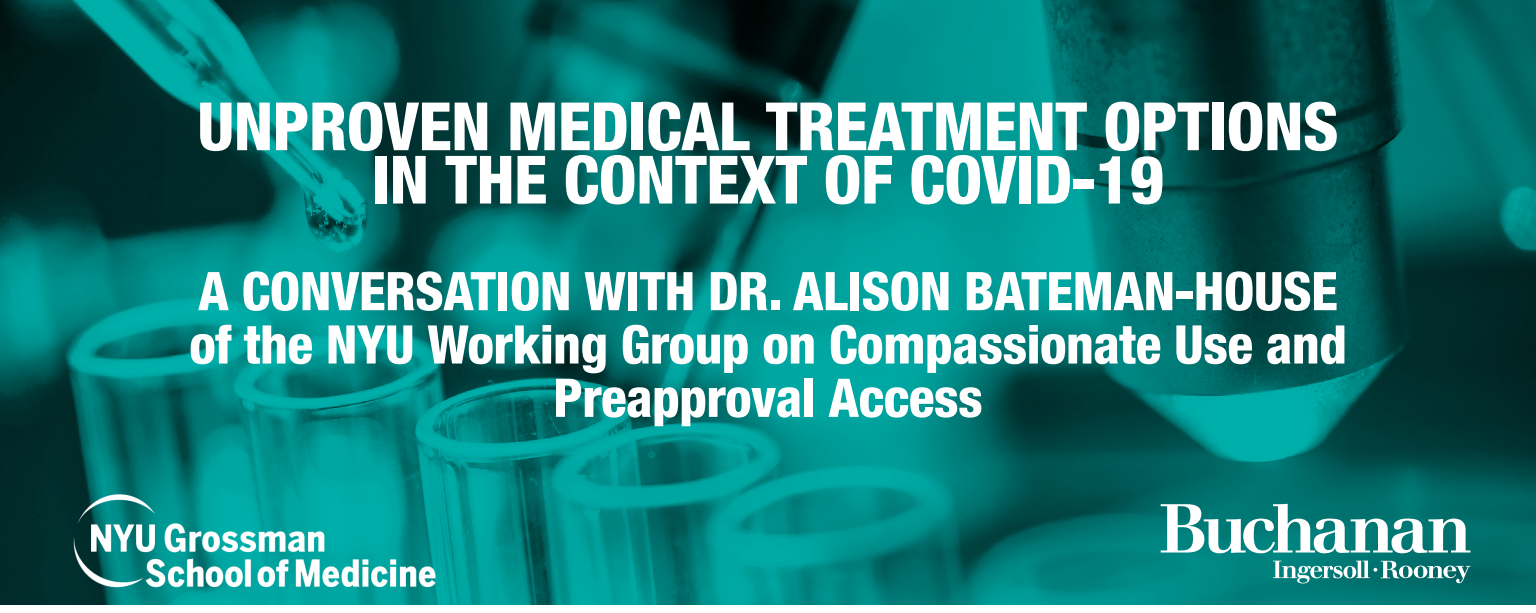

UNPROVEN MEDICAL TREATMENT OPTIONS IN THE CONTEXT OF COVID-19

A CONVERSATION WITH DR. ALISON BATEMAN-HOUSE of the NYU Working Group on Compassionate Use and Preapproval Access

NYU Grossman School of Medicine

Buchanan Ingersoll·Rooney

Webinar Transcript

Dr. Barbara Binzak Blumenfeld:

Thank you for joining us today for a conversation with Dr. Alison Bateman-House on unproven medical treatment options in the context of COVID-19. I am Dr. Barbara Binzak Blumenfeld, a shareholder in the FDA, Biotechnology and Life Sciences Group at Buchanan Ingersoll & Rooney, and I am pleased to lead this conversation with Dr. Bateman-House.

Dr. Bateman-House is co-chair of the NYU Grossman School of Medicine Working Group on Compassionate Use and Preapproval Access, which is an academic group that conducts research, develops policy and offers education on matters related to access to investigational medical products. She is a renowned bioethicist who has been asked by many individuals in recent days for her thoughts on the use of unapproved medical treatments for COVID-19.

We will be engaging in a short discussion of important considerations related to unproven medical treatment options.

Alison, thank you very much for joining me today and for sharing your expertise. I would like to start by asking you to describe the options for a healthcare provider who may believe that a medical treatment approved for another condition, but not for the Coronavirus, will provide benefit to their patient. What are those provider's options and what are the patient's options?

Dr. Alison Bateman-House: Hi, Barbara. Thank you for the opportunity to speak with you and your audience today.

So what you are talking about is what we call off-label treatment. This is a medical treatment that has been approved by a regulator, which in the United States is the FDA, for use in treating a specific condition or a specific illness in a particular patient group. And so, if you want to use that product in a different context, such as COVID-19, are you able to do that? And the answer is, yes, that is perfectly legal in the United States.

