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Presenter: Denise Hynes
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Unidentified Female: Hello, welcome to VIReC Cyber Seminar Series, Good Data Practices. The purpose of our series is to present issues related to good data practices and example from the work of VA researchers. Before we begin, I want to take a moment to acknowledge and thank some of those who have contributed to this series. We have an active informal advisory group that helps guide our choice of topics and concepts covered in each session each year based on suggestions from participants like you in previous years. This year’s advisory group included Matt Macheski (PH), Peter Groniveld (PH), Jennifer Garvin, and Jim Burgess. This year’s Good Data Practices Series, includes four sessions presented on Tuesdays and Thursdays this week and last. Last Tuesday, Sarah Krein and her session on planning for data early, often and ongoing reviewed the importance of planning for data early in the research process. If you were not able to attend the presentation, it will be available on the Cyber Seminar webpage soon. I will give you that information in the next slide. Last Thursday, Todd Wagner discussed the approaches he used to handle data limitations and data linkages in his session entitled Mind the Gap using administrative and claims data to answer your research questions. Today, Denise Hines will present the session on study design and analysis consideration with examples from comparative effectiveness research in her session, Decisions, Decisions, Decisions, selecting methods and tools for data analysis. In our fourth and last session this year, coming up on Thursday, September 24th, Steven Deppin (PH) will tell us about using the VA’s instance of the red cap data collection and management applications for longitudinal studies and studies that combine primary and secondary data. As I said, if you missed any of the good data practices series presentations, you can access them in the VIReC’s Cyber Seminar Archives at the url shown at the bottom of your screen and it is highly suggested you might want to copy and paste these from the presentation into your browser. With that, I will hand this over to Hera. Thank you.

Hera: Thanks Linda. Today’s speaker is Dr. Denise Hines. Denise is a nurse, a health service research and a health economist. With more 14 years research experience, she has studied quality access and cost of healthcare and she has managed informatics research resources. Denise is a director and research career scientist at VIReC at the information resource center. She holds a joint appointment at the University Illinois, at Chicago’s College of Medicine and School of Public Health. She serves as director of the Biomedical Informatics Core, part of the UIC Center for clinical and translational science, she is site principal investigator, and informatics co-lead for the Chicago area, patient centered outcomes research network better known as CORN. Before I turn things over to Denise, I want to remind you that any questions that you submit will be monitored during the talk and I will present them to Denise at the end of the session. Also, at the end of the session, a brief evaluation will pop up when you close out. If possible, please stay on to the very end and take a few moments to \_\_\_\_\_ [00:04:08]. And now I am please to welcome, today’s speaker, Dr. Denise Hines.

Denise: Thanks everybody! I just want to take a moment and make sure that I am broadcasting the slides as opposed to notes.

Unidentified Female: Right now you are in it is called presenter view, so we can see the notes and we can see the thumbnails across the bottom. If you put it in the slideshow mode, we should just have your slides on the screen. All the way over on the left. Perfect, that is just what we want. Thanks Denise.

Denise: Okay, let us get started. Thanks everyone for your participation. We are you know going to cover a pretty broad topic today and I would like you to keep in mind that this is intended to be introductory. So, I have tried to select some examples that will be most relevant for health services research so I have concentrated more on comparative effectiveness research. I will talk a bit about design and analysis for which question and for areas that I do not have a specific example, I will try to do a little bit deeper dive into study design elements that have implications for analysis. It is probably a good idea for me to get a sense of who you are. I would to have us implement this poll so we can get a sense of the audience here. I think when I last looked we have over 100 people on so it is kind of nice to know who we are talking to. So, if you can just tell us a bit about your research role, what exactly is your role in research? The poll is here on the screen. Would you categorize yourself as one, an investigator, two, a data manager/analyst, three, a project coordinator, or four another role and if you could just describe that in the Q&A chat box that would be helpful.

Unidentified Female: Great, and responses are coming in. I will give you all just a few more moments before I close the poll out and we go through the results. It looks like we are not getting any more in so I am going to close that out and what we are seeing is 29% research investigator, 47% data manager or analyst, 13% project coordinator, 11% other and we are seeing they are operations research investigator, post stock and informatics, statistician, and both a data manager and project coordinator. We just got in post services research doctoral student. Thank you everyone for participating.

