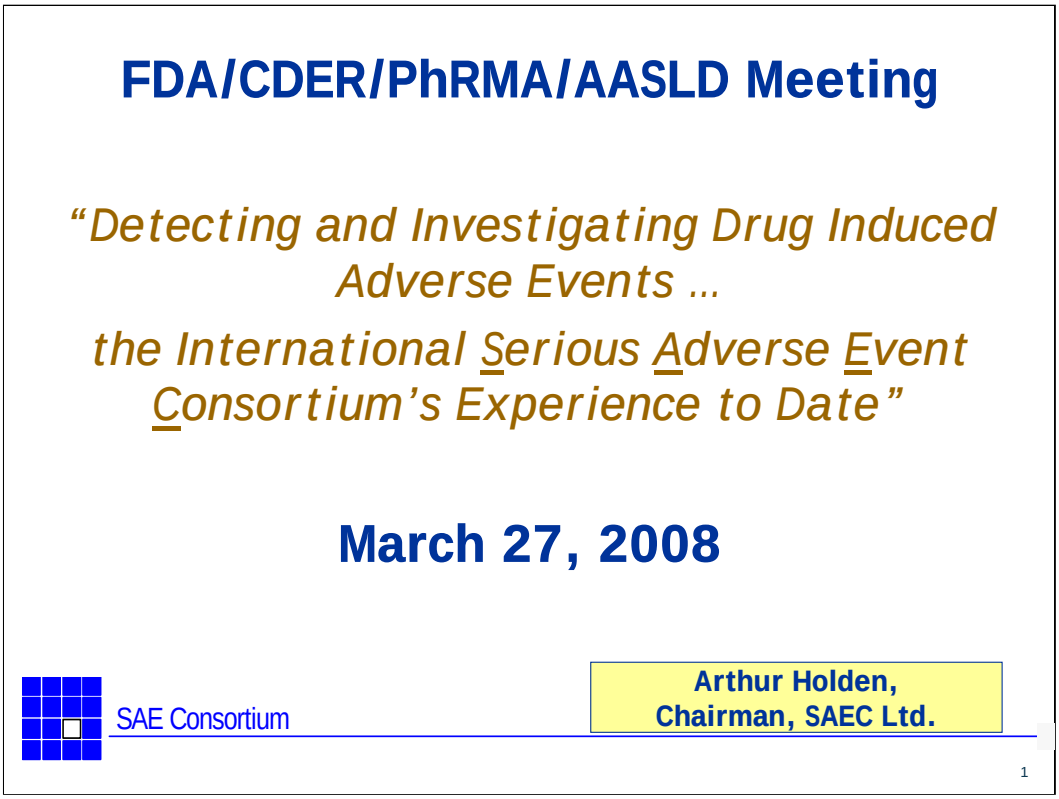

DR. PEARS: The last speaker this morning is Mr. Arthur Holden who is the Chairman of International SAE Consortium.

MR. HOLDEN: Thank you very much. Instead of thanking John and the organizers which I will get back to doing, anytime you're the last speaker on a program, you have to thank the audience for hanging around. (Laughter.) So for that I say thank you. I'd also like to thank John Senior, for his support of Consortium and his tireless work to move this agenda forward.

Two rather quick disclaimers before I make my comments is, number one, you won't hear Hy's Law coming from me. I am not a clinician or scientist. I am an executive. So I am a rare species in this group who is trying to facilitate this research..

Lastly, I am going to have to exit right at the end of my presentation. I have to get out to California and American Airlines unfortunately is grounding their MD80s.

So what I'd like to do, John has entitled this, John has a knack with his titles of kind of steering what he hopes you'll talk about, and my presentation or talk is on focused on the role of clinical trials in cracking this nut, and I'd like to thank Jack for setting a perfect context for me to come in and talk about what we're doing in the serious adverse event consortium and all I'm going to do in this presentation is to provide you with a couple of insights relative to our experience to date.

Presentation Overview

- Why its formation and what is the focus and the current methods of the SAEC?
- The SAEC's experience and challenges with its current SAEC methods
- Thoughts on a more integrated system for SAE research
- Q & As

SAE Consortium

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One, I'd like to discuss is what is the Consortium? Why it's been formed and where it is in its focus and its current methods because this is a snapshot in time for all and even more reasons than Jack articulated. This will be an evolution and the ability of this entity to evolve and change its methods as it gains experience will be essential, and hopefully we'll be able to do that quickly and effectively.

I'd also like to just highlight our experiences and challenges with the current methods that we've used, and then I'd like to close with some thoughts on maybe a more integrated approach to this type of research which I think will be in line with the Guidance and pending questions and answers.

ADR vs SAE

- ADR → "a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans…" [1]
- SAE → a response to a drug [at normal dosing] which is severely debilitating or life threatening and typically requires the cessation of the drug

1. WHO

SAE Consortium

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Just to be real clear, this meeting is focused on DILI, and there are a number of what we call serious adverse events beyond DILI. Just to be clear, what we're talking about within the Consortium when we talk about a serious adverse event is one where you have a response to a drug at normal dosing which is severely debilitating or life threatening and typically requires cessation of the drug.

Some Conclusions … beginning with the end in mind

- Impact of rare, drug-related SAEs on patient health and pharmaceutical development productivity is significant
- SAE research is difficult due to phenotyping, scale, and collaboration challenges → it's a "team sport"
- Current SAE research channels [i.e. academic investigator network] are disjointed, variable, poorly funded and "discovery research" oriented.
- Broadening the sources of "cases" and the "collaborative models" utilized, will likely expedite the full spectrum of SAE biomedical and outcomes research

