

ClinicalTrials.gov Webinar Series, March 2011

Overview of ClinicalTrials.gov

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I'm Dr. Deborah Zarin, Director of ClinicalTrials.gov and I'd like to welcome you to the first of several Webinars providing information about ClinicalTrials.gov. In this presentation, I'll be giving an overview of the system. First I will be talking about the rationale for trial registration and results reporting, go into a little bit of background, the basics of results reporting, and then a little bit about the ClinicalTrials.gov review process. Subsequent Webinars will be giving more information about each of these topics.

First, it's important to start by wondering what all the fuss is about. Why do we have this system? And why is there so much attention being paid to it now? It's important to realize that the suppression of research results impedes the scientific process in all areas of science. However, suppression of clinical trial data is particularly problematic and this is because of two things: One, trials depend on human volunteers and, two, trial results inform our medical decisions. ClinicalTrials.gov addresses three key problems that have been identified: one is that not all clinical trials are published after completion; second, when they are published the publications do not always include all of the pre-specified outcome measures; and third, unacknowledged changes are made to trial protocols that would affect the interpretation of the findings. One prime example of this is the fact that changes are sometimes made to pre-specified outcome measures without informing the editors or the reader of journal articles.

It's useful to think of various levels of transparency since trial transparency has become somewhat of a buzz word. Over on the left is knowledge that the trial exists and that was one the original goals of trial registries, just to document in the public domain that the trial exists. Over on the right is access to the full data set. Today, we'll be talking about the trial registration, which really documents that the trial exists and gives a summary of protocol details. And those are the two blue shapes to the left. In the middle is the summary of results, which will be accomplished by the results database that I will also be talking about. Others aspects of transparency are not addressed right now by ClinicalTrials.gov.

There are many reasons to register clinical trials and report results. Sometimes people ask what the main reason is and it's important to be aware that there are several reasons; they all interact and there is no one particular reason. For example, there are human subjects protections and related reasons, including allowing potential participants to find studies assisting the ethical review boards in determining whether the risks and benefits are in balance or appropriate balance for a particular study, and also promoting the fulfillment of the ethical responsibility to the human volunteers who participate in the study. There are reasons having to do with research integrity which have to do with facilitating the tracking of protocol changes and generally increasing the transparency of the research process. There are reasons that have to do with the practice of evidence-based medicine, which really boils down to the fact that you can't practice evidence-based medicine unless you have access to the full evidence base that's not censored by decisions about whether or not to publish. And there are allocation of resource issues. For example, it would be impossible to make rational decisions about what future clinical trials to fund if you did not have a complete list of all current and past research that had been

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accomplished.

So let me start with some background. ClinicalTrials.gov was developed in response to FDAMA, which is the Food and Drug Administration Modernization Act. Section 113 mandated the development of a registry, which was designed at that time to help potential participants find trials, and it was really focused on people with serious or life-threatening conditions, and it was designed to help them find certain drug trials. ClinicalTrials.gov was launched in February 2000 in response to that law. At around that time, calls for increased transparency were becoming louder, if you will, and many activities happened in the next 5 years, including the International Committee of Medical Journal Editors, the ICMJE, who released a statement in 2004 stating that as of 2005 they would not publish any articles about clinical trials that had not been registered. The State of Maine passed its own law about trial registration and results reporting, and there were many actions by State attorneys general in the United States. ClinicalTrials.gov accommodates all of these policies. Finally, in September of 2007, FDAAA was passed, and that stands for the Food and Drug Administration Amendments Act. One section, Section 801, involves expanding the registry and results reporting and I'll be mainly talking about that through the rest of this talk.

Just as some background, a ClinicalTrials.gov record consists of, well, first there's a point that there's one record per trial. So sometimes you'll hear about sites or trials that have a hundred sites and it's important to note that that trial would only have one record at ClinicalTrials.gov, even though it may be conducted at many sites around the world. There is the registration record and the results record. The registration record is submitted at trial initiation and it summarizes information from the trial protocol. It includes information about recruitment that might be useful to someone who is seeking a trial in which to participate. The results part of the record is generally submitted at trial completion and summarizes the trial results.

So, in the protocol section, which is sometimes called the registration record, there is descriptive information about the study, recruitment information, location and contact information, and other administrative data.

In the results part of the record, there is information, summary information about the results. It is important to note that there is no patient level data here; it's all summary information about the results of the study at the end of the study. It includes a section on participant flow, baseline characteristics, outcome measures, adverse events, and certain other pieces of information.