Denise: Then we have a second poll question to ask about your data experience. Can you tell us how many years of experience you have working with VA data, less than one year, one to two years, three to six years, seven plus years? Let us see if there is anybody who has lots of experience or lots of newbies.

Unidentified Female: Responses are coming in. I will give everyone again just a few more moments before I close the poll out here and we go through the results. We have a lot of people on the call, so it is a lot of people to try and get in there. Okay it looks like we have slowed down. So, what we are seeing is 40% saying less than one year, 15% one to two years, 26% three to six years, and 19% seven or more years. Thank you everyone.

Denise: Okay, so the 40% and the less than one year, I think is the first category is the winner. So, I am expecting lots of questions today and hopefully we will have a little bit of time. I would encourage you to put your questions in the chat box. Now, I put up here the session outline. I will go over study design and analysis issues and try to emphasize how they are related. I will also try to provide an overview of analysis decisions. I will try to give some specific examples. So, obviously, this will not be very comprehensive but I hope to give you some insight into some of the work that we have done and also to introduce you to the internal and external validity issues and how to deal with them. Ahead of time, we sent out a couple of references and if you do not have these, we can certainly resend these. I found that in trying to put this session together, it was important to get a sense of some of the conceptual issues that you can then think about as you are organizing steps within your own research or working on other projects. I found these three references particularly useful. There are numerous references out there on study design and statistics. What I liked about these three is can provide some context as you are thinking about a very specific research project. So, I will be referring to elements of these three key references throughout my talk today. I borrowed some of the examples that they used. They should be familiar to you if you have taken a look at these references already and even some of the tables highlighting particular aspects and we will try to apply these to some additional examples. So, let us start with which design for which question. The real take home message I would like you to have with this part of the lecture is that it is very important to think about both the study design and your analysis approach together. It is really hard to separate the two so in one sense your study design does kind of determine the rest of your life in your research project. You certainly can take a different path but the two are tied together and it is really quite impossible to think about analysis without thinking about your study questions and your study design. So, some key issues to consider, I have highlighted some of the questions the Arbogast article highlighted pretty well but these are some of the items that they highlighted. First, thinking about the study questions and is it appropriate for more of an experimental type of study design or non-experimental study design. Usually, when we think about an experimental design, we think about randomized clinical trials of some type as opposed to non-experimental designs, sometimes we refer to them as quasi-experimental designs. The non-experimental, quasi-experimental design is usually what we are thinking about in a comparative effectiveness research study. Within the broad design approach, what is the best study method to address this question? I will walk through an example they used. Also, to think about the design and analytic features together to ensure the validity, relevance, and timeliness of the study results. Those three components need to be balanced and then I also added my own question to this and that is as you are thinking through the design and analysis decisions of your research project whatever size it may be, you really need to make sure that you have the right study team helping you weigh those options. Generally speaking, it requires multiple disciplines, people with different backgrounds, statistics, particular subject matter expert. Usually, our teams have grown to be multidisciplinary. It is rare that we have a single investigator study anymore.