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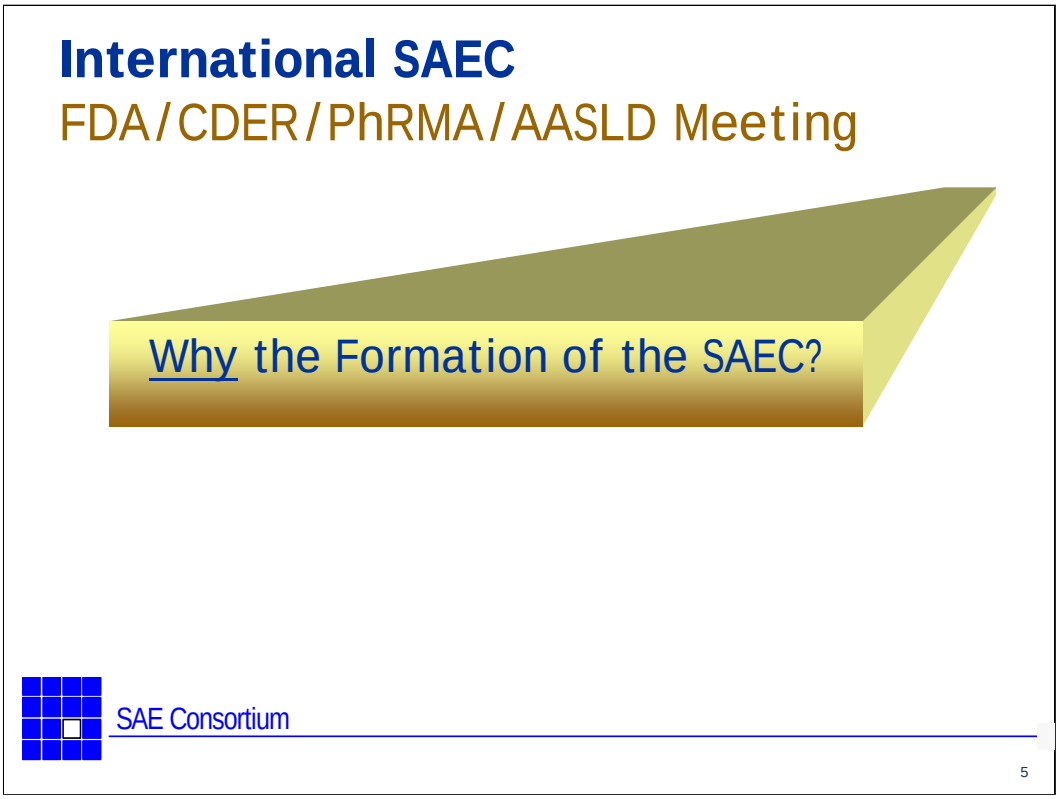
Let me just make, so you get the punch line if you do have to run out of the room, let me just begin with the end in mind here. So a couple of points: the impact of where drug-related serious adverse events on patient health and pharmaceutical productivity is significant. This is both a public health issue that's growing and emerging which I think we all have to keep front and center, but it's also a tremendous issue relative to productivity in an industry that's challenged because of this and many other issues.

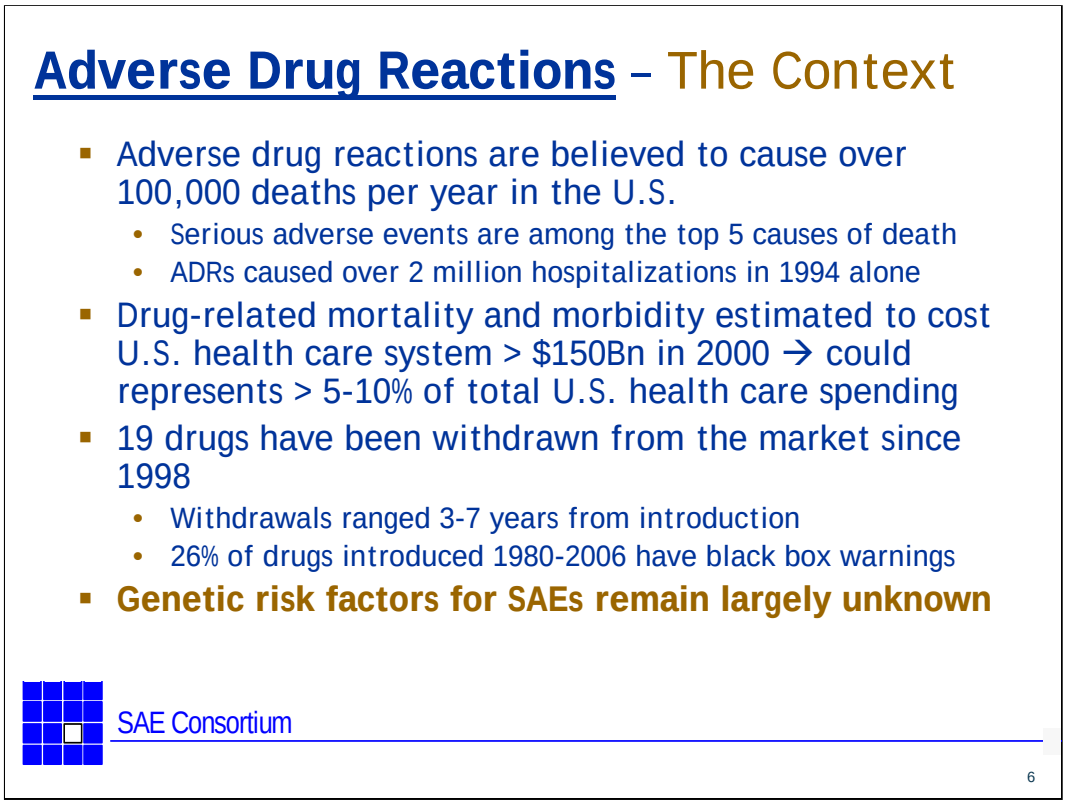
Secondly, this type of research is really complicated for all the reasons that Jack articulated. My summary statement is because of phenotyping complexity, some of the scale issues and some of the collaboration challenges that are required, you've got to get different people working together in ways that traditionally they haven't worked together. And so it's a team sport in my opinion. So the Consortium is being put together, at least one example, to try and facilitate and to explore this type of team work.

The current channels that are available for this type of SAE research principally what I'll call academic investigator networks, which are functioning around the world, typically functioning in a disjointed, pretty variable, in many cases poorly financed and they're failure oriented towards kind of initial discovery type research. And this continuing research, we need to do this work. It's going to have to cover more than just the discovery side of things.

And then broadening the sources of cases. This is where it ties to Jack's last point, and the collaborative models that are utilized, will likely expedite a fuller spectrum of this type of serious adverse event biomedical and outcomes research. And I do add the outcomes side of this because I don't think it's enough just to take the potential predictive value and extrapolate and say, well, you need this number of patients. It has to do with integrating not only the predictive power but also the relative economics of this specific situation that you're working with. So we have to broaden that a bit.