ClinicalTrials.gov also has a public archive for the records, so changes can and should be made to records. For example, estimated dates such as the estimated completion date will eventually become the actual date and this needs to be noted in the record; similar for enrollment. There may be other protocol changes. Overall recruitment status and site specific recruitment status will, of course, change as the study progresses. For example, it might go from "not yet recruiting" to "recruiting" to "no longer recruiting" to "trial completion." And all changes are publicly tracked, so that it will be in public view when and how the changes were made.

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So over the life-cycle of a clinical trial record, you need to have an initial registration, updates as necessary, the initial results reporting, and again updates as necessary. So it's really a dynamic record, not a static record.

So key policies and laws.

As noted previously, ClinicalTrials.gov accommodates a whole host of policies and serves many users. So the policies are listed above this oval and the potential users below it, and you can see that there are many of each. We've highlighted FDAAA, which is that Food and Drug Administration Amendments Act, the law that is currently being implemented in the United States, and the journal editors, the ICMJE, because those two policies have had probably the greatest impact on the use of the registry and results database. The users include potential patients and physicians who may be interested in recruitment information, journal editors, researchers and funders, institutional review boards, and health policymakers.

So, let's talk a little about FDAAA, which was enacted in September of 2007 and requires trial registration as a legal requirement for a broader group of trials than had previously been required under FDAMA. It also requires results reporting and this is the first law in the world that we know about that requires results reporting, although the State of Maine as I mentioned had a similar policy earlier. And it added enforcement provisions, including notices of noncompliance that would go on the public record, civil monetary penalties of up to \$10,000 dollars per day, and the potential for withholding of NIH grant funds. So the enforcement provisions are serious and presumably indicate the degree to which Congress felt strongly about these policies.

So, to review registration policies, as mentioned, the two most important policies are those of the journal editors and those of FDAAA. The journal editors' policy requires the registration of all interventional studies for any intervention type, meaning drugs, biologics, but also surgical studies, behavioral therapy studies, etc., and all phases, including phase 1, and without any geographical limitations—so the study could be done anywhere in the world and the journal editors require that it be registered as a precondition for publication. The law requires the registration of interventional trials that involve a drug, biologic, or device, and it's a drug, biologic, or device as defined by the U.S. FDA. It excludes phase 1, so phase 1 studies and similar small device feasibility studies are not included in the scope of the law. And it only covers those trials [of drugs, biologics, or devices] that have U.S. FDA jurisdiction, for example, trials being done under an IND or IDE or having at least one site in the United States. For more details about these policies, you need to see the particular page at ClinicalTrials.gov which will have the more detailed legal language.

For results reporting, the only policy that's currently prevailing is FDAAA. So the journal editors do not have a policy about results reporting in ClinicalTrials.gov. And FDAAA for results reporting covers the same trials as it covered for registration with one important caveat, which is that the studies only have to report their results once all of the drugs, biologics, or devices used in that study have been approved by the FDA for at least one use—meaning that if it's a study of unapproved drug or unapproved device, the results do not have to be reported unless or until

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those drugs or devices are approved or cleared by the FDA. And, generally, results have to be reported within 12 months of what we call the “primary completion date;” in the law, it’s called the “completion date” and I’ll review that in a minute. There are some reasons for delay that are possible under the law.

So key terms for understanding FDAAA. In the law they use the term “applicable clinical trial” and that’s really roughly what I just described in terms of interventional trials, excluding phase 1, that involve a drug, biologic, or device with U.S. FDA jurisdiction. There is also a date requirement, which is that the law only covers those trials that were initiated on or after the date of enactment of the law. The law also uses the term “responsible party” and that’s the entity that’s legally responsible for ensuring that these features of the law are met. And it’s roughly the sponsor, or if it’s an NIH-funded trial, the grantee, or they might designate the principal investigator if they meet certain requirements. And again, the specific language about this is included on our Web site. And then there’s this “completion date,” which we refer to as the “primary completion date” to distinguish it from “last patient, last visit,” which is the date that many people think of when they think of a trial completion date. The primary completion date is the date of last data collection for the primary outcome measure. So it’s possible that that might occur before the trial is actually completed if in fact there are secondary outcome measures that last longer.

A few notes about results reporting and trial publication. It’s important to note that the deadlines for reporting to ClinicalTrials.gov are independent of publication status. So it’s not possible to say for example that you’re not going to meet the legal deadline because you’re waiting for journal publication. On the other hand, the journal editors have made it clear that reporting to ClinicalTrials.gov will not interfere with journal publication. And ClinicalTrials.gov records are linked via the NCT number, which is the unique identifier that we assign the record, to publications.

And here’s an example of that. So here’s a ClinicalTrials.gov record. You can see that citations are inserted by ClinicalTrials.gov, although they could also be provided by the responsible party and then that’s a live link to PubMed, which links to many journal articles and vice versa. So in this case in the New England Journal of Medicine, you could link back directly from that journal article to ClinicalTrials.gov.