So, I am going to walk through the use case number one I call it just to kind of keep track. This is an example that was highlighted in the HRQ document and this is a chapter of larger document that was put out by HRQ. It really walks through some of the study decisions and choices and I am highlighting this particular example so that you can just see how the pros and cons as you are designing a study can weigh. Also, to highlight how this particular study really as they walk through the pros and cons advocated for more of an experimental design. Then we will have some other use cases as we go through. So, just to provide an overview, the research question that they were looking at and this particular study is the relative effectiveness and safety of the availability of an antithrombotic alternative. So, this is a medication in common language blood thinners. Medication that might come to mind for those of you who are not clinicians, medications like heparin. In patients, undergoing joint replacements or arthroplasty and the study design question is should this be an observational study or should it be experimental? Ultimately, they went with a large parallel group randomized trial. This next slide, I would like you to just see some of the pros and cons in weighing the different options. Obviously, when you are thinking about a study design, you need to have a lot of background in what some of the issues are and what the difference design topics are, what some of the issues are and I just highlighted some of them here. So, some of the pros for an experimental design, patient important outcomes. There is symptomatic issues with blood clots or VTE’s as it is referred to, venous thromboembolisms. Death is associated with this complication. These are very serious consequences. So, in this study they were weighing very seriously, should they be considering patient’s assessed outcomes or should these outcomes be assessed by some sort of objective measure other than the patient reporting it. Other issues that came to bear importance included the ability to be able to show differences in the event rates between different types of medication regimens and whether that would require a large sample size in order to determine. Other aspects had to do with events that are likely to be recorded accurately in administrative databases. Some cons in terms of weighing this as an experimental design versus an observational study was that in doing an observational study, it might be there could not be enough information known about prognosis of this particular condition and so it might not be that there is enough known Apriori to know which alternative agent might be best. Apriori at the time this particular example was put forward, there were no large cohort studies and often time having some preliminary research available would help with informing the design to assess risk prediction and methods to assess risk prediction. But at the time of the design of this study, there were none. It was also noted that the surgeons assessment of thrombus or bleeding risk and how that might affect choices of agents could actually influence decisions and how to do that in an observational study was very difficult. Then there were some other issues and the last one is here prognostic stratification again because of the lack of information in previous large cohort studies it will be very difficult to stratify patients. So the pros and the cons for weighing whether this should be conducted as an observational study in this particular example, kind of lead them more to thinking about an experimental design. When they looked at it in the context of an experimental design, the pros really won out. It looked like an experimental design might be able to balance some of these prognostic factors because they could get primary data. They would be able to power it for patient important outcomes although the study would need to be sufficiently large it was felt that that was doable in this context. In terms of cons, powering only for some substitute measures, a lot of times studies will try to look at surrogate end points so instead of symptomatic events. They thought about whether or not asymptomatic events objectively measured might be a proxy, they though that that would introduce some bias so having the ability to do an experimental design we could actually have some context with patients for example prospectively that may be helpful.

There was a downside in terms of the ability to engage patients introducing more expensive study design as a con. In the end, these are just sort of summarized and obviously, I cannot go into all the details in this lecture today but to just introduce you to some of the considerations that need to be weighed in determining whether a study design should be more experimental randomized and/or observational or non-experimental design. These are features generally speaking and you can also take a look at the other example that was provided in this particular chapter by \_\_\_\_\_ [00:19:13]. This example looked at feasibility, protection from bias, applicability, and cost. Generally speaking, an experimental design tends to be weighed a little more heavily on the cost side where as in the non-experimental design often you can rely on secondary data sources such as in a retrospective observational study and sometimes even a prospective observational study. There are obvious aspects to consider in terms of particular research questions with regard to protection from bias and applicability and how those weigh on a particular question may be different in your particular question, but these are aspects that need to be furiously weighed.

So, some other aspects in terms of design and analysis features that need to be considered is something you know we sometimes refer to as concealed randomization otherwise known as blinding but blinding remember does not always apply only to the subjects that you are engaging in the study or the caregivers but also to those performing the actual study, data collectors, the adjudicators, and the outcome analyst, investigators. These are aspects that depending upon how much the team determines, there could be bias introduced by unblinding. It could be taken all the way to conducting the analysis in a blinded fashion by a separate statistical team that is not communicating information to the actual principal investigator but also making sure that the analysis is done in the as randomized approach as opposed for example to an as treated approach and following through and making sure that the information is complete when the analysis is conducted. Also, important aspects, measurement of outcomes depending upon the particular research question, there could be some tradeoff. For example, in this first youth case example and the anticoagulation question. There is a balance between blood clotting and excessive bleeding, they have to weigh those two issues very carefully, and there may be some research questions that have those kind of important tradeoffs in terms of how you measure outcomes.

So, in summary, let me just say that there are some important aspects that need to be considered in weighing an experimental versus a non-experimental design. Either choice, there is important study design considerations. There are validity issues, trying to come up with approaches that will be sure to protect the results from any bias. Relevance ensuring that the study design and the results will have applicability to the question at hand. Timeliness, making sure that the study design that you ultimately determine is best takes carefully into account the timeliness of your study results. Your question may be very important and require results sooner. There may be some aspects about other design features that need to be weighed with aspects regarding timeliness. Therein could be a tradeoff and then analysis. Analysis, you really need to carefully consider the outcomes and the covariates of your study and we will get into that in a little bit more detail with some additional use cases.

