BBGuy Essentials 098CE:
"Simply REDS" with Steve Kleinman and Cassandra Josephson
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Cassandra: Hi, I'm Cassandra Josephson. I am the co-chair of the REDS-IV-P program sponsored by the NHLBI, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hi, everybody. Welcome back to Blood Bank Guy Essentials, the podcast designed to teach the essentials of Transfusion Medicine to learners everywhere. This is episode 098CE and my name is Joe Chaffin. This is really a unique episode. I'm very excited for you to hear it. We usually take a specific topic and really kind of dive into it and dissect it.

But today is actually more about a project, and it's not just any project. It's a huge multi-decade project known as the "REDS research project." We have today, the two co-chairs of the current phase of the REDS research project, and I can't wait for you to hear what they have to tell you about the exciting directions this is going.

But first, this IS a continuing education episode. The free continuing education credit is provided by TransfusionNews.com, and Transfusion News is brought to you by Bio-Rad, who has no editorial input into the podcast. This podcast offers a continuing education activity where you can earn two different types of credit: One AMA PRA Category 1 Credit™, or one contact hour of ASCLS P.A.C.E.® program credit. This activity also may be used to fulfill Lifelong Learning Continuing Certification requirements for the American Board of Pathology. To receive credit for this activity, to review the accreditation information and related disclosures, you just need to visit www.wileyhealthlearning.com/transfusionnews. Very important, don't forget: The continuing education credit is no longer available for this episode two years after the date it was released. In other words, **credit for this episode will expire on July 17th, 2024 [NOTE: I said "July 12, 2024," but the episode will be available from** .

All right. So, as I mentioned earlier, we are talking today about a project, but it really is not just any project. Let me just take you in a time machine for just a few moments back to the 1980s. Yeah, I know, for some of you that's way before you were born, I totally get that. But in the 1980s, there was a whole lot going on in blood transfusion world that was really, really scary. Certainly, HIV was the 200-pound gorilla in the room, maybe even more than 200 pounds, that was scaring everyone when it came to transfusion of blood. In fact, there were some very famous and widely known individuals who became infected with HIV as a result of blood transfusion.

But we also weren't sure what some of the other viruses were doing, including another retrovirus known as the "Human T-cell Lymphotropic Virus" or "HTLV." Well, as a part of the response to that, the National Heart, Lung, and Blood Institute, or the "NHLBI," put out a request for really a multicenter study to look at retroviruses in blood donors, specifically HIV-1, HIV-2, HTLV-I, and HTLV-II.

And five centers came together in response to that three of those centers from the American Red Cross, one from Oklahoma, the Oklahoma Blood Institute, and one, Irwin Memorial Blood Bank in San Francisco, and the "Retrovirus Epidemiology Donor Study,"

or "REDS" was born. And over 30 years later and after a whole ton of breakthroughs and really a shifting focus away from those retro viruses, we've now entered the fourth phase of REDS, which is called REDS-IV-P.

And today I have the two co-chairs of the REDS-IV-P phase of the REDS research project, Cassandra Josephson and Steve Kleinman to tell you all about it. And, if you have listened to this podcast before, you're certainly familiar with Cassandra Josephson. at the time that I recorded this podcast, she was a professor in Pathology and Pediatrics at Emory University, but she is now at Johns Hopkins University. Dr. Kleinman is a Clinical Professor of Pathology at the University of British Columbia. Please check out their bios at BBGuy.org/ 098.

Both of these physicians are extensively published scientists and they really want to share with you where REDS has been, as well as the incredible and exciting new directions that REDS-IV-P is taking us. You really won't want to miss this because this project is going to help shape the way we practice transfusion medicine in the future; both in the near future and the distant future. And I'm so excited for you to hear it.

So, without further ado, let's hear this interview on the REDS-IV-P project with Dr. Steve Kleinman and Dr. Cassandra Josephson.

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Joe: Steve welcome to the Blood Bank Guy Essentials Podcast.

Steve: Thanks, Joe. Good to be here.

Joe: Thank you so much. Cassandra, welcome back to the Blood Bank Guy Essentials Podcast.

Cassandra: Thanks Joe. I'm glad to be here too.

Joe: As I said in the introduction, everyone, I'm so honored to be able to talk to both of these wonderful physicians about the REDS-IV-P project. And there are so many things that we could go into about this, but I really felt like for the benefit of everyone listening, it would behoove us to get a real good background look at things that have been done in the past with the previous iterations of REDS and I think it starts Steve with just if we can, let's define for people who might not be aware, maybe they've seen that abbreviation. Where did that come from? And what's the origin of the whole REDS study?

Steve: This goes back quite a way, Joe, actually the initiation of the REDS program by the National Heart Lung and Blood Institute with NHLBI in the United States, which does a lot of funding of research started in 1989. It came out of the infectious disease concerns of the 1980s with regard to blood safeties, HIV, of course, being the predominant agent and also Hepatitis C, but NHLBI felt that they needed to have an ongoing program in looking at blood safety. HIV being a retrovirus, the study was termed the “Retrovirus Epidemiology Donor Study.”