We have a strict premarket approval process whereby clinical trials have to be conducted on a novel product to make sure that it is safe and effective in a given condition and a given indication in a specific patient population. But once those conditions are met and the FDA grants marketing authorization to the product, healthcare providers are widely able to prescribe that product for any reason, for any condition. The only real check on that is that if a patient is harmed and if they or their estate sues the provider, the provider really wants to be able to have expert witnesses testify on their behalf that it was a reasonable course of action to prescribe that drug. But other than that, you really can use any approved treatment, any drug, any device for other reasons other than what it was approved for in terms of legality.

Now, practicalities are another matter. You may have a company put some sort of restriction on -- particularly if there is limited supply of a product -- limiting who it is willing to give its product to. You may have a prescribing authority say that we are not going to allow a drug to be diverted for certain off-label uses. And probably the biggest gatekeeper is payers because payers can decide that they are not going to pay for certain uses of an off-label drug.

So legally, you can use an off-label treatment for Coronavirus, and the practicalities of it are a little bit more challenging. But in this situation, I would imagine it is probably not too hard to surmount those failures in many circumstances. And certainly, we see in the news a lot of off-label prescriptions happening at this point in time simply because this novel disease has no approved products at this point in time.

So that is what the provider would need to know about. What the patient needs to know about is that off-label use of an approved treatment is only one of their options, and it may or may not be their best option. At this point in time, we just don't have the data to know,

but it is important to keep in mind that simply because a drug is approved for one reason doesn't necessarily mean that it is going to be safe or effective for another reason.

So rather than putting all of their eggs in the off-label basket, I would urge people who are thinking about various options to think about clinical trials. You can have clinical trials both for off-label uses of products and for novel products and also for expanded access, which is non-trial access to preapproval products.

Dr. Barbara Binzak Blumenfeld: Great. Well, thank you very much. That certainly makes sense.

And in that vein, you mentioned expanded access. And we have heard so much in recent days about the terms expanded access, compassionate use, Right to Try and emergency investigational new drug applications, or what we often call INDs.

So could you explain a bit what the practical differences are in these terms and what it means again for the patient?

Dr. Alison Bateman-House: That is a really great question, and I am glad you asked it.

In practical terms, frequently these are all talking about the same thing, but they do have nuances and legal differences. So let me try to break that down.

Compassionate use is not a legal or a regulatory term. I actually try very hard to not use it. What it is talking about is non-trial preapproval access, so access to an investigational product that hasn't been approved for any use. And the reason I try not to say compassionate use is because it is not necessarily compassionate to give access to those products. It really depends on the circumstance. And to say that a company or a doctor or a healthcare system is not involved in compassionate use, when actually what they are doing is in the patient's best interest, is something I find inappropriate. So I try really hard not to use compassionate use, but it is a term that has been around for decades.

So what are we talking about if we are not talking about compassionate use? We are talking about non-trial preapproval access. So this is not off-label use, what we just talked about, where a product has been approved for some purpose. This is a product that has not been approved for any purpose that is being used but is

not being used for research purposes. It is being used in a treatment attempt.

So it is important to keep in mind that when I say treatment attempt, the actual regulatory definition of what I'm talking about and the legal regulatory term, expanded access. Expanded access includes more than just treatment. It can involve diagnosis; it can involve monitoring; and it doesn't just involve drugs. It can involve biologics, vaccines, devices. It is pretty expansive. But the idea is that you are using the product not to gain data or not to advance sort of a scientific inquiry or prove or disprove a hypothesis. You are using it to try to provide medical benefit to a particular patient or a particular patient group, so that is what we are talking about here.

Now, expanded access as a regulatory passway to access has a couple parameters. So let's see. What are those? It has to be for a serious or life-threatening disease or condition. Now, serious is by intention, a very sort of vague and flexible term. The example that I frequently give is blindness. Blindness is, generally speaking, nonreversible and a serious condition, so you can understand why someone might be willing to take some risk and be willing to try an unapproved product if they thought it would halt or roll back their encroaching blindness. But to the best of my understanding, the FDA has never said no to an expanded access request on the grounds that it wasn't sufficiently serious, so that is a very flexible category. We frequently hear about expanded access in the context of life-threatening diseases, though.

So the regulatory definition is that you have to have this serious or life-threatening disease for a patient. They cannot have other treatment options, either of an approved product that is available to them or through a clinical trial. Then, if you give access outside of a trial to this product for this particular patient or for a group of patients, that has to be perceived to not threaten the ability to enroll patients into clinical trials that are either happening at that point in time or are expected to happen. The idea is we really need clinical trials to happen. It is how we get data to be able to approve new drugs, to be able to protect the public health and consumer protection and really know what it is we are doing in terms of an evidence-based medicine. So we can't divert people away from clinical trials. So to the extent that expanded access is offered as an add-on to clinical trials, that is great, but it can't be seen as jeopardizing clinical trial enrollment.

And then the other criteria for expanded access is that there has to be an anticipated risk-benefit ratio that really supports using that unapproved product in this specific situation. So those are the criteria for expanded access and then expanded access comes in three flavors.