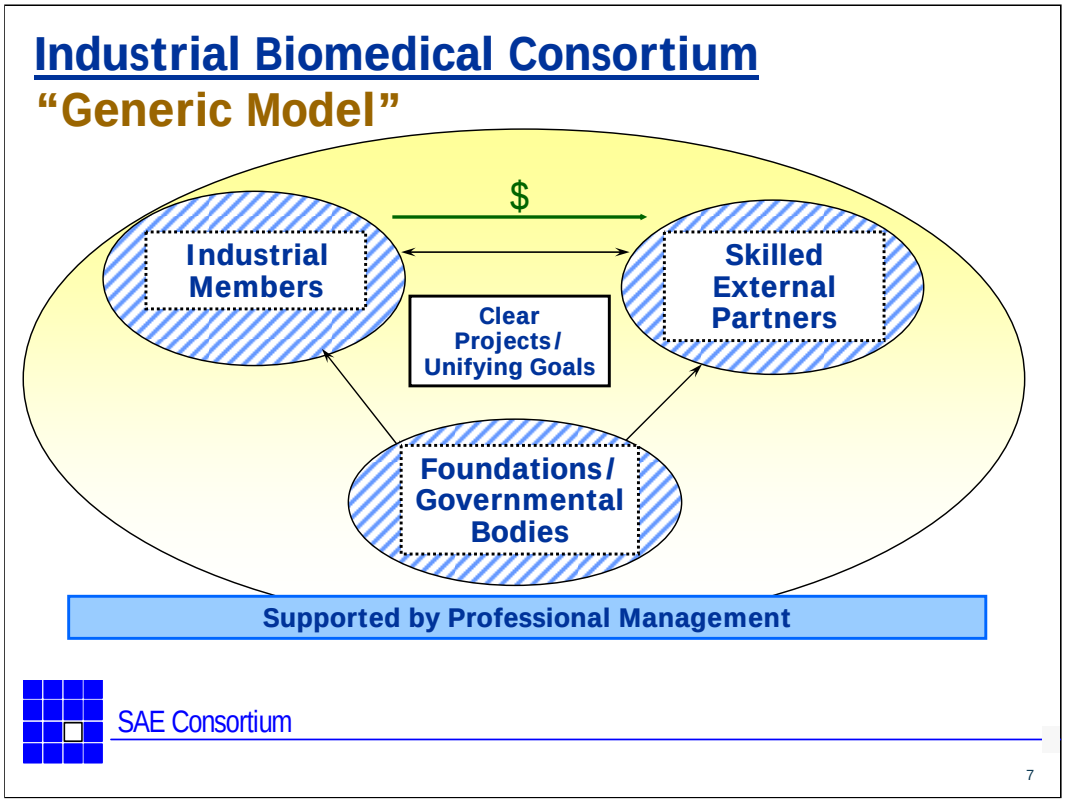


The Consortium came about for three reasons. One is there is a public health issue that continues to grow and it is amazing to me in light of its growth and in light of the potential economics associated with it, how poorly understood this is from an epidemiologic and healthcare economics point of view. But those two factors are very important I think in driving the focus of this consortium.



As I alluded to before, it's a productivity issue, and it's one that this entire community, not just regulators, saying that the main factors have to do things differently, it's us working together can begin to do a better job of reducing what we call drug attrition in the case where you truly have a good drug and you've got some variability in response and you need to manage that.

And then lastly, I think the other factor that's there is we have some insights into genetic factors that are active here, but we hardly have scratched the surface in my opinion, and they remain largely unknown.



So the model we're working with here is we take industrial companies and their resources and talents, put them together with the best skilled external partners because you don't want to build a lot of infrastructure. You want to leverage what's there and do a collaborative model, with very clear projects with unifying goals where financial resources are put to play on very well defined projects with clear deliverables and milestones in a certain time period, and that's supported by dedicated professional management, and hopefully that's the secret to getting some things done.

In terms of this type of model and I'm going to go into the specifics of Consortium, there are a few things that are important to understand. This is set up as a 501C3 in the public good. So what we do as -- is defined by how we can facilitate everyone in this community using this data and information. So it tends to focus on very focused projects with strong operational management that are pro-competitive, meaning it's going to help all parties to be more competitive, and that's important because our membership is large companies and you have to make sure there aren't any antitrust considerations.

We also are completely dependent upon the skills of our members and collaborators in order to execute through well-organized subcommittees to get the work done. And the goal is, wherever possible, and we certainly try to use the best external collaborators and investigators to do the work we do.

IBCs → Operational Tenants

- Unifying objective → industry and public good [501 c 3]
- Focused projects, with strong operational management [*business reasonable contracts & incentive alignment*], that are pro-competitive & NCRPA compliant
- Strong "quality" and "time to result" orientation
- Clear and uniform "membership requirements" → *anti trust considerations*
- Extensive leverage of members' skills via well organized sub-committees
- Strive to collaborate with the best quality external advisors & investigators
- Public release of data → after appropriate IP management actions to ensure "openness"

SAE Consortium

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And lastly and very importantly the data that we generate to the extent to which it's allowed by the consents and IOB approvals, will go out into the public domain, and by that I mean accessible to the broad public to qualify researchers to use this information. And our goal is to have no intellectual property constraints on these markets, and for me, there's the motivation, in order to operationalize this down the road to the extent to which they are marketable, it will have some clinical utility which that remains to be seen, is we're likely to be able to put these on common grades and integrated platforms without having to worry about IP variants and that will help both the quality and the cost of this down the road.

So there's a slide in your packet and I'm not going to go through, what gave birth to this particular activity and I'll just make a couple of comments in the interest of time.what gave birth to this particular activity and I'll just make a couple of comments in the interest of time.

Part of this came because as I chatted with the heads of R&D from most of the major pharmaceutical companies at the end of 2006, this was the major issue that they felt they could not address alone and needed to work collaboratively on. It is not a scalable activity within the context of an individual company to go after this. So that was very important. Obviously that's driven by the productivity issues but it's also managerial and it's tough to do this from a scale point of view.

In addition, the FDA had significant interest through an Industrial Advisory Group of setting up an effort that would do this type of work that mimicked an activity I had the pleasure to develop -- Consortium, but we would have a very specific focus on the pharmacogenetics of serious adverse events.

Another aspect of this which is so incredibly important, not only from the practicality of drugs is used around the world, and they're used in a variety of patients from an ethnicity point of view, but that this needs to be international. It isn't one platform we're functioning on, and to the extent to which we can facilitate this on an international basis, that becomes important.

And then lastly, I think very practically, there are limited resources that go into this area. This is an area that needs significantly greater funding and part of our agreement is to at least make some private sector focus on this.

So the Consortium's mission is very concrete and very specific at this point in time. It can evolve as we get more data and information but it's to identify and validate DNA-variants useful in predicting the risk of drug-induced serious adverse events.

Mission / Key Objectives

Mission

The SAEC will identify and validate DNA-variants useful in predicting the risk of drug induced serious adverse events.