So I will now show you a sample posted results record.

This is the sort of full text view which is the first view that you would see in a particular record.

This is a breast cancer study. And you can see in this full text view, you can see details of the condition, the intervention, the arms, etc.

It also has various linkages that ClinicalTrials.gov inserts into the record to help different viewers. So here’s a link to consumer health information at MedlinePlus. In this case, it linked the breast cancer term.

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In the tabular view, which you can choose, you can see a more tabular listing of the data elements that might be more appropriate for an academic or a researcher, or perhaps a journal editor might find this view more user friendly.

And then there's the study results tab, which for those records with study results would have the results.

So the first module – the results are divided into what we call “modules” – and the first module is participant flow. And this is the legal language from the law, which defines what is required in the participant flow module.

Here's a sample participant flow and you can see there are two arms of the study, which are represented as the columns, and the number started and the number completed. In this case, they provided details about the reasons for noncompletion for those participants who did not complete.

The next module covers demographic and baseline characteristics, and again this is the legal language.

And this is what a sample baseline characteristics table would look like. Again, you have the two columns, which are the arms, and a total column, which the law required. Then you have the total number of participants in each column, and then you have different attributes of those participants. So here are two different ways of conveying the age of the participants and gender; at the bottom a little bit cut off would be the region of enrollment, which would list the different regions of the world from which the participants came.

Then you can see in this particular example, the responsible party entered a lot more detail about the participants, including various clinical characteristics of the participants that they felt were important to understand the results of their study. This would be akin to Table I in many journal articles.

The next module are the outcome measures modules – and these are sort of the heart of the ClinicalTrials.gov results record – and this is the legal language, which notes that it is legally required to give the values for each of the primary and secondary outcome measures. And it's important to note that it says “each” and not “key” because the journal editors' policy requires only key secondary outcome measures, whereas the law requires that all secondary outcome measures be reported. And it requires reports of statistical tests that might have been done on those measures.

So here is an example of a primary outcome measure from this breast cancer study; and you can see the number of participants analyzed for each of the two arms; and then the values for this primary outcome measure, which was whether or not there was a local, regional, or metastatic relapse, or a second primary cancer or death from any cause. And you can see the number that

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had that outcome. Below that, you can see results of a statistical analysis, which included a log rank test with the P value and a hazard ratio and a confidence interval around that hazard ratio. And this statistical analysis applies to that table of outcome measures.

And here's another outcome measure and another set of statistical analyses from that same study.

The final module is adverse events and this consists of two tables. One table of serious adverse events, and you can see here the legal language that requires that.

And this is what it would look like. So again, there are the two columns, which are the two arms of the study, and a series of serious adverse events that occurred organized by organ system, which the law requires us to do.

And then another table of frequent adverse events and this is really those adverse events that were collected, that were not considered serious. The definition of serious is really the definition that's used throughout the FDA regulations.

And here is an example of the frequent adverse event table.

There is a final section of the results record which is called Certain Agreements. That is the phrase that was used in the law and this is the legal language. And it's basically getting at whether or not there were any contractual agreements between the principal investigator and the sponsor that would limit the principal investigator's access to the data or the ability to report results.

And this is the method by which you would convey that information and this is what would be seen on the public site. So in this case, there was an agreement. It was in the "other" category, and the data provider gave details about what the agreement was.

So what are our review criteria for data that come into ClinicalTrials.gov?

On the protocol registration side and on the results side, the basic criteria is that the data must be clear and informative and responsive to the meaning of the data element. The review focuses on logic and internal consistency, apparent validity, meaningful entries, and formatting. It's important to note that ClinicalTrials.gov does not have essentially the source material, so that we don't have the actual study protocol and we don't have the patient level data. So we never know specifically whether a piece of data is correct, but it turns out that there are many instances where you can tell that it can't possibly be correct and I will show a couple of examples of that.

You can find details about our review criteria at the Web site listed above, the PRSinfo site, and there you can see lists of the data elements and definitions and our detailed review items and criteria for both the protocol side and the results side.

So what are some problems we've seen in results records?

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First, it's important to note that there's a great need for rigor and precision because one thing that I didn't mention is that the results tables are stand-alone tables with very minimal opportunity for narrative text, and there is no space for discussion or conclusion. So unlike a journal article, there is minimal narrative text. It's important that the specific words be used very carefully. So in this cartoon, the person says, "I used to think correlation implied causation." And then he says, "Then I took a statistics class and now I don't." And his friend says, "Well, sounds like the class helped." And he says, "Well, maybe." And that level of precision in language is what's really important for entering results.