So the one that we typically hear about is single-patient expanded access. You hear about it in newspapers or movies or TV shows where you have one patient who is in extremis or otherwise having a serious problem and we are just trying to get access to something for that one patient, but that is only one type of expanded access.

There are two other types of expanded access allowed within the United States, and they are both intended for groups of similar patients. One is called treatment IND, and that is intended for a very wide number of patients. So for example, think of an oncology drug that has completed phase 3; the data looks really promising in terms of efficacy and not too bad of side effects; and we really anticipate that there is going to be regulatory approval coming forth; and there are no other options for that particular group of cancer patients at this point in time. The company, if it so chooses, can open a treatment IND that would allow widespread use of the drug in that sort of interval between the end of the clinical trials and when the drug is approved and on the market.

So the two ends of the spectrum are the single-patient IND and then the treatment IND, and in the middle is something called the intermediate expanded access. And it really, I would say, is for more than two patients and less than many. The regulatory definition doesn't have specific numbers written into it. And the reason that we have these sort of group programs for the intermediate and the treatment access is that, whereas single-patient expanded access works really well for a single patient, it gets burdensome when you have multiple patients trying to be funneled through it. So the two cohort versions of expanded access are intended to be a bit more streamlined in order to maximize the number of patients who can use it while minimizing the amount of effort that goes into it.

So that is expanded access, which is the main and the oldest way that patients can access non-trial preapproval access in the United States. And it really dates from the HIV epidemic and patient efficacy saying you want us to only get access to investigational products through clinical trials, but there are not enough clinical trials, and the

clinical trials that exist don't have enough spaces to accommodate all of us, so we are dying, we have a fatal disease, and we are willing to take some risk, why can't you accommodate us. And the answer was we can accommodate you, and that is where the FDA expanded access program was birthed.

Now, Right to Try is almost two-years old at this point, and it is what I would call sort of a stripped down version of expanded access. The idea was that perhaps expanded access was burdensome, which I actually would push back upon. I don't think it is unduly burdensome, but the idea was that perhaps it was, and so maybe we should strip out some of the oversight and protections in expanded access, and that is what became Right to Try. Right to Try is now a parallel pathway to access in the United States. It is on the books, it is legal, but not very many companies are choosing to utilize it. As of this point in time, I am only aware of about 10 patients who have gotten access to any investigational products through Right to Try, and I am not aware of any use for COVID-19 through that pathway.

And then I think the final term that you mentioned was emergency INDs. So this expanded access pathway, it can accommodate those emergency requests and non-emergency requests. And so an emergency IND has certain changes made to it to try to make it even faster than your normal expanded access. And I believe the last time I looked at the single-patient expanded access numbers, it looked about 50/50 in terms of how many of them were emergency and how many of them were non-emergency.

So I will pause for a second to see if there is any response or question you have about that, but then I would like to come back and actually walk through the process of what is entailed in seeking expanded access for a single patient.

Dr. Barbara Binzak Blumenfeld: No. That would be great. And you mentioned that there are only about 10 patients so far, to your knowledge, who have accessed the Right to Try pathway. What I am curious about with respect to all of these pathways that you have mentioned so far is it seems like it could be very overwhelming for the average patient and their family, particularly a patient and family who are dealing with the stress of a potential COVID-19 diagnosis.

So I am wondering, what do you think is the best way for patients to sort through this and these options? Would it be, first and foremost, to speak to their physician?

Dr. Alison Bateman-House: Yeah. That is a great question and definitely leads in to sort of the process that I wanted to go through.

So this is overwhelming for patients and their families mainly because it is something that is not very well known even among healthcare providers. I spend a lot of time talking with doctors and nurses and even hospital administrators who are not very familiar with expanded access.

In fact, during the Right to Try lobbying effort, one of the reasons that it was a successful effort and really in a bipartisan manner is many people thought that there was no pathway outside of a clinical trial to access investigational drugs for people who have no other options and who were unable to participate in the clinical trials. And I have already mentioned that we have had that pathway since the AIDS epidemic of the 1980s, so there is a really just weepingly large lack of knowledge about this. And it is something that we need to address, and we particularly need to address on the part of the medical providers because they are the ones who have to guide patients through this process. No matter how motivated the patient is, this is not something a patient can do on their own. It has to go through a medical provider.

So why don't I talk about the process for expanded access and then the process for Right to Try and then we can -- if you remind me, we can talk about how that might look a little bit different in the COVID-19 situation.

Dr. Barbara Binzak Blumenfeld: Certainly. Please go ahead.

Dr. Alison Bateman-House: For expanded access, as I said, it really has to start with your doctor, so the idea could come from the doctor. They could say, I want to try drug X in my patient, because they can't get into a clinical trial, but I think drug X seems promising for them; or the idea could come from the patient who then goes to the doctor and says, what about drug X, what do you think. Regardless of who comes up with the idea, you have to get that doctor on board. And if you can't find a doctor who is willing to advocate for expanded access, it is not going to happen, and this is the problem sometimes for patients in particularly rural

areas or smaller hospitals that aren't familiar with investigational medicines or aren't familiar with clinical trials and just see this process as overwhelming.