Pretty explanatory actually, because we were looking at epidemiology of HIV, but it was much broader than that. We were looking at epidemiology of all infectious agents of concern.

So, when we first began, actually one of the contract requirements was to enroll people, donors who identified as HIV positive, and learn why they donated blood, but by the time the program got underway in 1991/92, after the funding was achieved, that had already been done by other agencies in the US government.

So instead we did a large study of donors who were infected with HTLV. Human T-lymphotropic virus type 1, also a retrovirus. And that was the first huge study done in REDS that followed people over time for disease manifestations. But the first rendition of REDS lasted 15 years, same centers, three, five-year contracts that were renewed and the real emphasis there was blood safety and blood availability.

Joe: Just for clarity, were these blood centers or were these hospitals that were involved in the study initially?

Steve: Back in the first two renditions of REDS so the first 20 years it was a donor-based program. Multi-center because we needed to have geographic diversity within the United States and also, we needed to have large numbers of data points.

And one of the main functions of REDS was to build an infrastructure that would allow this kind of research to be done. As you probably know, most blood centers, at least the back many years ago, have their hands full just with being operational. And doing all the things they need to do to get blood to patients while there was some degree of research that was going on at blood centers, there just wasn't the financial support and the infrastructure to conduct the kinds of large programs that were needed. The original reds had five different blood centers that were part of the program and they were large blood centers.

We were able collect data on, maybe I'm guessing about a million or more donors per year.

Joe: Wow!

Steve: And all of those data files obviously anonymized with appropriate confidentiality were transferred. REDS could do these big kinds of epidemiological associations, correlations, laboratory test performance, compare natural history studies, the whole bulk, which required a lot of participating centers.

Then after REDS II, which ended in 2012, NHLBI took another look at what was important in transfusion medicine safety and said, we've got good studies in blood donors now, in fact, through our program, other research institutes in the US that are centered at blood centers really are doing great research.

American Red Cross, Vitalant, several other blood centers had the opportunity to put research programs in place. The question then became, what should REDS do if it goes further? And the answer was, we should focus on recipients. We should do some donor

research, but we should also start to focus on recipients. There was a subtle change to the name of the program.

We kept the acronym REDS, but we changed the “retrovirus” to “recipient.” We became the “Recipient Epidemiology and Donor Evaluation Study.” REDS III. That study, while still doing some donor research and some very significant donor research in the area of precision medicine also started doing recipient-based research and built what we're calling a vein-to-vein database.

That's where hospitals were brought in, REDS III. In REDS I and REDS II, it was only donor centers, but in REDS III, each donor center needed to bring in three affiliated hospitals. We had four donor centers and 12 hospitals. We were able to gather recipient data from the electronic medical record and build what was the first, I think, in the US vein-to-vein database, that's being expanded in REDS-IV-P as I'm sure you'll discuss in a little while.

Joe: You had mentioned in the original REDS that we were looking specifically at the United States, has there been, or was there between REDS I, II, and III or original REDS and REDS II and REDS III, was there an attempt to expand this internationally?

Steve: Yeah, absolutely. When REDS-II began, it was about 2006. We'd been going for about 15 years. And we recognized that, although there were still outstanding issues, for example, with HIV transmission, we just had really accomplished a mark increase in safety in the us. So, we couldn't really ask those questions anymore. We just didn't have enough positive people.

And so, the NHLBI, I decided to expand into other countries where you could do this kind of basic research. And so, REDS-II added blood centers in Brazil and blood centers in China. And then REDS-III continued with that and it became even larger and added blood centers in South Africa, which I think as most people know had one of the biggest and continue to have one of the biggest HIV epidemics in the world.

And so, we were able to do modeling, mathematical modeling of incidents, risks for HIV, evaluate new testing algorithms to see if they improved risk based on bringing in the south African cohort. REDS-IV-P scaled back a little bit but has continued its research in Brazil. So, we're still international.

Joe: I would like to, if you don't mind, just take a little side trip based on something that you just said, because I think that a point that you made is massively important for learners and it may feel like I'm pulling a small point out of what you said, but I think it's so important. You mentioned that once we got to the phase of looking at REDS-II, and I'm paraphrasing you, because I'm sure I'm not going to say it exactly as you did, but that there were such a small number of positives in the United States that we needed to expand internationally.

And I'm not sure that's something that's necessarily widely appreciated. Simply because there's been over the years so much focus on the safety of blood. And especially among our clinical colleagues, there's been concern. I think those of us in transfusion medicine have known the small numbers of people that test positive over the years.

But what's your perspective having seen this from the start to, until now about how blood transfusion safety in particular, in regard to infectious diseases, transfusion, transmitted diseases have changed.

Steve: Well, if you take the perspective back to 35 years ago in 1985, of course the situation was so different with IV causing lots of infections from 83 to 85 and hepatitis C just beginning to be appreciated.

