The American Journal of Bioethics

ISSN: 1526-5161 (Print) 1536-0075 (Online) Journal homepage: http://www.tandfonline.com/loi/uajb20

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To cite this article: Eline M. Bunnik & Nikkie Aarts (2018) A Model for Communication About Longshot Treatments in the Context of Early Access to Unapproved, Investigational Drugs, The American Journal of Bioethics, 18:1, 34-36, DOI: 10.1080/15265161.2017.1401170

To link to this article: https://doi.org/10.1080/15265161.2017.1401170

A Model for Communication About Longshot Treatments in the Context of Early Access to Unapproved, Investigational Drugs

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When seriously ill patients run out of standard treatment options, they may consider nonstandard treatment options such as expanded access, also known as "compassionate use." Through expanded access programs, patients are given access to investigational drugs that are still under development and not yet approved for marketing. As the safety and efficacy of unapproved drugs have not been fully established, it is uncertain whether these drugs will offer medical benefit. Especially when the compound is in an early stage of the drug development process, its odds of success may be low or "longshot." Expanded access raises ethical concerns, notably that seriously ill patients may overestimate the benefits of an investigational drug and underestimate its safety issues, fail to make informed decisions, and become susceptible to false hope and exploitation (Darrow et al. 2015). The communication model proposed by Weiss and Fiester (2018) and its central distinction between low-odds and no-odds treatment can be used to assist seriously ill patients and their treating physicians not only with decision making with regard to initiating expanded access to investigational therapies but also with monitoring and managing their effects. Thus, it may help to overcome some of the ethical problems associated with expanded access.

Systems for expanded access differ across countries, but have a set of conditions in common: Patients must be suffering from serious or life-threatening diseases must have exhausted standard treatment options, and must not be eligible for participation in clinical trials (Jarow et al. 2017). The managing physician must believe that the potential benefits of the drug will outweigh the risks. A regulatory authority such as the Food and Drug Administration (FDA) will need to approve the request (FDA 2017). In some countries, including the United States, requests must also be evaluated by an institutional review board. Importantly, the pharmaceutical company must be willing to supply the drug, often at no cost. Finally, patients must provide informed consent.

Requests for individual patients are usually initiated in "back against the wall" situations by treating physicians who believe that a last-ditch intervention might save or benefit their patient. Expanded access has a therapeutic aim, not a research aim. The odds that the drug will benefit the patient, however, may vary depending on the physical condition of the patient, on the drug itself and its stage of development—and consequently on the level of available evidence. Early in the drug development trajectory, for instance, the odds of success are slim. Among patients enrolled in oncology Phase I clinical trials, average response rates are around 5% (Kimmelman 2016). Response rates are probably lower in patients who fail to meet the inclusion criteria of trials because of poor physical condition. Enrolling patients in Phase I trials can be thought of as very-low-odds to no-odds and is therefore considered nontherapeutic.

On the other end of the spectrum are drugs that have successfully completed Phase III clinical trials. It usually takes up to a year for the regulatory authorities to evaluate the dossier and decide on marketing authorization (Downing et al. 2012), and, in many countries, another couple of months or years before health technology assessment bodies make reimbursement decisions and the drug in effect becomes available to patients (Bergmann et al. 2016). In the meantime, patients may seek access to the drug through expanded access programs. Pending marketing approval, a drug is not (yet) standard of care, but high-level evidence on the drug's safety and efficacy is available. Thus, expanded access to post-Phase III unapproved drugs is not an example of longshot therapy. Doctors and patients can make evidence-based decisions on whether or not to initiate the unapproved therapy.

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In contrast, Phase II unapproved drugs can be thought of as a form of longshot therapy. Weiss and Fiester (2018) distinguish longshot care "where there is a low likelihood of success" from fantasy care "where there is no chance of success" (4). A meta-analysis of more than 500 Phase II cancer trials showed a median response rate of 30% for personalized or targeted therapies (Schwaederle et al. 2015). Although notoriously few newly approved drugs are in effect lifesaving or fully curative, patients seeking expanded access may instead be aiming for prolongation or quality of life. While Phase II investigational drugs may have a low likelihood of success at providing these benefits, this likelihood is not zero. Just like in referral pediatric care, the physician proposes something that he or she knows is "unlikely to work [but] conceivably could work (and sometimes does)" (Weiss and Fiester 2018, 3). Expanded access to early-phase investigational drugs may thus be considered a form of longshot or low-odds therapy, but not fantasy therapy.

Expanded access is usually only pursued after the drug has completed Phase II a/b clinical trials, that is, after either basic safety and efficacy studies have been conducted in patients with the relevant indications. After all, the doctor should have considered the available evidence and established a favorable balance of risks and potential benefits, before deciding to request expanded access for the patient. This balance may be both acceptable and low-odds. When patients are seriously or terminally ill and have run out of standard treatment options, it is not unreasonable for them to pursue a longshot therapeutic option.