So the first step is you have to get a doctor on board. That doctor has to reach out to whoever is developing the investigational medical product, so in this case, I will just say a drug. So the doctor has to reach out to the drug developer, and that used to be really hard. I mean, just imagine some multinational drug company and trying to figure out who the correct contact person to call or to e-mail.

This is easier now due to a bill called the 21st Century Cures Act. It was a huge bill, but one of the provisions, like 200 pages into it, was a provision that said once a company has an investigational product in phase two of testing, they are required to make their expanded access policy available to the public. Now, most companies have interpreted as meaning -- as saying that they need to put some language up on their website. And if you look at those statements on the website, they could say we don't provide expanded access to our drugs at all or they could say the only way to access our drugs is through clinical trials or they could say, yes, we do allow expanded access. And in that case, they could say it is only going to start when the drug is in phase three or it is only going to start once the clinical trials are fully enrolled. The company gets to set their own parameters of when, if ever, they are going to make access. There is no requirement for a company to provide an investigational drug outside of a clinical trial.

The other thing that 21st Century Cures required is that the company provide contact information so that that physician knows how to lodge the request. So normally there is an e-mail address or a phone number that is really the place for physicians to be channeled to lodge this request, and once those requests are lodged, there has to be an indication of how long it will be until they get a response.

Now, I was actually involved in drafting this provision, and I can tell you, for those of us who were involved in it, the idea was when you got this indication of how long it would be until you got a response, we meant an answer to the request, a yes or a no. It seems that many companies have interpreted that as how long until you get some sort of confirmation of receipt of request, which is not really the same thing. When you are sitting by your computer waiting desperately for a yes or a no, to get an e-mail back saying your

request has been received and within five days you will get a receipt of request notification, that is not really what we had in mind, but it seems some companies are doing that. Regardless, the fact that companies now are putting this information on their website really is making it easier and faster for physicians to figure out how to lodge the request.

Now, as I said, the companies have no legal obligation to grant access. Some do, some don't. In my experience, it seems that the companies that are more likely to grant access are your larger, more well-capitalized companies that potentially have more people and power available, potentially have more familiarity with expanded access, potentially have more capital and more ability to generate supply, as opposed to your smaller companies that are sort of handicapped on all of those fronts. But that is not a hard-and-fast rule. There are always exceptions.

If the company says no, that is basically the end of it. I mean, we do see social media-type campaigns where patients or their families or supporters try to pressure companies into giving access, but other than trying to appeal to a company to change their mind, that is really the end of the story there.

If the company says yes, then the physician reaches out to the FDA to seek access and approval from the FDA.

In the case of a single-patient request, the form is quite short. It is about one-and-a-half pages. It is anticipated to take about 45 minutes to fill in, and it basically asks for the patient's medical history and what the treatment protocol is. This has to be filled out in conjunction with the company because there will just be some information from the company that is needed, and that goes to the FDA.

Now, if it is an emergency -- as I said, this emergency IND -- you don't have to fill out the form. You can do this over the phone on a hotline with the FDA, but if it is a non-emergency, you do fill out the form. The FDA turns this around very quickly. If it is an emergency, they typically are able to turn it around within the same day. For non-emergencies, I think the last data I saw was about four business days, which is still pretty fast. And what they do is they have reviewers from the appropriate division look over and just make sure does this risk-benefit ratio seem to hold for this particular patient, and looking at the protocol, are there any changes, based on the knowledge they have

of the drug or drugs in that class, that need to be made to the plan. So for example, whereas the FDA approves almost all of these requests that it receives, it does make some modifications. I think about 11 percent are modified, and that could be in terms of changing the dosage that is going to be used or changing the sort of monitoring plan.

Once the FDA gives permission for the process to be carried out, then you have to get permission from the Institutional Review Board, or IRB, of the trading institution. Now, keep in mind that some institutions do not do research, and, hence, they may not have an IRB. So in the past, that has been a logjam, and I will discuss that in a second. But if you do have an IRB there, they have to be involved basically to make sure that the informed consent provisions are followed. This is an investigational product. We don't know if it is going to provide benefit. It could actually cause harm, and we need to make sure that the patient or the patient's surrogate decision-maker understands that and is aware of any sort of conflicts of interest or any other issues out there that they should know about in deciding whether they want to do this or not.

Now, with regard to the institutions that don't have an Institutional Review Board, it used to be that they would just have to sort cast about and that the physician would cast about and try to find an Institutional Review Board that would be able to give permission for this attempt to happen. More recently, the WIRB-Copernicus Group, WCG, which is one of the independent IRBs, has been offering free IRB review for individual-patient requests. I am not affiliated with the company. I don't know any of the details of this, but that is an option out there in the last couple years that I am aware of.

And another change that has happened to try to streamline all of this is, under Scott Gottlieb, the rules were changed. It used to be that when one of these requests went to the IRB for a single-patient expanded access request, the entire Board had to convene to consider the request and to approve it or not approve it, and now there is an option for the physician to ask the IRB to just have one designated review. So that obviously makes the process faster by having just one person have to sign off as opposed to a whole Board.