And that of course infected even more people over the many years. So, I think as we move forward, we began with HIV, Hep B and C, those were the ones we were concerned with. We thought we had brought risk down and then West Nile Virus came on the scene in the early 2000's. And so, we now had another infectious agent that was actually causing mortality in transfusion recipients, but that problems got solved.

And clearly emerging pathogens have been an issue that those of us in transfusion medicine who are into the infectious disease part have kept a front and center. And that has been one of the really important aspects of REDS in that we have been able to piggyback onto REDS what we called the rapid response capability.

When a new agent comes on the scene, it needs to be studied. But if you go through the grant making process of having to obtain the money, you're six months, a year, 18 months out, and you've missed the boat. What NHLBI was able to do is through this structured REDS program. Say, if something new comes on, we can go and get some additional funding and put it through the REDS program that has the capabilities, having an excellent virology laboratory has an excellent analytic capabilities and statisticians and large donor database. That capability is there to study a new agent. We can get studies off the ground really very quickly. And so over the course of 15 years, we've done this with West Nile Virus as I mentioned, dengue virus, which needed to really be studied where it was, which was in Brazil, couldn't do that in the US. Zika virus, which again was studied both in the Brazil and the US because you may remember we were doing Zika virus testing in the US for about four years. And now in this current wave, we've actually done studies on SARS-CoV-2, which fortunately turns out not to be transfusion transmitted.

But the REDS group has done several studies to actually, I think, supply the best data about transmissibility of SARS-CoV-2 via transfusion. If it exists, it's extremely rare. Obviously not something we have to worry about. So we've kept the blood safety capability, but clearly once we got to the mid-2000s,, it was not the most important issue because we had it under control, took the major part of the REDS program and moved it over to issues that was still transfusion safety issues.

I don't know if you recall, but REDS-II had two major projects. One was on TRALI, transfusion-related acute lung injury, and monitoring the donor population, specifically, females looking for HLA antibody and doing some of the baseline research that led to the policy shift of either not taking female plasma, or if you take it by HLA.

And then the other issue that we studied extensively in donors was frequency of donation as it's related to iron deficiency.

Joe: So important. And I think that a lot of times to people either in or out of transfusion medicine, the role that this project has played in things like implementing things, such as you just mentioned with TRALI and taking a fresh look at donors and their iron status, I think it has felt to some, a little bit "invisible." I'm really glad that you brought out the fact that this project has contributed so much aside from just the infectious disease stuff over the years.

Before we get a little bit more into the REDS-IV-P project, specifically in this particular iteration, two questions come to mind, Steve, as you were talking. The first is I think that to the public, even in transfusion medicine, it's a little hard to understand when we say "REDS has done this," or "REDS has done that," I know you mentioned like for the first one, there's a, there were five US centers. Is there an infrastructure to REDS? How is all this coordinated? Is it done through NHLBI? Is there a separate organization? How does that work?

Steve: That's a great question, Joe. Basically, it's a multi-institutional project and it's coordinated at the highest level by NHLBI. And they're three major pieces. Well, maybe four. Participating blood centers/hospitals, that's one or two pieces, depending how you look at it. They're called hubs. And then there's a data coordinating center. And that has changed in the different iteration of REDS. Currently, it's actually the first two versions and it's REDS-IV. There's a company called Westat out of Rockville, Maryland that does this kind of work.

So, they coordinate everything. They have fantastic resources. In terms of data management and data analysis and statistical support. And then there's a central testing laboratory, which is now at Vitalant Research Institute in San Francisco that coordinates any laboratory testing we are going to do either they do the laboratory testing themselves, or they source out the laboratory testing to a very accomplished laboratory. So, all this comes together and then we have several committee structures within REDS. The overall decision-making body is the executive committee or executive steering committee. And so, we have a PI, a steering committee chair, and co-chair, that's Cassandra and I for REDS-IV-P. I had the fortune to also do this in REDS-III.

And we have the project officer from NHLBI actively participating and being sure that we're doing things that are responsive to what NHLBI wants us to do.

Joe: I guess one last thing before we dive into the details of REDS-IV-P or at least the overview of REDS-IV-P. I'm telling you in advance, this is an impossible question. I know it's an impossible question, but you've already hit some of the highlights of some of the benefits that came from REDS, REDS-II, and REDS-III. And if I have my dates correct, we're looking at a project that in various iterations covered a 30 plus year timeframe. I would ask you to try and as best you can, thumbnail for us, because we don't have time to go into each one, but some of the, what you would consider the most major contributions to either the literature or our practice or our knowledge that came from these three particular iterations.

Steve: Yeah. That's, that's a tough question. I have my favorites…

Joe: I warned you!

Steve: But yeah, you did. So, to me, the first breakthrough that we really had that was novel, I think was beginning mathematical modeling of what residual risk of infectious diseases--could we quantify it? And so, we came up with what we call an "incidence window period" model, and I won't go into details, but it was the first application. We used to study transfusion transmission by actually measuring the events. We put together these large repositories of thousands or tens of thousands of hundreds of thousands of samples and test them and come up with numbers. Too expensive and just too hard to continue to do. As risk came down, in order to quantify these risks, we needed mathematical modeling now, and we needed to bring in people who knew how to do that because we don't get that training in transfusion medicine.