- Coordinate international network[s] for obtaining well phenotyped cases and controls for SAE PGx research [*discovery and validation*]
- Evolve the content for optimal SAE genotyping panel[s]
- Identify the computational methods to effectively apply whole-genome SNP mapping technology to SAE marker development
- Create a publicly available "knowledge base" to identify PGx markers for predicting key SAEs
- Manage IP relating to PGx markers useful in predicting SAEs to ensure broad and open access
- Develop a cross-disciplinary forums to address clinical and scientific issues related to PGx of SAEs
- Support the execution of the FDA Critical Path

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So pivotal to doing that is the building and coordinating international networks of well phenotyped cases and controls across a variety of serious adverse events, both for discovery as well as validation and eventually outcomes research. And there are a variety of other factors that we're working on that are sub-objectives within that context but it all adds up to what I think is one of the seminal activities from the private sector to support the real execution of the FDA critical path and could lead to those other elements.

The membership of the Consortium is expanding and growing. This is significant because in order to be a member of this, you have to pay money. People have to say this is worthwhile to invest in. We now have 10 major pharmaceutical companies. I'm pleased because for the first time we've been able to bring in major Japanese pharmaceutical companies which also work on a global basis but it will also help us in building our networks internationally.

There are a variety of collaborators which are on the right side of this slide, and I will try to put some sense and logic around that in terms of what we're doing in the remaining time. And then pivotal to this, the FDA has been a very important collaborative partner but we will expand it out as we grow. EMEA has been involved to some extent principally from an education and kind of consulting point of view. As we move forward, the regulatory bodies across the world will be integrated.

SAE Consortium -- Phase 1 Strategy

1. SAEC research activities will cover two distinct phases over time:
   - **Exploratory/discovery** → focused on identifying initial associations → hypothesis generation
   - **Assessment/"Qualification"** → Hypothesis testing, focused on replication studies to confirm or reject the hypothesis, and/or to better characterize the nature and magnitude of the association between marker and SEA incidence
2. SAEC's scope is broad, but it will initially focus on two SAE WGGT projects → drug-induced liver-disease (DILI) and Serious Skin Rash/SJS.

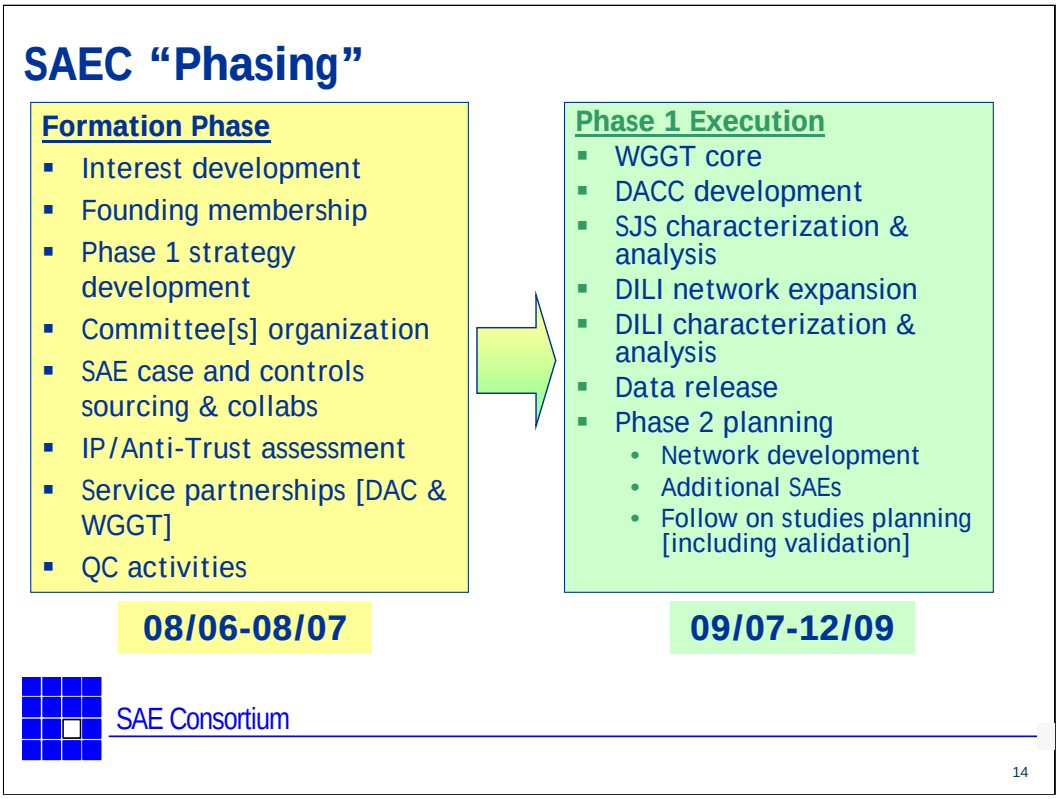
   Rationale:
   - Reasonable time frame to result due to availability of case-control DNA sample collections
   - Priority ranking of importance (DILI) and feasibility, informatics and DCC development (SJS)
3. Simultaneously, explore the feasibility other important SAEs based on importance and availability of appropriate collaborative partners.
4. Adjunct S-T activities:
   - **Standard ADME WGGT panel recommendations**
   - **Develop a publicly available control set[s] for the PGx studies**
   - **Networking partnerships → NHSs, VA, PHSs, etc.**
   - **Industry registry of Rx related SAEs**

So what's the strategy of the Consortium? Right now it's to focus on the genetic variance and try to understand that as best we can. It is an area where we are focused initially in doing non-hypothesis driven discovery association studies using large enough case control cohorts so that we can look at the entire -- across a variety of causes of a specific serious adverse event in terms of drug, mechanisms, looking to try and identify are there overriding genetic factors that may be at play.

And then secondly, using that dataset which would be publicly available, using it as a basis to stimulate more hypothesis-driven types of studies which will build on this genetic database. So this is only the first part of building a foundation for this research.

We started off focusing on DILI and serious skin rash for very practical reasons. We felt that the availability of existing cohorts was there in large enough numbers for us to get going while building our infrastructure in order to do this work and I'll explain to you and give you a couple of examples of that.

Simultaneously we wanted to look at the feasibility and define the priority of the serious adverse events which we could begin to take through this paradigm, and that very much is dependent on the availability of collaborative partners.



And then lastly, as we did this, there are some adjunct activities that we've done, and I'm going to come back and put a context around those in a minute, but I will kind of tie to Jack's point relative to the development of more comprehensive and standardized ADME panels to do this type of genotyping. As a kind of spin off to the Consortium, Lilly, GSK, Rick Hockett and Eric Lii (ph.) came together and formed a working group, and they have standardized requirements for what we'd like in ADME genotyping so that as we do these types of adverse event studies, we've got a much better common platform of requirements, putting that up for the technology community with a challenge, hey, make these arrays work and we'll see what happens. But those types of things help stimulate the research.