And then I think the last thing that I want to say with regard to the expanded access process is that, again, for the emergency IND, you can actually skip the IRB up front if there is no time to go to it. In that

case, you are required to inform the IRB within five business days of the use of the investigational medical product on the patient, and you definitely have to involve the IRB before there can be any readministration.

So that is the expanded access process. Once the product is used on the patient, any serious and unanticipated adverse events that happen have to be reported both to the FDA and to the company. And the company, if it so chooses, may ask for more information back, such as efficacy data or some sort of pharmacokinetic data or something. That is at the company's discretion. But by law, the only thing that you are required to pass to the FDA is the safety -- serious adverse events that happen.

So I will stop and see if you have questions about that, and then I will go through the process for Right to Try since it does vary.

Dr. Barbara Binzak Blumenfeld: No. That is extremely helpful. Thank you very much.

I am just wondering, the sponsors are obviously really concerned about making sure that they can get through the FDA approval process. And as you mentioned, one of the hallmarks of that is to have sufficient data to show that a new treatment is both safe and effective. So I'm wondering, can sponsors collect data? You kind of alluded to this, but I'm wondering if you could elaborate on whether they can actually collect data through expanded access and how that can be used. I mean, does that actually, more or less, turn it into a clinical trial?

Dr. Alison Bateman-House: So there is a lot in there. And I want to remember also to go through the process for Right to Try, so you will have to help keep me on course to cover all of this information.

But with regard to your specific question, yes, a company can collect data from expanded access; and, yes, that does potentially start making it look like a clinical trial. So if you have a clinical trial that is open label where there is no randomization, every patient knows what they are getting, and you are collecting data from it that looks very similar to, say, one of these expanded access cohort programs where you have a group of patients who are getting access, they know exactly what they are getting, and some data is being collected.

So the distinction really is the idea of what is the intention here. Is the intention collecting data or is the intention treating patients? And, of course, in a clinical trial where the main intention is to collect data, there is also a secondary motivation, which is to hopefully be able to help those patients, but that is not the primary motivation. And then you just flip it around. In expanded access, the primary motivation is to potentially help patients, but, yes, some data can be collected as well. They look very similar.

Now, of course, whether something is expanded access or research has great implications in terms of legalities and the sort of regulatory technicalities, so there are pros and cons of going about things both ways. But just to answer your question, yes, you can collect data from expanded access, but what you need to make sure is a) that the patient or the patient's surrogate is informed about what it is that you are going to be doing. This should not be sort of a cheap and surreptitious way of collecting clinic trial data. That is unethical, as well as legally problematic. So if it is an expanded access program and you are going to be collecting data, the patients and the patients' surrogate decision-makers need to know that.

And the other real consideration is normally clinical staff are paid to participate in a clinical trial. They put effort into it and clinical trial budgets include line items to help cover faculty or salary expenses involved in the conduct of the clinical trial. Expanded access doesn't do that. No one is paying for that provider's time, and it is typically offered pro bono. So in that case, you want to be very cognizant of how much burden you are putting on the provider. Because once it becomes too much, especially if they are not getting paid or in any other sort of way compensated for that effort, they are just going to decide not to do it. So if the intent is to help a patient, but you put too many restrictions on it in terms of, well, you need to fill out all of these forms and you need to upload this data and we need this many scans, physicians are just not going to do it.

But I will tell you that the Reagan-Udall Foundation for the FDA, maybe a year ago at this point, maybe a year-and-a-half ago, did have a day-long meeting about the idea of can you collect data from expanded access that would be used both as part of your regulatory packet and also maybe of interest to payers. The FDA was there, I was there, several other people were there, patient advocacy groups were there. And in general, people endorsed the idea as long as it was

understood as sort of an adjunct source of data collection, not a replacement for clinical trials.

So I am going to move on now just to go through the process of Right to Try to make sure I explain that simply because it does contrast to the process for expanded access, which I have already gone through. So just to remind you, the process for single-patient expanded access is you have to get a willing doctor, then you have to get a willing company, then the FDA permits it to go forward, and then the IRB gets involved. Now, Right to Try started on the state level. It was an initiative by the libertarian Goldwater Institute, and they started on the state level. So we currently have 41 state Right to Try laws in effect. They are not all the same. They have different provisions. And then we have one overarching federal Right to Try law.

Now, generally speaking, a federal law would preempt state laws, but there are some provisions in the state laws that are not in the federal Right to Try law. And so it is a question for you lawyers, Barbara, to figure out whether those provisions in the state laws still stand or not, and I haven't seen any definitive decision on that matter. So despite the fact that there are some differences in the various Right to Try laws, and particularly in how the state and the federal laws interface, generally speaking, the idea is that they cut the FDA out of the process and they cut the IRBs out of the process. So in order to use an investigational medical product -- and in the Right to Try context, it is only a drug. It cannot be a device; it cannot be a vaccine. It is only drugs. You just have to have a willing patient, a willing doctor, and a willing company. Those are the three factors and then you can move forward.