And so, we developed the incidence window period model for determining risk in your country, widely used internationally now been modified into several other models, but this was the sort of heart and soul of it. And that has allowed, I think, in every country for policy makers to say, "Here's the current risk that we estimate, should we put in the next intervention, whatever, should we upgrade our testing that always comes with a cost, right?" That we don't have unlimited funds. That allowed people to at least say, "If we put this in, here's the benefit that we expect to get," and then they could ask further, "Are we ready to do that in our country?" So, I think that was a very significant one and it really highlights that the science that we do is integrated with public policy, whether it be blood bank policy, or broader policy. So, I think that was an important one.

I think the other really important one is the establishment of these linked databases. So, we now can follow a donor, gives a unit. We have all the information about the donor. The unit goes through a number of manipulations. Maybe it gets irradiated. It gets made into a red cell and a plasma. The red cells get irradiated. If it goes to a hospital that's participating in REDS-III or REDS-IV, now we can trace the individual who gets it. And we can get the whole medical history on that person from the electronic medical record. And it begins to allow us to ask questions, "Are there donor component or recipient factors that actually affect the outcome of this transfusion?"

Now, the outcomes that we're able to measure are varied. We've focused on in-hospital mortality because it's the most definitive endpoint, but I think you might hear from Cassandra there's some other things going on. So, I think now there are vein-to-vein databases in other countries. But I think we brought ours in around the time that other people were thinking about theirs.

So I think we're kind of the first, or maybe the most extensive one, we're not the only one anymore, because there are national blood services in other countries that have done the same thing, but of course it's quite useful to be able to do these comparisons everywhere. It's a good thing that we have multiple ones, but I think that is a step forward into the recipient stage of these studies.

So, I guess those two stand out for me really on top of the list.

Joe: We will expand on certainly on the second one as we move forward. Thank you so much, Steve, for that incredible overview and a lot of things that I think will open people's eyes a bit, and this project has been just incredibly helpful in advancing our

knowledge and really influencing practice in transfusion medicine today and into the future.

Cassandra, how did you get involved? I know obviously you were at least watching much of this, but at what point did you become involved and how did you become involved?

Cassandra: That's a great question, Joe. I think that what happened is that as time went on and things shifted into a more recipient-focused REDS program, they looked at different recipients. And of course, my whole career, as people know, has been dedicated to pediatric transfusion and so with my research background, plus with the focus on Peds, and REDS-IV-P really the "P" standing for pediatrics. I think that the thought process was that I would be a good compliment to what had been going on with REDS-III, and that was majorly focused on adults.

And so that was where I fit in to ask to do this, but I do want to say that there were pediatric patients that wasn't the inclusion criteria for being in REDS-III, but by being in REDS-IV, we were able to look back at the REDS-III public use database after it was used by REDS-III, and we were able to add value to what pediatric data there was and add stuff to the literature. That's how we have bridged the two.

Joe: Got it. So, let's be specific then. What are specifically the things that REDS-IV-P is targeted towards? Whether you want to talk about the mission, the purpose, et cetera, in whatever level of detail you want, Cassandra. What is REDS-IV-P designed to do that either supplements REDS-III or the previous iterations of the study, or it takes it in new directions?

Cassandra: I think it's just to piggyback onto what Steve said is that basically the seesaw has shifted a little bit more towards the recipient. However, the donor is really, really important, and that was really found out by many of the studies that came out of REDS-III. And what happens to the blood that's donated and what those donors contribute different aspects to the blood itself that's going into the recipients. What REDS-IV-P is more focused on is not just children, but it is over the lifespan.

So, we're more maternally-fetal focused, which was not a focus of REDS-III and different types of populations, such as patients with hemoglobinopathies, sickle cell, thalassemia. Looking at special populations is more of a shift with REDS-IV-P and absolutely special populations are children because even though pediatrics is grouped as one, it's really made up of multiple subpopulations and pre-term infants and neonates were really not part of the scope of REDS-III.

And so, if I was going to say a shifting difference between the first couple of iterations and now has to do with the effectiveness of transfusion, safety's still there, but the minimization, or trying to understand adverse outcomes and ways that we can look for modifiable, either risk factors or modifiable interventions, eventually based on epidemiology. I think one of the big steps forward with REDS-IV-P is that the epidemiology in children, there was no real mechanism to study that in the transfusion donor realm. People have tried to piecemeal that in different areas myself included with

different grants and things, but for the first time, the epidemiology of children and pediatric transfusion medicine is the main focus.

And that's really what is necessary, to build more studies going forward that would eventually be like phase two, phase three, but we just don't have that information. That's one of the other big, important aspects of REDS-IV-P that's different than the rest.

Joe: Okay. And one of the things that you touched on there that I want to make sure that people understand, Steve mentioned the vein-to-vein database that was a big part of the breakthrough, and one of the big accomplishments, really of the REDS-III iteration of this project. How is REDS-IV-P expanding that database? It seems like that is a really crucial part of what's happening and what the plans are moving forward, unless I'm misunderstanding. How is that plans to expand and what's the usefulness of that?