I have highlighted here just papers that have been published on the three use cases I am going to highlight here today and the complete references are also at the end of today’s lecture. So, let us shift into just talking a little bit about some of the analysis decisions and which analysis for which outcomes. Again, I am going to just introduce some topics here that certainly would be covered in far more detail and many references and more courses that are available and I would encourage you to take advantage of those additional resources. But, given that so many of you are new to VA data and new to VA research, let me just consider that this will be some introductory concepts that you will talk in greater detail with your research teams. So, three areas of focus, descriptive analysis or descriptive statistics, sometimes we refer to this is as unadjusted. Adjusted analysis and regression modeling.

Starting first with descriptive analysis. Descriptive analysis can be the entire scope of your project where you might be trying to characterize a population or describe some survey or questionnaire responses. But often times, it is the first step in a more comprehensive analysis that we will look at and also include adjustment and potentially regression analysis. But just generally speaking, descriptive analysis really how you conducted depends upon the nature of the measures that you are looking at. So, a continuous measure. So, let us think of age as a continuous measure. Obviously, it is not really. You do not see many people going over certain ages but often times it is looked at as a continuous measure and in a descriptive analyses of a continuous measure, you looking at aspects of range, measures of dispersion like standard deviation and central tendency. Categorical measures if you think again of age, age could be divided up into segments or categories of age, five-year intervals, ten-year intervals. You might be looking at the number in percents of those in a particular category or you might present it as plots for evaluating data distributions. Some variables obviously you can present such as age in both modes. Others may only be either continuous or categorical. Sometimes when you are presenting information whether it is the first stage of your analysis or it is your comprehensive analysis, it is good to show some context when you are providing your descriptive analysis. Let me just use a second use case to show you what I mean by that. So, just to introduce you to this example without getting into too much of the detail, this is a study we conducted here at Hines looking at the impact of erythropoietic stimulating agents guidelines on changes on cost of cancer care. ESA’s I will use that shorthand, are used to treat anemia in cancer patients and there are particular guidelines around when to use that for clinicians and they tend to be very expensive medications. So, the balance between guidelines, adherence to guidelines, and the cost of care have often been for about the last ten to fifteen years and important health policy question. This is highlighted in one of the references that I mentioned led by Dr. Kevin Stroup and colleagues and the research question here that is relevant is would anemia management cost, ESA cost, and overall cancer treatment cost decline with mandated changes in ESA use. The study design was a retrospective cohort study. It went over many years and the outcome measure of interest here was cost of specific and overall treatment for lung and colon cancer care. The exposure of interest another way to think about it a major covariate is a pre and post period. Now I used this example to highlight descriptive analysis. I also want to introduce just another concept that will be important here in this particular use case is we also define a chemotherapy episode of care and this is important in just characterizing our population. So, not only did patients receive this particular medication, ESA, but we also wanted to characterize the period of time that they were eligible for receiving this medication during their chemotherapy episode. This is also straddled around a pre and a post period, which you can see here that is indicated by something in this box called FDA issues black box warning. So, the study was designed as a pre and a post period. So, in terms of presenting our descriptive analysis, and providing context to our readers and to our audience, it was important for us to show this particular exposure or major covariate. So, in presenting descriptive analyses, as shown here on this slide, there happens to be two categories we did both lung and colon cancer but if you focus on the lung cancer description, these are descriptive statistics. We present for example age of diagnosis, as a continuous measure, we also presented as a categorical measure but it also important for the audience or your stakeholder readers to see the distinction between the pre and post period in our experience just showing some of the groups. It is also important even the descriptive analyses to show some descriptive statistics so although this is unadjusted, it does present some meaningful information to show how your particular covariate or characteristics are distributed across your groups.