That being said, one of the state Right to Try laws – I think California – does require that the IRB be used, and a number of medical institutions have said it is our grounds, it is our campus, we get to set the rules here and we want the IRB to be involved even if it is not required by law. And some companies have said in their policy that the IRB has to be involved, also. So whereas the federal and most of the state Right to Try laws did cut out IRB review in many cases, that has actually been added back in by other parties. In that case, there is no reporting of serious adverse event data to the FDA except for once annually, so it is not a sort of real-time feedback loop.

The patient population that can use Right to Try is stricter than in expanded access. So for expanded access, I said it had to be a

patient who was seriously or life-threateningly ill who had no other treatment options and who was unable to participate in a clinical trial. For Right to Try, they still have to be unable to participate in a clinical trial; they still have to have no other treatment options, but the patient must be life-threateningly ill. You can't just be seriously ill. I mentioned that it is only for drugs, as opposed to all different types of medical products.

And the other real big difference about Right to Try and expanded access is that Right to Try is only for drugs after they have successfully completed phase one of clinical trials, whereas expanded access is a pathway that you can use to use an investigational medical product at any point in development: pre phase one; during the clinical trials process; after the clinical trials are closed but the FDA has not yet granted marketing authorization for a product; and even, in some rare circumstances, for a product that was authorized for marketing use but then was withdrawn from the market due to side effects that were discovered after the fact for the patients who really still do need access to that drug even though it is at a higher risk level than we would accept for the general population. They can still access that product after it has been withdrawn from the market via expanded access, again, so long as the company is willing to provide access.

Dr. Barbara Binzak Blumenfeld: Well, that is extremely helpful. Thank you.

I'm wondering, do you have a sense of why there have been so few reported cases of individuals getting access through the Right to Try? Do you think it is a lack of knowledge that this pathway exists or do you think that there is pushback from the companies to provide the drug product under this particular pathway?

Dr. Alison Bateman-House: I actually think that there is more awareness of the Right to Try pathway than there is the expanded access pathway, and I think many people mistakenly take the expanded access pathway as being Right to Try. I think the idea that you can get some non-trial provision, in people's minds, just is Right to Try even though Right to Try is only one forum that is available in the country.

I think the reason why we haven't seen much of it is -- keep in mind, these companies, their aim is to bring a drug to market. And if you are going to bring a drug to market, you generally don't want to alienate

the FDA, and you see the FDA as a partner in this process. And to say, we are going to provide access to our drug in a pathway that deliberately cuts the FDA out both to review the request up front but then also with regard to us pushing to them quickly any serious adverse events that happen. I think the idea is that that doesn't set you up for a good partnership with the FDA. Now, I am not saying that the FDA would hold this against any company. I don't know that they would, but I think a lot of companies have just decided there is nothing wrong with expanded access. It works perfectly fine, and given that there is no real motivating reason not to use it, why would you potentially alienate the FDA.

Dr. Barbara Binzak Blumenfeld: Understood. Because as you and I both know, the relationship with the FDA is incredibly valuable when you are dealing with a new drug approval. And, of course, there may be hesitancy to jeopardize that relationship, so that makes sense. Thank you.

I did want to, in the light of Coronavirus, just bounce an example off of you. We have been hearing that Gilead has transitioned non-trial access to Remdesivir from individual compassionate use requests to an expanded access program. So perhaps building on everything you have explained so far, can you explain what this means and what the implication would be for a patient who is being, quote, unquote, "transitioned?"

Dr. Alison Bateman-House: Sure. And, I mean, this is a really timely example, and I know it is one that caused a lot of concern when it was announced in the paper, so I am glad you mentioned it. And I should mention that whereas I work with lots of companies, I have had no contact with Gilead, so this is just me as an outsider opining on what is happening without any inside knowledge.

So Gilead agreed to provide this particular drug, this Remdesivir, to patients suffering from COVID-19 outside of clinical trials, even though it appears that they are doing a really good job of prioritizing putting anyone who does qualify for a clinical trial in a clinical trial. And remember, in terms of the legal criteria for expanded access and just sort of the ethical obligation to collect data for the good of advancing evidence-based treatments, we really do want people to get in clinical trials as much as possible. But for people who could not get into clinical trials, Gilead was willing to grant access. And I saw reports in the media that they gave several hundred doses of the drug to individuals through this individual-patient expanded access program.

So keep in mind, for every single one of those, the doctor had to reach out to the company and then the doctor had to get in touch with the FDA and the FDA had to review the request for that individual patient and then that individual patient request had to go to an IRB. And whereas that works really well as sort of a one-off or maybe a two-off, it is overwhelming when you start having high volumes.

So what Gilead did is say we are not going to be using this individual-patient expanded access pathway as our default pathway. We are going to switch over to one of these cohort expanded access pathways, for the most part. And so in that context, what you are going to do is you are going to have a physician who is sort of like the physician for a particular institution. That physician is going to be in touch with the company; find out, yes, we can get the patient in on this program; but the protocol has already been approved by the FDA, and there is going to be use of a central IRB. So it really does cut out some of the procedural steps in terms of the fact that the physician just has to get permission to enroll the patient into this expanded access protocol. It really is more similar to a clinical trial. And, again, many physicians are more familiar with clinical trials than they are with expanded access, so this would be something that they are more familiar with navigating.