Cassandra: To think of it as the backbone of the project and the program is the best way to do it because it's going to be used in studies that are going, that are prospective studies that are planned for REDS-IV-P. It's also going to be used as the format to do analyses of different questions that could be queried, as Steve was saying.

The big difference is there's been an evolution, obviously from the one, two that the recipient stuff was on paper and a lot of stuff, even at the donor centers was in its infancy. And then when you go to REDS-III, you have the evolution of the electronic health record and things now we can abstract electronically, so that's much more efficient and we can tie it with the donors.

The issue of developing a database, as everybody knows, like we all try at our places to try to understand things, is that we try to have to decide what we want to collect. And make sure that we're including every single thing that we might have to control for, and God forbid we should miss something because then we have to go back and that's like the kiss of death.

Joe: Yes.

Cassandra: Oh my God. Now I can send somebody back in and even then, it's still partial manual, partial electronic. What I think the evolution between the REDS-III vein-to-vein and the REDS-IV vein-to-vein has to do with the change in database architecture and using something called the observational medical outcomes partnership common data model.

And that's like, really a lot of words. And I had to learn about really what it was. So, I don't sound that smart, even though it sounds pretty smart. So, people call it “OMOP” and basically there has been code that has been built that really makes different things, different observational data bases have common coding, so it can all be brought into one central way of looking at it.

And Medicaid and other places have already stepped into this modeling process and have been using it. Now, they haven't been using it for transfusion medicine, so they haven't been using it for components and they haven't been using it for how you transfuse the product and things, but they have been using it to grab stuff out of the electronic medical records, such as vital signs, such as diagnosis codes, but get really into the flow sheets, get into like how much fluid was given.

Which is different than just doing like an administrative database where you just get the ICD-9 or ICD-10 coding. So, what they've done with this common data model is pull things together. And now we can actually transform by asking the hubs because there four hubs in the United States with 22 hospitals and six of which of hospitals are now children's hospitals. And we can ask those places to submit data and it can be transformed into this common data model. And we also Westat is working to also translate and work on building code for transfusion data, which is really novel.

And the reason this is so important with this whole structure is because when REDS-IV-P is finished and there becomes a public data set that data set is going to be so "plug in-able" for lack of a better term, into other databases.

So basically, you can start asking really huge questions because you can combine a whole bunch of data and patient information. And other places are now going to be able to have code built that has to do with components and transfusion and modifying those components and all those things that we know are so important and are somehow missing everywhere.

That's really what's happened between the REDS-III structure. It's not really a continuation of REDS-III. We are rebuilding because as Steve said, there is a recompetition, so the same hospitals in the same blood centers are not exactly the same as REDS-III. But this kind of model the OMOP is what's going to go forward.

Joe: That's exceptionally cool. There's so much again that we could dive into with that, Cassandra, you're very well aware. And by the way, you did sound very smart there. I just wanted to let you know that was at stand.

Cassandra: Yeah. I practiced it a lot.

Joe: That was very cool. By the time this interview is published, I believe we will either be right about at the time that you guys have a paper coming out in the Journal TRANSFUSION either right about the time this podcast comes out or shortly after. And everyone I'll have a link to that on the show page for this episode, which will be at BBGuy.org/098.

Please check that out. The paper that's coming out and you guys have been kind enough to share with me somewhat of an advanced version of it. Describes a whole lot of research that's already begun regarding REDS-IV-P and there's a lot of super exciting stuff in there, including one that's very near and dear to my heart and that's looking at ABO-nonidentical platelet transfusions. I'm so excited to finally maybe get some sort of an answer about what's happening with that, but that's a topic for another day, but Cassandra, for the rest of our time talking, I would like to focus in on two projects that are happening now that are summarized in that article.

And in particular, I know both of them are near and dear to your heart. The first one that I'd like to hear from you about is the "TIPI study," the "Transfusion In Pre-term Infants" study. So, what can you tell us about what's going on with that and how that fits in with REDS-IV?

Cassandra: As I was alluding to before epidemiology is key and really preterm infants are one of the most, as you've heard me say before, transfused patient populations that we have.

We don't have any database that exists in the whole world, including the one I'm going to tell you about that we're going to connect to that actually collects transfusion and blood bank data. What this gives up an opportunity to do with TIPI, it's actually an extension of the vein-to-vein.

So, there's no intervention here. There's no…we're not collecting blood. We're not doing sampling of anything. This is purely an epidemiologic study and by using the vein-to-vein, we are in this OMA configuration. We're actually joining with something called the "Vermont Oxford Network." And they are a quality improvement education, somewhat research-based organization that looks both at academic and private hospitals and looks at outcomes.