Let me introduce regression models and the concept of just weighing different approaches. There are many books written about regression models and I will just highlight a couple of the key issues that are important and I will introduce a couple examples to just show you how some of these aspects can lay. So, with traditional multiple and regression, I will just tell a brief story here. When I was in grad school, I was not sure which statistics or analysis for us to take. So, I first went to the one in my home department in health policy and administration and our emphasis was there was in econometrics and advanced econometrics and advanced statistics. Then, I also went over to the sociology department and they focused on logistic regression and then when I went over to the economics department they had a little more calculus requirements but the bottom line is the overarching mode was the same. You could take and see regression models presented from different disciplines but the underlying math is the same. So, you will see some course books and courses presented from different disciplines perspectives but when it comes down to actually implementing the approach, these are some of the issues that often come up most often. There is often issues related to time varying aspects, temporal relationships. I will give you an example of that today. Propensity scores that is some method that actually assigns a probability of receiving a treatment that might be conditional observed covariates and propensity scores are appropriate when adjusting for large number of covariates. Again, just think of this as being introduced to the terms but I would encourage you to consider some additional resources if this is an area that you are further interested in or considering for your studies. Latent class analysis is another area and disease scores, thinking about sort of grouping particular classes of subjects that might allow one to estimate the probability or the rate of a disease occurrence as it occurs in a particular you know grouping or with latent class analysis it does not necessarily have to be relevant to a particular disease class. It could be to any grouping. Instrumental variables allow a mechanism to identify a particular index variable that might be used as a condition variable or one that might be a precursor to a latent outcome measure. Again, just some concepts to introduce you to and let me give you some examples to just walk you through some of the aspects that I have mentioned. Again, going back to our ESA and cancer costs as I had introduced previously, looking at anemia management cost or ESA cost. What we looked at is components of cost, not only the medication itself but also blood transfusion, overall anemia management, and also overall cost of care including inpatient and outpatient care. Well, in order to look at this particular question, we considered a couple different aspects and that is some issues around not only the fact that patients you know experience this particular episode but then they also be inclined to having care more or less often. So, we looked at a logistic regression as a means to predict whether any cost was incurred. Some patients may have very low cost where as some patients may have very high costs and trying to take that distinction into account, we felt was very important that was part one of a two-part model that we used. Then a second step in our consideration of measuring this particular outcome measure is something called GLM, generalized linear modeling and we used a particular distribution again. You definitely need to be familiar with some statistical terms here with what the distribution is of your outcome measure and also having some understanding about what kind of tests you might conduct to validate that you have ascertained the right distribution of your outcome measure and the right approach which we conducted using this modified part test. But also, to look at the second step was looking at modeling those patients that had nonzero costs or had some experience with getting healthcare and accumulating cost. Then in a two-part model, there are mechanisms by which you can combine these two steps and apply those to produce a predicted cost so that you can see exactly what a per patient cost would be. In our study, we also looked at, we separated the anemia management cost, the cancer related, and overall healthcare cost. Just to give you another perspective on how this information was presented, we in this slide here, I highlight how we presented the predicted cost once those two-step models were actually calculated and it gives a nice presentation based on the different categories. So, I had mentioned that we looked at the anemia management cost and the components and you can see those here. The overall cost, the cancer-related cost, and then the components of the anemia management cost. It takes it to information at the patient level and here it presents the different between pre and post periods.