Now, my understanding from publications put out by Gilead is that they are still also going to be doing the individual patient request at the same time, and the reason for that is the cohort expanded access programs, they are going to have some sort of inclusion criteria. They are going to be very low because the point is treatment, not data collection. So it is probably going to say something like the inclusion criteria is that this has to be a patient with diagnosed COVID-19 infection, in serious condition, maybe on a ventilator, hospitalized. I don't know what it is going to be, but there is going to be some sort of inclusion criteria or maybe even exclusion criteria. For example, no pregnant women. And then, if you have a patient who does not qualify to go into one of those programs, that is where the individual patient request will come into play, and they have said that they are going to continue accepting those individual patient requests for people who do not qualify for the cohorts. And one of the categories that they mentioned specifically was pregnant women, so if you are a pregnant woman and you cannot get into the Remdesivir cohort expanded access program, your physician will still be able to put in a request for you through the single patient.

And so I think there was a lot of concern about what does this mean, especially because they stopped accepting single patient applications for several days as they were transitioning over, but I think that was just necessary. My understanding is that they were falling behind in being able to respond promptly to requests, and this just really was a move to make things smoother in the long run and able to accommodate a higher volume of patients in a fast manner.

Dr. Barbara Binzak Blumenfeld: Great. Understood. That was very clear. I wanted to --

Dr. Alison Bateman-House: And actually -- I am sorry, Barbara. I just want to add into there that in these cohort programs, it is easier to collect data than it is in these single patient requests. So if they are collecting data from expanded access, which I believe they said that they are doing, it will be easier in this sort of more protocolized format than it was when you are dealing with a bunch of individual patients -- sorry -- individual physicians, individual IRBs, and all of that.

Dr. Barbara Binzak Blumenfeld: Understood. That makes perfect sense. Thanks for clarifying.

I was hoping I could just circle back to something that you mentioned regarding off-label use. And one thing we have been hearing a lot about in recent days, as recently as today, in fact, is that there are all sorts of products out there that have been approved for whatever particular use, and they have people who need those drugs every day. They are now being considered as a possible option for the treatment of the Coronavirus, and I am sure you have seen as well there have been even some popular press articles where some of these patients have lamented the fact that they cannot get as easy access anymore to a drug that may be lifesaving to them for a completely different indication that has nothing to do with Coronavirus.

And I don't know if I have so much of a question or if I just wanted to kind of gauge your thoughts and your reaction to this when we have sort of a -- we are pushing up against people who need an approved product and we are having a lot of interest from another sector that thinks this could be useful for Coronavirus. I just open that up to your general thoughts, if you would.

Dr. Alison Bateman-House: Sure. So I have two general thoughts. One is that I have zero problem with us trying drugs that are approved for one indication in a new indication. If there is scientific reason or a valid hypothesis that it may

work, then we certainly should be looking at it. The problem is that there is a difference between looking at it in a controlled, systematic way where we collect data that will help us develop evidence-based procedures moving forward in terms of this works, this doesn't work, these are the side effects that we need to be aware of versus a series of one-offs. And so if you are doing off-label prescription outside of any sort of protocol and without data collection, that may result in individual patients getting access to things that we think may offer them some help, but it doesn't get us any closer to the final goal in terms of finding a treatment that actually works for this disease.

So whereas I have no problem with us trying to figure out if it is a good idea to repurpose some preapproved drugs, we really should be doing it in a trial setting or, at the very least, in some sort of setting, a registry or something where we are getting some useful data. So that is the one point that I would like to make.

The second point that I would like to make just as an ethicist is it is absolutely inappropriate to divert drug to an unapproved use at the expense of people who could be using that drug for an approved use if there is no data to support the utility of that. You really need to do the trials to find out if it works or not. If this drug being repurposed to COVID-19 is a safe and effective treatment option, then we need to have the hard discussions of, in a situation of scarcity, who should get it: the COVID patient or the lupus patient who has been using it for years. But we are not at that point right now. At this point, we have one approved use. For example, lupus or malaria or stroke or whatever the treatment that we are talking about is. And then we have a hypothetical unapproved use. You should never be taking a drug away from patients who we know are going to benefit to divert the drug to people for whom the treatment is not validated yet. It is just absolutely inappropriate, and I am really dismayed to see that that has been happening in some situations.

Dr. Barbara Binzak Blumenfeld: Yes. Like I mentioned, I know we have both seen these articles, and I think your explanation was excellent about some of the not only legal and perhaps regulatory, but also some of the ethical hurdles that this presents.

So I'm wondering, basically, do you have any other thoughts, in general? Do you have any parting comments that you would like to provide? I know we have covered a lot of ground today, and there is

certainly a lot more that could be said. What haven't I asked you that you would like to get out there and make known?

Dr. Alison Bateman-House: Did I talk about charging?Did I talking about charging under expanded access or Right to Try?