And they've actually been doing this for over 30 years, looking at outcomes in pre-term infants. They have a very rigorous way and definitions of outcomes that are common to pre-term infants. What we have done with the pre-term infant study is connect the vein-to-vein to the Vermont Oxford and ask those questions of how do modifiable variations within transfusion products, the thresholds, and the modifications that we do to the blood, how do they affect adverse outcomes in very low birth weight infants that weigh, their birth weight is less than 1500 grams. The kinds of outcomes that we worry about, and we've got a composite outcome for this particular primary outcome looks at retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, late onset sepsis, intraventricular hemorrhage, or death.

Those definitions and that data is going to actually be identified through the VON, through the Vermont Oxford. It's going to be tied back into what is being collected from the donor donation component information, as well as what's being collected like things that aren't in Vermont Oxford, like the vital signs like the fluid chart.

What's going to end up happening is we could do logistical regression and different things within the analyses and tie those together to get some of our answers that we do not know. We're going to study like almost 3,500 babies. We're going to study a lot of patients. And one thing that's really unique about the vein-to-vein is we also have babies that are not in people that are not transfused. So, we collect all the information about the patients that are in the hospital at that time. So, you can actually get denominators and be able to see who the controls are, who is being transfused. Who's not. And this vein-to-vein database has that capability. The other thing is, there's a waiver of consent, but we have a common IRB and we're able to get this information without having to get consent, which is a huge step up.

We can really collect all this information freely. We have to define to the IRB what that information is, but it's done in a way that's de-identified and we're not going to be able to, we don't need to have consent from the parents.

Joe: It sounds like there's an awful lot of currently unanswered questions in transfusion in this super vulnerable population that hopefully we can start to get some answers to

including, and I liked what you said because it's something that's not always thought about.

Not only donor characteristics, but modifiable blood product characteristics. You and I have had conversations about that in the past, such as things like anticoagulant preservative solutions and additive solutions and things like that.

Cassandra: Right. This is going to help us with the CPDA AS-3 question for these preterm infants who get over 20 MLS per kilo.

Joe: Right?

Cassandra: We're going to get to some of those really granular, which we talk about every day. Other things, like how about giving O blood to all preterm infants because it's easier so you don't have to figure out like what blood type they are and match. How's that affected? There's a lot of integral questions that we're going to get to some epidemiologic answers.

Joe: Excellent. So again, we could talk about that for a long time, but let's talk about the second one that is obviously hugely important and I'm going to try and make sure I get this name right. “The Red Blood Cell: Improving Transfusions for Chronically Transfused Pediatric and Adult Recipient study,” also known as “RBC-IMPACT.” So, what can you tell us about that, Cassandra?

Cassandra: Well, the first thing is that this is really focused on red blood cell survival in patients with hemoglobinopathies, such as sickle cell and beta thal, but also patients with oncologic disorders, people who are being chronically transfused in that manner, because there are two aspects to this red cell survival thing.

First of all, is how long do the red cells survive when they're transfused? We really don't understand very well. And we know that from REDS-III, we know that there are certain genetic characteristics of donors that are important about red cell survival in the storage solution and about oxidate capabilities and other different genetic variations within those donors that could really affect things.

We also know that when we give transfusions, we're loading in iron onto people, because genetically we sort of can look at the donors and see if there are certain donor characteristics that are making some of the iron overload issues, worse for recipients who are chronically transfused. But what this study is doing is looking at red cell survival from all the different ways that we can. In a sickle cell patient, we want to look at the hemoglobin A versus S and we can do that with hemoglobin separation. We basically can look at those donors and look at how long the hemoglobin A is lasting in those patients.

Every time somebody comes in for their chronic transfusion, whatever the indication with a patient with sickle cell, we're going to be able to measure that. We're going to draw blood before, we're going to draw blood after, and we're going to actually for the donors, look at a precision transfusion medicine array, and we're actually going to be able to look at some of those genetic characteristics, the SNPs and polymorphisms that are not

related to antigens, like not related to Kell and to Kidd and et cetera but other different characteristics of the blood.

That is one really important thing that we're going to be able to study, because we're going to be able to look at what happens with that donor and then into a specific recipient.

The other piece is if it's a patient with thalassemia, we're going to look at their hemoglobin change because everybody's got hemoglobin A, they just don't make it. It's ineffective erythropoiesis in those patients. The reason we're chronically transfusing them, different reason, but still an issue because the idea is if we could find the optimal red cell, that's going to last, for a longer period of time in the patient, the best one. Then we want to pick those donors that are really good for those recipients.

Potentially there are donors out there who aren't like, let's say like G6PD deficiency. Is that really a problem? Do those cells not last as long and are there other enzyme problems in the donor that could be causing a problem for the recipient and causing them to have to get more transfusions.

The other thing is the second aim of the study is to really look at that iron question that I was telling you, iron overloading. They're going to measure serum iron, actually in the recipients and measure some of the different aspects in the donor as well and match them up. We have a lot of oncology patients nowadays, who are actually getting tons of transfusions. The thought is not about how much iron they're getting, but we're finding if they go to transplant or if there are other complications for survivors that have to do with iron overload, that could be a real issue.

