accessed November 8, 2017.