As described by Weiss and Fiester for quaternary pediatric care, however, the use of investigational drugs may gradually turn into fantasy therapy. As physicians usually resort to expanded access only when all other options have failed, most patients are very sick. Investigational drugs, like all other drugs, may have side effects or lead to serious adverse drug reactions, and thus harm patients rather than help them. Also, there may be psychological and social opportunity costs associated with "fighting" and not accepting that death will be likely. In order to avoid these harms and minimize suffering, the physician may at some point wish to discontinue the investigational treatment. When doctors and patients are deciding whether or not to pursue expanded access, they should discuss this scenario. The communication model proposed by Weiss and Fiester can be of help.

Despite important differences, in particular that adult patients are capable of providing informed consent and that decision making takes place within the doctor–patient relationship rather than among a hospital-based team of professionals and parents, the four stages described by Weiss and Fiester through which last-ditch pediatric interventions go awry can be translated to the context of expanded access. In the first stage, the physician and patient decide—together—to initiate a request for expanded access. In the second stage, the investigational treatment commences. In the third stage, the patient does not respond to the treatment as hoped, and the physician—and possibly the patient as well—begins to understand that the odds of success are "moving toward zero." In the fourth and final stage, the treatment has clearly "reached the fantasy stage" and should be stopped. In the first stage, as part of the informed consent process, physicians should not only inform patients about the low odds of success in general terms, but also paint a picture of what will happen "in the likely event that the treatment fails" (Weiss and Fiester 2018, 3). What may occur in Stage 3? What would success of the investigational treatment look like, and what would failure look like? When will the line between Stage 3 and Stage 4 be crossed, and what will discontinuation of the treatment look like? Ideally, the physician and the patient should agree beforehand upon benchmarks for success and failure, and how these would shift the care plan.

Before patients and their treating physicians venture into expanded access, they should go through an informed consent process that explicitly addresses likely scenarios of failure and involves agreement between doctors and patients upon benchmarks for continuation or discontinuation of the investigational drug. This would help to elicit a realistic understanding by the patient of the (small) likelihood of success of expanded access, reduce therapeutic misconceptions, and prevent false hope and unnecessary harm. Drawing lines between low-odds and no-odds therapeutic interventions will always be both difficult and arguable, especially for early-phase drugs. Nevertheless, the informed consent process for expanded access to investigational drugs will improve through a discussion of these lines and an agreement between patients and their treating physicians upon a course of action in the [likely] event of failure, prior to the start of the investigational treatment.

As the—often criticized—Right-to-Try movement in the United States is raising awareness of expanded access and seeking to increase its accessibility (Holbein et al. 2015), demand among patients for unapproved drugs around the world is expected to rise. Adequate informed consent processes that explicitly rebut unwarranted therapeutic optimism will be crucial for morally responsible practices of expanded access in the future.

FUNDING

This work was supported by the Netherlands Organisation for Scientific Research (NWO), within the Responsible Innovation (MVI) program [grant no. 313-99-311]. MVI stimulates public-private partnership. myTomorrows was involved in the research project as a private partner. ■

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Reframing Fantasy: Toward a Common Language of Hope, Dying, and Death in Long-Shot Pediatrics

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This response piece engages the target article's suggestion for a communication rubric around long-shot pediatric medicine (Weiss and Fiester 2018). We offer constructive criticism of the authors' proposal of "fantasy" as a framing of the inappropriate expectations parents may have of their child's care. We suggest that harm reduction could be facilitated by more nuanced understandings of both medical and parental roles, as well as of the broader cultural contexts of biomedicine.

Clear and unambiguous communication between clinical care teams and families of the sickest children is ethically essential, particularly when navigating low-odds, "longshot" curative treatment. For children with severe or unusually complex health problems, practitioners will often undertake medical action that offers an improbable but possible chance of recuperation. In "From 'Longshot' to 'Fantasy,'" Weiss and Fiester propose a four-stage rubric for medical practitioners who must communicate to a patient's family that their child's curative odds have slipped from low to zero. Through two affecting case studies, we see how such treatment can slide from improbable to impossible, often with great rapidity. The authors respond to this by delineating a pathway from "longshot hope" (Stage 1), through "initial actions" (Stage 2), to "threshold" (Stage 3), and "fantasy" (Stage 4); the transition between Stages 3 and 4 presents a particular challenge for practitioners. While the authors' intent to minimize potential harms through a formalized communication rubric is worthwhile, we reject the prescription of nonmedical "fantasy" terminology.

We identify a degree of semantic slippage in the authors' use of the term "fantasy." They employ "fantasy" to describe a medical reality ("fantasy care where there is no chance of success," 4), but also propose that it be used as a communicative device ("a colloquial, nonmedical concept that carries a precise meaning to lay individuals," 8). Specifically, they attempt to position the term as a replacement for both "the highly criticized 'futility' and the newer concept of 'potentially inappropriate treatment'" (3). They note, as well, that "fantasy" differs from these terms "both theoretically . . . and practically in use with families of very sick children" (3). It is primarily the term's communicative application that we take issue with.

The term "fantasy" as proposed is based on a limited rendering of the family, which reproduces a divide between "rational" experts and "irrational" laypeople. The authors claim that "fantasy" offers families "a lay terminology that conveys a very precise meaning, namely, that the goal of cure is now only 'wishful thinking,' 'unrealistic,' and 'make believe'" (22); no evidence is

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