So, I have introduced you to some pretty advanced concepts but I want to take it back home to what really matters here. Obviously, when you are working on any particular research question and you are considering your study design and making decisions about your analysis, these are the aspects that you really need to work through with your team. You need to take into account the study design that you have set up or you are about to set up. What are the characteristics of your outcome measures that really matters? Obviously, looking at cost measures or mortality or health services use, have very different statistical distributions and characteristics and need to be taken into account in determining an analysis approach. What your covariates look like? What are the covariates that are determined by the conceptual framework here using to look at the outcome questions? What is the structure of those measures? Are those categorical? [Inaudible] Also, what is the temporal relationship of outcomes in your covariates? Are your measures single? Are they repeated? This relevant for both your outcome and your covariate measures and these are really important aspects to consider in determining your analysis approach. I want to do a time check here because I want to make sure that we have enough time to go through this. I have a third use case here to just introduce you to a prospective study. I think that we can go through this and I think we will still have time for some questions. So, let me just give you another example of just thinking through an analysis approach. This study led by Anna Porter and colleagues including myself. Our research question here was, could we improve a patient’s quality of life by implementing a new model of care? In particular, this study was focusing on patient centered medical home, PCMH, for chronic kidney disease, CKD. The study design is a multi-site prospective intervention, pre/post design. It goes over two years and our main outcome measure is a quality of life measure that is specifically designed for kidney disease patients. It does have repeated measures every six months and it does have clustering. It is a two-site study. I will not go into a lot of details but I wanted you to just kind of get a sense of pragmatic study, not so much a pragmatic study design but this is happening actually, as we speak. I am not going to show any results tables but I did want you to get just sort of an example of you know thinking through the concept and trying to make some design decisions. The snapshot here that you see is there is an existing care team that is mandated by Centers for Medicare and Medicaid Services or Care for Dialysis Patients. That is what you see in yellow. There is a particular care team that is required in a dialysis unit. Our study proposed to introduce the blue boxes adding not only the dialysis and a nephrologist specialization which already existed but adding the General Internist and Advanced Practice Nurse who is a care coordinator, a community health worker who we call a health promoter and a Pharmacist and then of course the patient and their family or caregiver is central to this. So, considering our major primary outcome of patient’s quality of life, we endeavored to consider really important aspect here is the differences in our two sites. I am presenting on this table just so you can get a sense of how important it was in considering site differences and I would highlight this as aspects related to clustering. We had Apriori very important differences in the population makeup of our two sites. In one site, we had very highly prevalent Hispanic population and at the other site, we had a much more predominant African-American population. So, these are important aspects that we will need to consider as a covariate and in our study design going forward and making sure that we take into account sites as we conduct our analysis. Of course, while quality of life highlighted in the top left side of your screen is our primary outcome, like many studies, we hope to look at many other outcome measures and again, this is where you really need to think about aspects of repeated measures. Repeated measures does not necessarily only apply to aspects of measuring the same concept for your subjects, but measuring many concepts for the same subjects and those are aspects that you really need to think about in your analysis approach too. I also want to introduce the concept here just so you can be reassured that it is important to think about these aspects Apriori. In this study, we are still collecting data but when we submitted our proposal, we proposed specifically the type of analysis that we would do and the particular procedures that we anticipated to apply. Now, it might be when actually get to the place of actually caring out our analysis and we are about six and a half, seven months into actually collecting data, we are already in the position of testing out our models so that we can actually do an initial run of the models that we proposed to do. So, it has been our motto with our Good Data Practices course of having a living protocol. It is also good to have a living analysis model to actually work it as your conducting your study. That is the ideal and sometimes it does not actually happen until the end of your study but the sooner that you can test your models and apply them to the data that you are actually collecting, the sooner you will be able to do your results papers but also feel confident that you have chosen the right path. Also, in this study in terms of aspects about designing it so that we will avoid bias, we are doing careful assessments of looking at missing data. We are also planning to do sensitivity analysis that will allow us to look at our outcome measures in different ways and trying out different methods for exploring the impact of missing data on results and also thinking about some propensity adjustments and looking at some group analysis.

So, to summarize, I have introduced a lot of concepts but I thought this table that is from Arbogast and VanderWeele and it is one of the references that I included. This presents I thought a nice working presentation if you will. It may not also be complete. You may have your own ideas of particular examples to put in here. But, thinking about dimensions that drive analysis approaches, your outcome measure whether you have a single measure that includes clustering and whether your measures are repeated or not and whether they are at six intervals or variable intervals. These are some of the categorizations that they present whether you are using logistic regression for dichotomist measures which it could be multi \_\_\_\_\_ [00:45:47]. It does not just have to be two levels. It could be multilevel as opposed to continuous which puts you in the category of linear regression. Also, thinking about your follow up measures and time intervals with regard to the clustering and the nonclustering but also the temporal relationship, time to advance, and whether it is aggregate or counts and these are some of the methodologies that might be used for these types of measures.

I am going to skip to some of our last sessions because I have given you a paper for that last model and I would like us to get to this poll just to get a sense of what your experience is with research grants or contracts. How many grant proposals or contracts which is often sometimes intermixed with grants have you worked on as a PI or part of a team? We have a couple of categories here, none, not applicable, one, two to three, over three. I should probably ask you whether you would use logistic or linear regression to analyze this but just answer the poll question and we will not worry about how we would analyze it. I think that this just kind of gives us an idea of you know are you thinking through grant proposals and the study design? Are you somebody who is working on manuscripts? Heidi?

Unidentified Female: Responses are coming in. We have a lower response I am guessing because not everyone is working on grant proposals but I think I am going to close it out here, it has slowed down. So, what are we seeing is 35% none or not applicable, 15% one, 17% two to three, and 35% over three. Thank you everyone.