So here is an example of an invalid entry from a portion of a data table. So you can see here are the two columns for the two arms of this table and the data have to do with hours per day of sleep and it's "mean plus or minus standard deviation" hours per day of sleep. And you can see for the first arm the data were "823 plus or minus 92 hours per day of sleep," even though we don't know how many hours per day of sleep participants in this study had, we know that this is an invalid entry because you can't have more than 24 hours per day of sleep.

Similarly, here's a more complicated illustration of internal inconsistency. In this participant flow table from this study, there were three periods—a double blind period, a followup period, and a crossover period. And you can see that the number who completed the first period was zero for both arms and yet 150 or so participants started the next period and that's not possible. So in general in a participant flow module, the participants need to flow and the goal of this is to show how they flowed through the stages of the study. So this set of tables doesn't make any sense. Again, although we don't know how many people really started and completed each part of this study, we know that what they've conveyed here makes no sense.

And this leads us to quote Wolfgang Pauli, who famously wrote to a colleague on a physics paper, "This isn't right. This isn't even wrong." So when we get really nonsensical entries, we will push back and will not post them. In another presentation in the series, we'll go over the review criteria in more detail.

Just to show that it is possible to use our system to provide very detailed information, this is an example of an outcome measure called Pregnancy Rate using something called the Pearl Index. Most of you have probably never heard of the Pearl Index and we hadn't either, but you can see that they used the free-text box to explain it in a very succinct way so that it was then possible to understand the data presented when there is 2.74 pregnancies per 100 women years exposure in this arm of the study; you can understand what that data mean.

So what are some of the issues in reporting results that we've come across?

First, it's important to really understand that entering results in ClinicalTrials.gov is similar to writing a journal article—meaning it's cognitively similar to writing a journal article. The data provider, the person entering the results, must be able to understand the study design and data analysis. It cannot be done by machine; it requires a thoughtful process, and it requires typically

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the investigator and or the study statistician, it requires their involvement.

Second question that comes up is who is the audience? And the easy answer is that there is a variety of potential audiences, this is a public Web site, and all sorts of people will use it. But if you think of this sort of spectrum, from at the top, the potential audience could just be the principal investigator and their research team, all the way to the audience of the lay public or other readers of consumer health literature—you can see that there all sorts of levels in between. It's important to note that it doesn't make sense for Congress to have mandated us to build a whole Web site just to help the principal investigator talk to his or her study team. So sometimes people enter data using shorthand—using imprecise language that would only be understandable to their immediate colleagues—and that's simply not helpful. So at a minimum, we think the results data entries need to at least be understandable to other readers of the medical literature in other fields— so somewhere in the middle of the spectrum.

Again, the fact that that's the intended audience is different from the intended beneficiaries, we believe that the ClinicalTrials.gov results records help the public in general by helping to fulfill all of those needs and ensuring that key decisionmakers—including their own institutional review board, health policy makers, clinicians, and others—have access to all of the data from all clinical trials that are done on drugs and devices in this country.

It's also useful to note that FDAAA mandates pertain to reporting not to the conduct of clinical trials. So, for example, there might be a trial that simply did not collect nonserious adverse events. This section of FDAAA does not in fact mandate that they go back and collect those data or of course it doesn't mandate that they report data that they didn't collect; it simply has to do with reporting what was collected. And again, as mentioned before, we believe the results reporting to ClinicalTrials.gov complements but doesn't replace journal publication. For example, our study records have structured data entry; there's a requirement that all outcome measures be reported, which isn't typically required by a journal. On the other hand, it's lacking narrative background and lacking discussion and conclusions, which you would find in a journal article.

And this is what I mentioned before, which is this is a statement from the International Committee of Medical Journal Editors saying that results posted in ClinicalTrials.gov will not interfere with the consideration of that manuscript at the journal. And it's also worth noting that at any given time, only about half of the results in ClinicalTrials.gov have associated publications—meaning that ClinicalTrials.gov is, at any time, a unique source of results for many trials that either do not yet or never will have journal publications associated with them.

So some sample uses of the data in ClinicalTrials.gov, including the ability to access information about specific trials, including the ability to track progress and protocol changes and to eventually see the results, to assess the available evidence relevant to a specific clinical topic— let's say breast cancer, what's new with breast cancer trials? What trials are being done? Or what are some results from trials? — to assess the nature of current and past research in a given area, and to review methodologies used in clinical trials. There are many more uses but these are some

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examples.

And here's a list of some select publications from our group giving more detail about some of the issues that I discussed.

And here's some Web sites for additional details about many of the issues that I discussed. As I mentioned there are other presentations in this series of Webinars which will go into more detail for all of these topics.

Thank you.