SAEC Research -- Evolution Pathways

Research Focus	Heptatox	SJS/TEN	Prolonged QT	Rhabdomyolysis
1st Generation WGGT Association Study	2007-2009	2007-2008		
2nd Generation WGGT Association Study				
Fine Mapping Studies				
Hypothesis Directed Study 1				
Hypothesis Directed Study 2				
Other Studies				
Marker Validation Study				

Additional SAEs

Additional Studies

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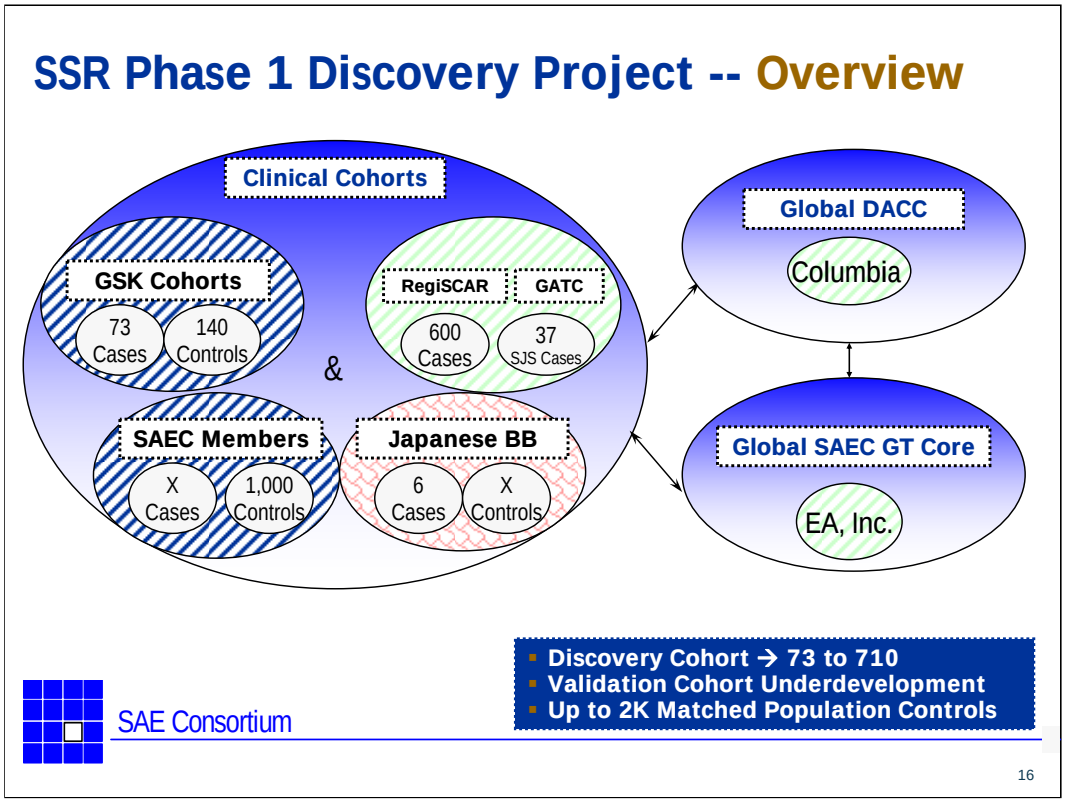
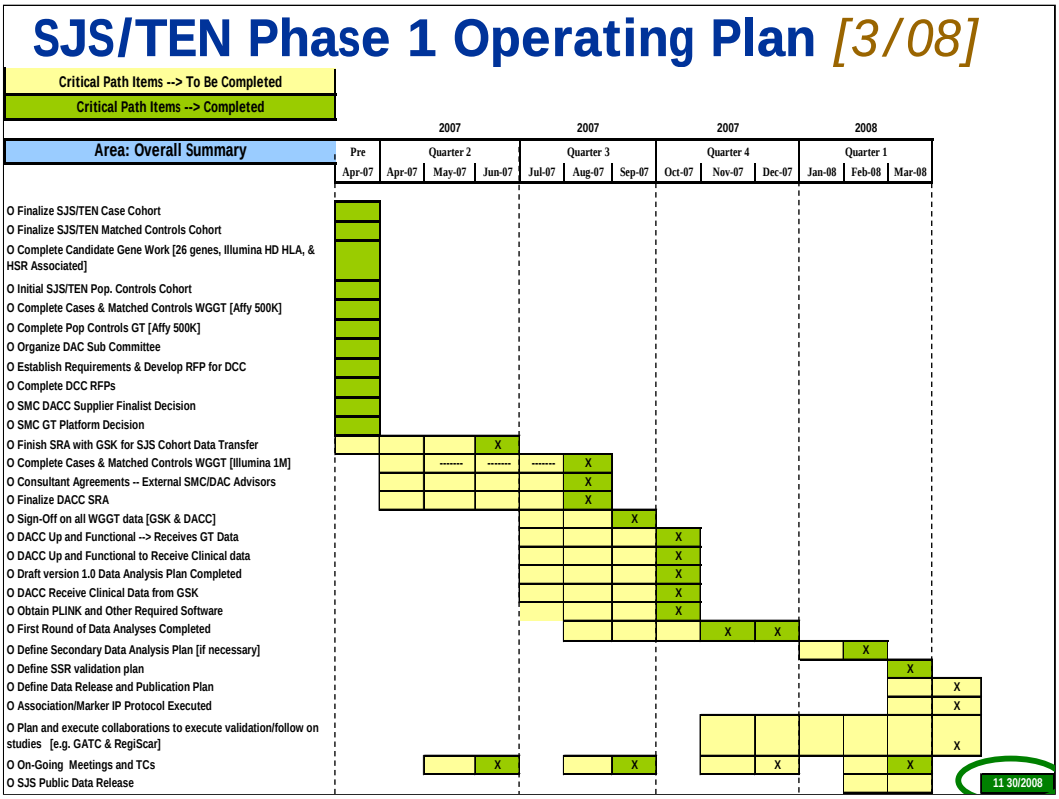
So the concept that we have from a research perspective is to start off and do these first generation whole genome studies initially focused on hepatotoxicity and serious skin rash, expanding those over time and then as we get data and results, crafting how we need to move forward even doing larger studies, depending on the effects that it would play or more focused studies again depending on the data and results that we get. And the idea that eventually develop some sort of framework, we could make it a predictive marker or markers that could be used for certain purposes, that will evolve out of this.



The serious skin rash project that we've done, essentially that which a commercial cohort, one which had been develop by GSK, both cases and controls that were contributed.



We have done the initial whole genome analysis on that and I will skip to this.