Denise: Okay, so we sort of have a bimodal distribution here. This next session I wanted to introduce because I thought it was a very useful tool and again I would refer you to the checklist that Arbogast and VanderWeele had and if you just, think about this. They have this guidance from the perspective of what you should think about including in a statistical analysis session of a grant proposal but I like to also think about this in sort of more terms of critical appraisal. Think about, looking at your own projects and asking these questions as not only when you are designing your study but also as you are carrying it out. So, I have highlighted, this is just another way to think about some of the concepts that I have already introduced but think about the key variables of interest with regard to the factors that determine appropriate statistical analysis. So, independent variables I refer to it today as covariates, but these could be you know interdependent. Sometimes they are used interchangeably. When are they measured? When are they fixed or time varying? Should you think about, you know, you really need to talk about your dependent or your outcome measure, again, whether it is categorical or continuous, single or repeated, and also you should be very mindful of whether there is a multiple level analysis. So, are you looking at analysis at the patient level and the practice level? So, for example, in the example that I provided with the patient-centered medical home and chronic kidney disease, we want to look at both at the site level as well as the patient level. When you are proposing descriptive analysis or a graph according to a treatment group, you really need to think about the available numbers per group. The number of missing covariates, distributions, or graphs that might be needed to decide if transformation is needed. So, I did not even mention this before but sometimes a measure might be more easily analyzed if it transforms for example into exponential or logistic log function in order to actually carry out the model but then to present the results you might want to turn it back into showing how the measure might be predicted for a particular subject or per month or per year. For, example, as what I showed in use case number two. You analysis should include any potential confounders. You should think that through and any effect my modifiers to assess initial covariate balance by study group. A third aspect is the model that you are going to use to actually conduct your analysis. I have introduced several of these concepts already but these are definitely aspects that should be not only as you are carrying out the study but think about it for your grant application and then these three concepts are just presented in a table as is in that particular article. I found this to be a good checklist. You may add your own dimensions to this as well.

In your future research studies, let us do another poll. Let us think about together, tell us if you are thinking about working either in an experimental or randomized clinical trial design. Perhaps you are working in a cooperative studies program where there tends to be more use of RCT’s or experimental designs or you are working in a quasi-experimental observational study. If you are not sure, or do not know, or it does not apply, choose number three.

Unidentified Female: Responses are coming in. I will give everyone just a few more moments before I close the poll out and we go through the results, just waiting for it to slow down a little bit. Okay, so what we are seeing is 19% experimental, 47% non or quasi-experimental, and 33% not sure or do not know yet. Thank you everyone.

Denise: Thank you! So, what I would like to go to next is would like to just introduce some of the concepts but I do not really have good examples for and you may have some of your own examples but important concepts that I thought were highlighted really well in Matt Masiaski’s (PH) article in 2013, Looking at Design Elements. Now, when they presented this article they looked at it both from a retrospective kind of a critical appraisal thinking about how one might look back at a study after it is completed, but you could also take these same concepts and think of it prospectively. So, again I would refer you to this article and I am just going to spend my last five minutes here just introducing you to some of the concepts that I thought were important and I want to make sure that we have a little bit of time for some Q&A.