Dr. Barbara Binzak Blumenfeld: I think you may have in passing mentioned it. But please, I would love it if you could expand on that point.

Dr. Alison Bateman-House: So this is a situation that I see a lot of confusion about, so I just want to clarify that real quick. Under both expanded access and Right to Try, a company is able to pass along to the patient or to the patient's payer, if the insurer is willing to pay those expenses, the cost of creating and providing that drug.

So, for example, if it costs a company $500 to make a drug and to ship it over to that patient, you can charge that patient that $500. What you cannot do is attempt to profit from an unapproved drug. So I see a lot of companies saying, well, we can't possibly provide access to our investigational medicines because it is going to cost us money. It is going to cost you money because you are going to have to have staff, you are going to have to figure out legal advice and take time to write policies and procedures. It is not a cost-free initiative.

But in terms of the actual cost of drug and the cost of provision, that can be passed along to the patient, and I'm not sure many people understand that. In Right to Try, when the federal bill was being debated, there was a provision that did allow for charging a profit, and that was removed when the bill was actually signed, passed in the final iteration. So it is the same rules for both Right to Try and expanded access that you can only pass along cost, you cannot profit.

Dr. Barbara Binzak Blumenfeld: Great. Thank you. Yes, that makes sense.

I am wondering -- and forgive me if you did touch on this as well. Like I said, we have covered a lot of territory. But can you access vaccine via expanded access or any of these other pathways?

Dr. Alison Bateman-House: Definitely through expanded access, not through Right to Try. Right to Try is only for drugs.

Dr. Barbara Binzak Blumenfeld: Okay. Very good.

What would you recommend -- obviously, you are a tremendous resource for a question such as this, but are there other places that you would recommend people look to perhaps gain more information about all of these pathways? I know you talked about educating healthcare providers, which is one of the main and the first and foremost challenges.

So I'm wondering, you and your organization, what kind of resources do either you provide or are you aware that others may provide that could also be helpful?

Dr. Alison Bateman-House: Well, thanks for the opportunity to put in a plug for CUPA, which is the group that I coach here. CUPA is the Compassionate Use and Preapproval Access working group out of New York University School of Medicine. It is an academic group, and one of our self-imposed missions is to provide education about this very complicated area. So if you just Google NYU CUPA, C-U-P-A, you will hit our website, which has a frequently asked questions page that we keep updated, and we also do a free monthly newsletter that anyone can subscribe to. We also provide webinars and frequently asked questions, handouts to -- say, for example -- patient organizations. So we try to provide a one-stop shop for people to get information about this.

Outside of us, the FDA has a lot of information on its website that I recommend. And one of the newer options that is available for people is, as I mentioned earlier, the Reagan-Udall Foundation for the FDA has gotten involved in this issue, and it actually created something a few years ago called the expanded access navigator, which is a repository for companies to post their expanded access policies in one place instead of doctors having to go from website to website. And there is also just information about frequently asked questions about the process there. So there are some U.S.-centric resources out there. CUPA tries to be global, but I am not really aware of that many other places outside of the United States where you can get this information.

Dr. Barbara Binzak Blumenfeld: Great. That is extremely helpful because we know we are all receiving a barrage of information these days regarding Coronavirus and COVID-19, so those sound like some excellent resources.

Before we close up, did you have any other parting comments that you wanted to provide perhaps in closing?

Dr. Alison Bateman-House: So I guess I would just take a moment to stand on my soapbox as an ethicist and to say there are some serious ethical concerns here that people need to think about. Particularly, in a pandemic, where there is no approved treatment and where there is mass morbidity and mortality, there is a desire to just throw anything at the disease in hopes of helping people, but we really can cause harm. Even if a patient is dying, it is quite possible that an intervention can hasten the dying process or make it more painful. So there really should be some checks and balances in terms of what we are exposing patients to, even under the best of intentions.

I just want to caution people that any time you give an unapproved or an off-label product to a patient and the patient improves, we just tend to default to think, wow, it worked, that was great, whereas if the patient dies, we tend to attribute it to the underlying disease process. And that is just human nature. That is how we are. But we really do need the data and the evidence to be collected to be able to make these evidence-based treatment protocols. And that is important both on scientific and just evidence-based grounds, but it is also important on ethical grounds. We have a duty both to the patient in front of us and to the patients in the future to try to do the best we can to make sure that we are treating them according to evidence as opposed to just hypotheses that we have not bothered to test.

So in the initial wave of this disease, I think we are going to be seeing people throwing everything, including the kitchen sink, at the disease, which I think is reasonable. But at the same time, we have to be collecting evidence so that we can start weeding out the harmful treatments or the ineffective treatments as quickly as possible in order to give both current and future patients the absolute best chance we can.

Dr. Barbara Binzak Blumenfeld: Understood. Well, thank you.

Dr. Bateman-House, I know you have been extremely busy lately and very generous with your time, so I would like to thank you for sharing your expertise on these issues. These certainly are trying times, and we know the medical landscape is shifting daily, but your perspective has really provided some valuable insight, so thank you.