And again, understanding in that context, especially some patients as they're starting to come back from their chemotherapeutic aplasia, chemotherapy-induced aplasia and reconstitute. That's when they're really having these iron issues. We're going to try to study that as well. That study is going to include altogether the RBC-IMPACT study about 500 participant,s and we're going to be joining with Brazil, because Brazil has a sickle cell patient cohort that they've been studying longitudinally.

And we're going to incorporate just patients with sickle cell in that particular part of the study. It's going to be two years, we're going to look at each patient over two years and look at their chronic transfusions. And we're going to be able to look at intra- and intervariation. It's a lot of coordinating between the blood centers and between the hospitals, but I think that it's going to be manageable and actually in this last week, very exciting, we've had five patients enrolled in our first study and it's super exciting! It's in the United States and gradually you're going to see this is going to pick up the pace, but that's where we are.

Joe: And again, there's a whole lot more that we could talk about on that topic, Cassandra. I know you could go for a while. There's no question about that in my mind, but with the background of those two wonderful and hopefully really potentially fruitful studies that are going on, where would you assess where we are right now in terms of, I don't know if there, if you guys have developed kind of phases of REDS-IV-P or stages in terms of its lifespan?

Because my understanding it's intended to be a seven-year study and we're like three years in. Is that, am I accurate on that?

Cassandra: Right at the beginning of April, we'll make it three years. And we've been in it for three years. There have been multiple publications about SARS CoV-2 in all different aspects, including some of the convalescent plasma testing, all of those things. And that's been one area that's been extremely active. Another area that's been extremely active has been looking at what we could learn from the REDS-III database.

And the pediatric groove has been huge. What could we squeeze out of there where they had gotten children involved? And some of it, it was really hard to study neonates because they weren't even recording like the birth date of the babies, because that wasn't really part of REDS-III. So, finding unique ways to do that, but we have, we've looked at that, we've published some of that data, which kind of was helpful as we build the structure for REDS-IV-P's vein-to-vein. There have been multiple things there and there have been a lot of activities which you're going to be able to see as publications still come from REDS-III that needed to continue and be finished.

Some of those things continued in REDS-IV-P because there was just so much to do. And really this audience needs to know that the REDS-III database is a public use database. There are grants that can be written for databases that are out there that you can actually go study, because that information has not been completely looked at the way it needs to be because there are so many questions that we just can't afford to answer all those questions. But the people who are listening to this podcast can because big data's a big thing and I'd love for them to go ahead and access that. The other thing is that what we're building right now in the future, they will be able to access. We can't answer all the questions that need to be answered even in the next four years.

Phase one was the first two years. Phase two actually started in the third year and will carry to another two years from here. And then there will be the third phase, which will be more of the looking at the data and analyzing all these studies, as well as doing some data analyses, which the investigators in REDS-IV-P right now are starting to putting together as to what do they want to study project wise from this REDS-IV-P database that aren't those two studies that we just mentioned because there's still a lot to gain from this new database.

Which by the way, is mostly what we do every day is the hospitals are working with the donor centers to get that information into this database because the database is tons of information, but it's QCed all the time. But it's not curated yet for the different places that we're going to need to answer questions. That all takes a lot of energy and time. We have a QCed vein-to-vein database, meaning every Monday that I'm a part of, we're constantly looking at the data and getting it to a very good integrity that we feel confident in what the data is in that database.

Joe: That's awesome. What you just said, triggered something in my head a little bit. And Steve, if you wouldn't mind, I'd like to come back to you and ask you to put on your, I don't know, how can I best put this? Imagine that you are a young investigator right now, and you are someone who has, maybe you're just getting, going in your career and you have some questions.

You have some thoughts about things that you would like to investigate, and you would like to jump on and figure out how you can make a contribution to our transfusion medicine, body of knowledge. I guess what I would want to hear from you is, if you were in that role, how would you try to get involved with either some of the previous REDS data (as Cassandra mentioned, the database is public for REDS-III) or even something in the current REDS-IV-P project? What would a young investigator who's just getting started, need to do to try and get involved in some of that?

Steve: One of the things in the REDS program is that we do have a lot of young investigators. They happen to be people who are at the institutions, who are part of the program. And one of the goals of REDS has consistently been to give young investigators the opportunity to fully participate to the extent that they have time and funding available and to even lead specific projects and author papers under the auspices of senior people.

So, there's definitely a training component to it. We have brought in fellows and assistant professor level people along the way, and some of them have emerged 15, 20 years later as senior people in the field. More difficult though, for people who are not at these institutions. We do have a way to collaborate with people outside of the REDS-IV program. And that is if a person outside has an idea on how they would like to study, what they would like to study that's part of REDS-IV-P, they could seek out an investigator who is part of the project and try to partner with them. It's getting a little later in the program now, so it's a little harder to do because we have a portfolio that's not as fluid as it was a year ago when we were still making decisions. Certainly if somebody wants to be involved in research that either uses the databases, but in addition to databases, we have sample repositories that are also in the biolink part of NHLBI and people can actually request samples to test for a specific research protocol.