SRR – Accomplishments & Challenges

Accomplishments to Date

- Assembled initial cohort & matched controls
- Completed WGGT [1M]
- Assembled "best of breed" analytical pipeline [Columbia]
- Phase 1 analysis completed [*12 month data release*]
- Phase 2 analysis plan in place
- Dramatically expanded initial cohort via international collaborations

Challenges To Address

- Validation vs re-analysis
- Lack of ethnic variation in current phase one cohort
- Priority vs other investments [DILI and other SAEs]

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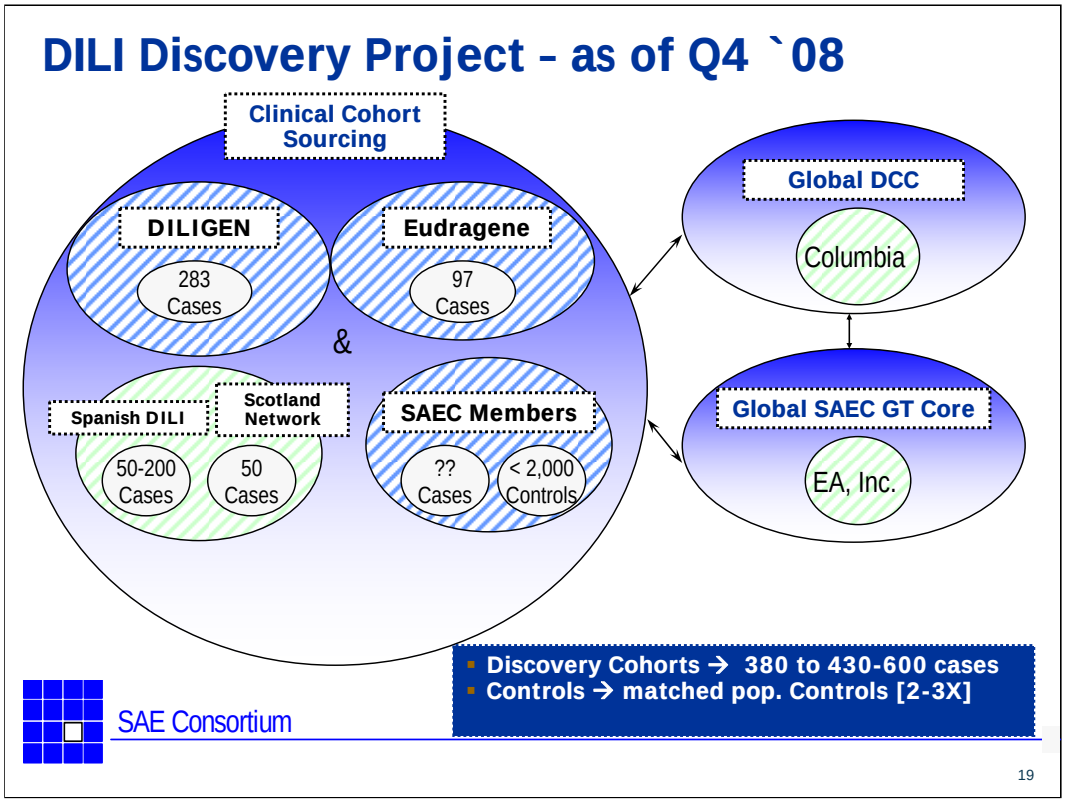
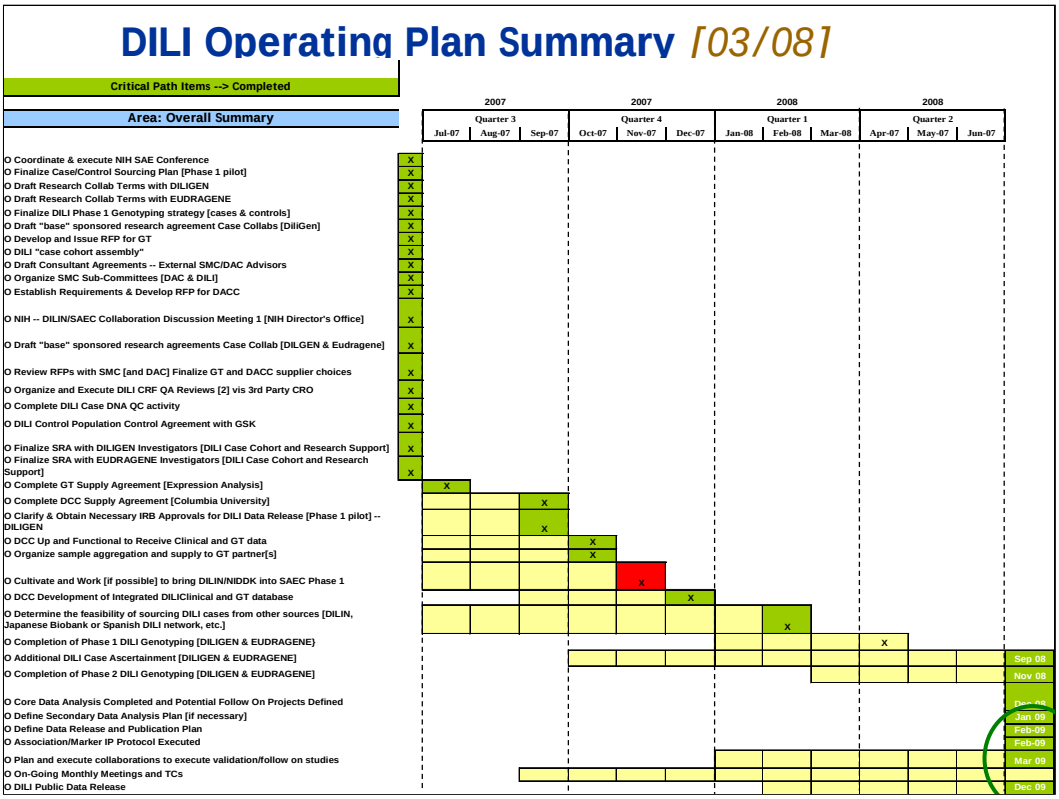
This is kind of the accomplishments and some of the challenges we've had in this area.