Design elements to improve internal validity. Again, just to introduce some basic concepts here. So, internal validity is a really important concept and it has to do with the actual structure of your study and whether the study is actually designed in a way that really addresses the question of interest as opposed to external validity, which looks really more at generalized ability. If you fail at internal validity, you can have a totally flawed study and that is obviously a really important issue here. With regard to external validity or generalized ability, you certainly would not want to design a study that has no generalized ability, certainly that could be a fatal flaw as well. But generalized ability tends to be secondary to internal validity. Some aspects that could improve internal validity and the appropriateness of your study inclusion of control groups, pre-intervention measurement or baseline measurement and then inclusion of \_\_\_\_\_ [00:55:14] outcomes. I am going to go through this pretty quickly here to just to introduce the concepts but there is different types of control group designs one could have. Control groups just give you such a great advantage in any kind of study but however you design it, it really needs to address a distinct threat to internal validity and that means you know aspects around some important drivers of you know your study question in terms of whether you could do a pre/post cohort design. It could be just a post cohort study or a pre/post design with multiple control groups. When you are defining a control group, it is really important to apply your inclusion, exclusion, criteria very carefully. Consider matching criteria so that you have a control group that is matched to your intervention group and it is really important to make sure that your control group has no assess to the treatments. In other words, that there is no cross contamination. You want to make sure that your control group really is you know your control group and it is all effective by the treatment. I thought that it was a really important concept that they introduced in this article looking at treatment effects. I would encourage you to take a look at that article and really understand this concept carefully. Often times when we are designing studies, we try to design them ideally with what we call a treatment effect that would apply to the population but practically speaking because of a lot of the sampling that we might do, it often sort of evolves into a sample, a subject group that you actually might have chosen. I use this example from one of our own studies that this just sort of shows you how you go from your original very large end of over four million subjects and when we get to our random sample, it gets us down to only 129,000. Well that random sample might be representative of the overall population but then when we start applying additional exclusion criteria, we have to question whether we are still looking at a population representative sample or if we have evolved into something smaller. Again, each research population to sample cohort needs to consider these issues very carefully. Design elements to improve external validity really has to do with these three major concepts. I think there is good discussion in the article, looking at treatment settings, prognostic risks of patients, and whether or not there should be decisions or again if you are looking at diseased groups, aspects around prevalence or incidence users or subjects. I think it is really useful in studies to carefully consider this for example in our own work in looking for example at kidney disease patients, if you focus on incident cohorts there may be a smaller population available with less statistical power and those are some important considerations. If you are using a prevalent cohort, i.e., where it is not just the new cases but ones that have had the disease for a longer period of time. You may be able to benefit from a larger sample size in particular. Another important aspect to just introduce is remembering the limits of observational data and potential ascertainment bias. This could introduce misclassification problems. There is always the risk in observational studies of unobserved events and even sometimes in experimental studies, carefully considering the limits of administrative data or even your primary data collection mode that might not capture every possible consideration and sometimes you can look at longer look back or index periods and sometimes considering multiple sources. So, again to improve external validity and with regard to treatment setting, it is always good to think beyond academic medical centers. We tend to think that being researchers probably predominantly in academic medical centers in the VA, prognostic risks of patients thinking about different types of approaches that might be indicative or it might be able to use index measures for prognostic risks and prevalent in incident cohort aspects and also aspects regarding potential treatment misclassification.

So, important takeaways today, I know I have gone through a lot and we all would appreciate your feedback on today’s lecture. Was it too much? Was it too little? Was it too introductory? Please provide us that feedback. But some important takeaways, keep in mind that your study design and your analysis decisions really go together. You cannot do one without the other. Also, to be reflective, use critical appraisal principles as you plan and execute your study. You should constantly be looking in the mirror so to speak at what you set out and whether you are on the right path and whether it is working. Sometimes it is good to think about it not only iteratively that you do not always have that luxury but think about it as if you might be reading your results paper and the different elements that you should be considering and carrying out your study as you are designing it. So, I want to make sure and acknowledge those important aspects of funding for which the examples and some of the time and energy gone into this could not have been done without. Also, just to make sure that you have the citations of the study examples that I cited as well as the key references that I introduced at the beginning our lecture. I think that is my last slide. So, I want to see if there are any questions and I realize we are probably at the top of the hour.

Hera: Hi Denise, yes thank you so much for your presentation. We are at two minutes after the hour and I do not think we have time to go over any questions. If anyone did have any questions that they did not submit or they did submit, one that was not answered, you can email it to Denise or to VIReC at the help desk at virec@da.gov. Our next session will be presented by Steven Deppin. His session is entitled, Using Red Cap, Data Management in Studies Linking Primary and Secondary Data. It is scheduled for Thursday, September 24th, at this time so 2:00 p.m. Eastern. We hope to see you there. Unidentified Female: will be posting the evaluation shortly and we have mentioned it a few times during this presentation, please do take a minute to answer those questions. We go through all of your feedback and do consider your evaluations when planning new sessions. Thank you.

Unidentified Female: Thank you Hera. I am going to close the meeting here in just a moment. When I do, everyone will be prompted with a feedback form. As Hera asked, if you could take a few moments to fill that out, we really do read through all of your feedback and we would appreciate your feedback. Thank you everyone for joining us for today’s HSR and the Cyber Seminar. We do hope that you can join us for Thursdays Red Cap Session. Thank you everyone.