That of course are valuable samples so that it has to go through an approval process, of a scientific overview that it's worth doing. But there are these resources, so it's not closed to outside people, and there are some specific steps they would need to take. Again, if they particularly want to participate in ongoing research, they would need to get together with a person inside the program currently.

Joe: Okay. Cassandra, it sounds like you have a, based on what you were saying about that, the database, it sounds like you have some thoughts on that as well.

Cassandra: I do. And I think there are multiple things depending upon the learner level and what the idea of what the person would want to be, how they would want to be involved.

One of the things is about the database, the public use database for REDS-III, and that goes for the repository too. We would be happy to discuss the different things that are available if people were interested because for the process, there's a process, but it's doable to write a grant, to have an idea. That's one way.

Another way is that we're trying to reach out and educate people about transfusion and about what REDS-IV-P is going to be providing and about transfusion medicine to other physician scientists who are not transfusion medicine specialists. One of our big things is trying to get transfusion medicine physicians, or people who are trained in this to get

out to people who are the end users of blood and understand what questions are out there and how you can get to those answers. It's a little tangential to REDS-IV, but it's because one of the purposes of REDS-IV-P is to encourage more transfusion medicine research.

The other thing is that all of us want to mentor people. If you're a blood transfusion interested person and you reach through your blood center or reach through your hospital, there are ways to get involved that are maybe not the exact direct route, but I would say, ask. This is supposed to be broad. You can ask me anytime you want, people can write to me or whatever, and I will answer them.

Joe: Wait. You're willing to talk to people, Cassandra? I'm shocked!

Cassandra: I know it's a shocker. It's a shocker!

Joe: Before we go, I wonder if either of you has any last thoughts on something that maybe we should have talked about that we didn't get to. Steve, I'll let you go first.

Steve: The third major thrust, I think for REDS accomplishments to date, is it really set the stage for the impact study that Cassandra was talking about. And that is the beginning look in REDS-III at donor genetics. We laid the groundwork for that in that the group developed a precision transfusion medicine array that could be used that had multiple snips on that were relevant to transfusion medicine. So, it was really a new tool that was developed. And now there are several of these that have built on each other. One of those things that actually, I don't think that what we've learned so far from it has been that big a deal, but it set the stage so that we may make some advances into the precision medicine area, but we might make some more advances in this iteration.

Cassandra: One thing we didn't mention, which kind of closes the circle about infectious disease is pathogen reduction technologies. And one of the really cool things about REDS-IV-P at this moment in time is that we're going to be able to incorporate for the first time that epidemiology, as people have put in this, into their transfusion medicine arsenal for platelets.

There's going to be information coming out, but it'll be very interesting how that plays out as we start to understand the implications of needing possibly more transfusions. It's not part of, one of the things we talked about, but since this is transfusion-transmitted disease, this is the beginning of understanding that epidemiology as those technologies start to be put into place.

Joe: Thank you both so much for taking the time to hang out with me today. I am even more excited than I was before about REDS-IV-P and the possibilities that we have with this going forward. Your expertise and your leadership in this project is greatly appreciated.

And I think all of us in the transfusion medicine and really the transfusion community in general owe both of you a big, huge, thanks. So, thank both of you so much for talking to me today.

Steve: Joe, thanks for having us on. It was a pleasure to be able to discuss.

Cassandra: Yeah, same here. We really enjoyed this and hope that people really enjoy listening to it.

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Joe: Hi, it's Joe. Just a couple of quick closing thoughts: First, I want to make sure that you're aware that you can go to BBGuy.org/098, which is the show page for this episode. There, you can find a whole bunch of resources on the REDS project, including summaries of the first three phases of REDS, as well as an article that came out in Transfusion earlier in 2022, outlining the details of the REDS-IV-P project.

This project really is going to shape the way we practice, and it already has shaped the way we practiced in the past and today and in the future. So, I really hope that you take the time to become aware of it.

Also, just be sure that if you're a physician or laboratorian, don't forget to go to Wileyhealthlearning.com/transfusion news. There you can get an hour of completely and totally free continuing education. You can also get there by clicking the link at BBGuy.org/098. As always, thank you for the continuing education sponsorship to Transfusion News, to Bio-Rad who brings you Transfusion News, as well as of course, to Wiley Health Learning.

I've said this before, I really hope that you take just a few minutes to go to Apple Podcasts and give this podcast a rating and review. I do read every review that's on there. I greatly appreciate those that have done so. and if you put a review on there, you might just have it read on a future episode of Blood Bank Guy Essentials.

So, the next episode, I'm not going to spoil the surprise, the next episode is going to be a little bit different. It's going to be episode 99. And that is a precursor to my very big "Centennial episode." Is that right? Yes. The 100th episode of the Blood Bank Guy Essentials Podcast is coming very soon. Lots of special guests for that particular episode. And I can't wait for you to hear it.

But until that time, my friends, I hope that you smile, have fun, tell the ones that you love, just how much you do, and above all, never, ever stop learning. Thank you so much for listening and I'll catch you next time on the Blood Bank Guy Essentials Podcast.