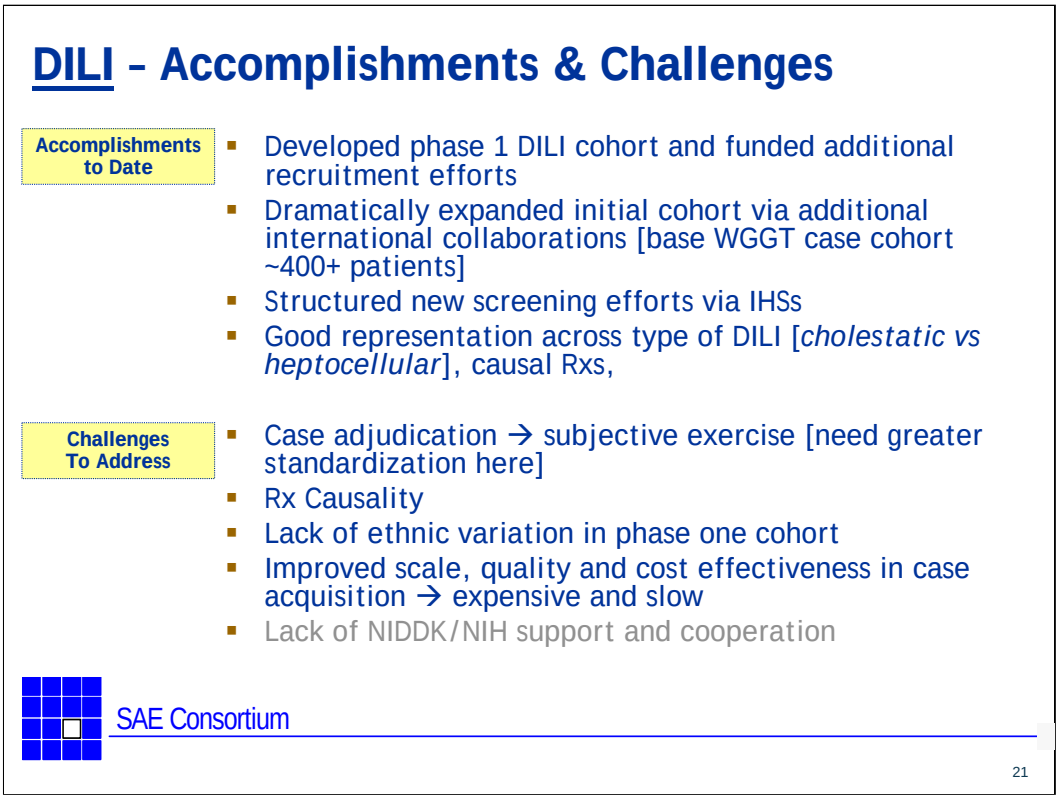


We've taken the 210 patients, we've done the whole genome analysis. We put together what we believe is the best of breed analytical pipeline using the best of academia and the best of commercial entities. That's now housed at Columbia. We have done kind of a first level QC on the data, and we're now executing on a second phase analytical plan to look at these data. We also felt that from the initial preliminary results, it was going to be important for us to expand this cohort.



So I'm going to skip back here. So fortunately, again using academic collaborators, there's been a European network run by Jean Claude Rousseau (ph.) and his colleagues called RegiSCAR, which we are partnering with them, to combine our resources to now take this case cohort from 73 patients up to 710 patients, and then continuing to fund the develop in some targeted areas on how to build this cohort.

So in addition, there's a Canadian network that has had initially 180 target cases. We've adjudicated those down to 37 to include -- we hoped we would be able to bring some Asian participants through the Japanese BioBank. That has not proved to be productive for us. the matched controls in order to do this.



So in terms of challenges, one of the issues is, is when do you start to validate versus when do you add on and do reanalysis? I think right now we're at a point where we want to add on and do some reanalysis based on the preliminary finding which was admittedly a relatively small cohort.

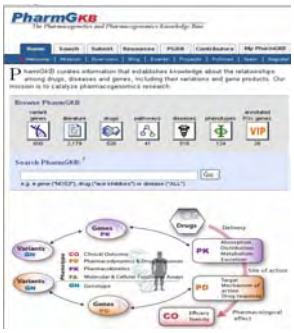
Another factor for us, that we're very cognizant of, is the ethnic diversity in our cohort. This cohort continues to be primarily Caucasian. We want to expand that out. Our current collaborations will not allow us to do that.

If we look in the DILI area, it's a similar type of framework. We have leveraged significantly European collaborators. Jack Bloom mentioned Chris Day and Anne Daly from the UK. DILIGEN is a very much focused effort much like the DILIN network here developing a quality cohort of serious DILI to do the type of research on. So by the end of quarter 3, beginning of quarter 4, we'll have 280 cases roughly through AU. Eudragene (ph.) is a very interesting experiment that I can't go into from a timing point of view, but they will be generating about 100 cases for us in addition to a collaboration that we've done with Scotland, Southern Scotland where actually have gone through using an electronic medical record environment with a very clear phenotype definition and yielded potentially 1100 cases of which have been adjudicated down to 100 cases of serious DILI and we put together a coordination between the Scottish DILI and the DILIGEN network to enroll those cases and to bring them in again by the end of this calendar year.

In terms of accomplishments and challenges, clearly to build the initial cohort is a significant accomplishment in getting that going. We want to continue to expand to bring new collaborators into it. We have also, as you'll see, been structuring collaborations with integrated healthcare systems using the standardized phenotype to see how we might be able to yield cases from these environments where you've got a high quality electronic medical record, a well-functioning clinical data warehouse which can be mined with reasonable sophistication and then the ability to yield these cases and adjudicate them. That's kind of what we did in the scholarship experience and we're looking to expand that to other environments.

Data Release Options

- Via SAEC Website
- Via FDA Website
- Via NIH Websites



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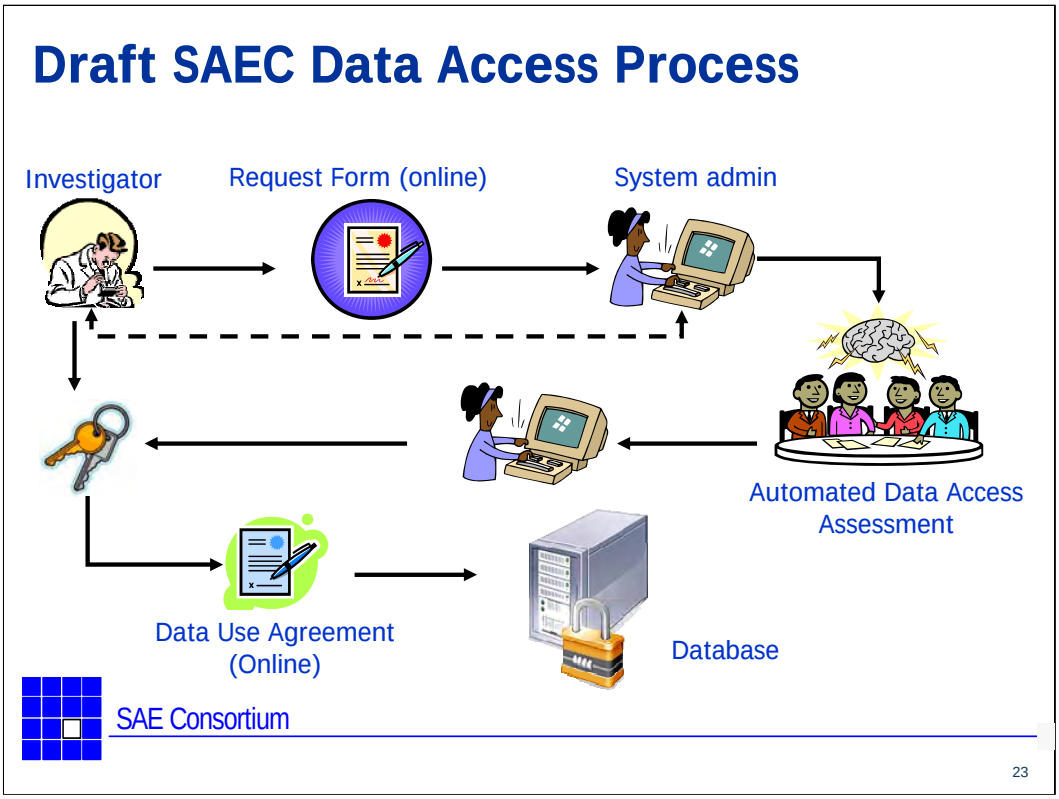
In terms of data release, how these data will go out. We will have our own website but we're also exploring whether there will be appropriate channels to put this information out through either the FDA or NIH. And again, in the interest of time, I won't go through this in detail except to say that I expected the functionality that it's going to require to make this optimally usable both for academic researchers as well as industrial researchers, will dictate that we set up a specific operational platform that meets those needs.

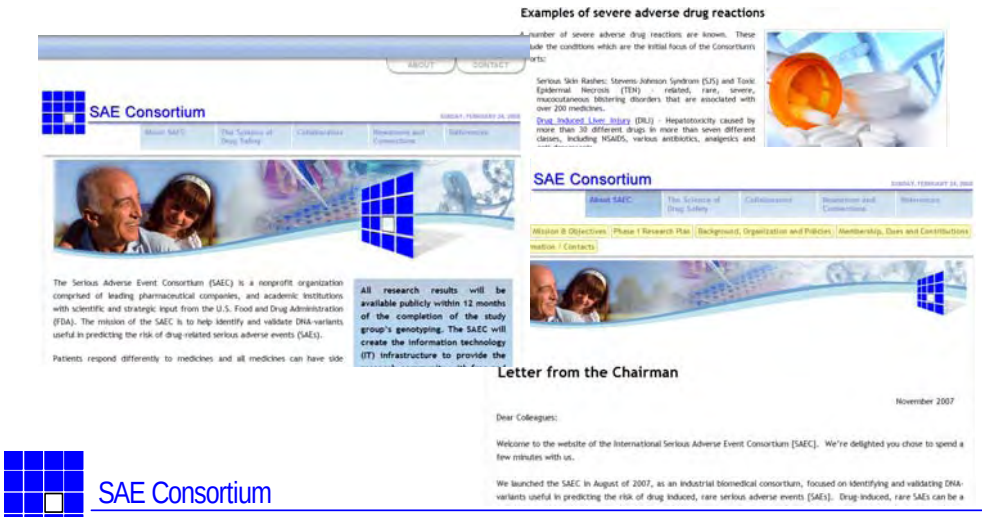
This was precisely what we did in the SNP Consortium which then became dbSNP within the NTBI and NIH databases.



So the idea of data release, when we talk about it, and again this is very crude, is that there will be a request form that will come in from an investigator, that will be processed by an administrative function at data analysis and coordinating center. As much as possible, we want to have an automated data review and access assessment, if necessary, from a small committee.

SAEC Web Site

http://www.saeconsortium.org



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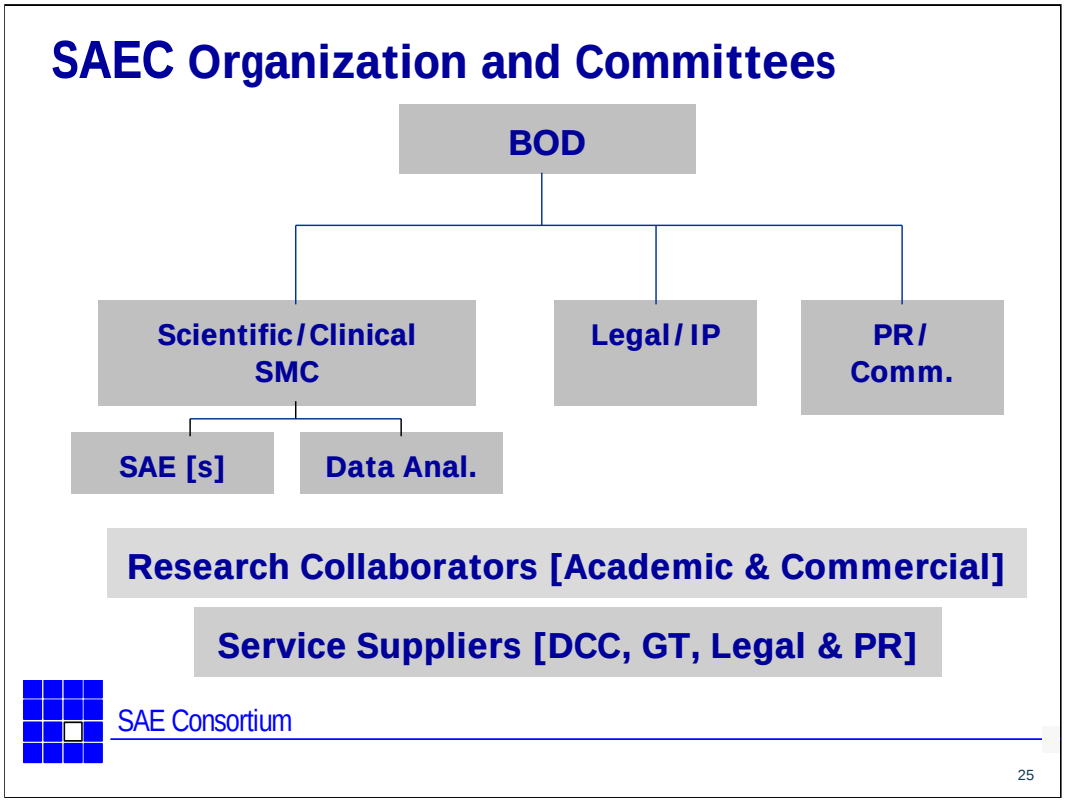
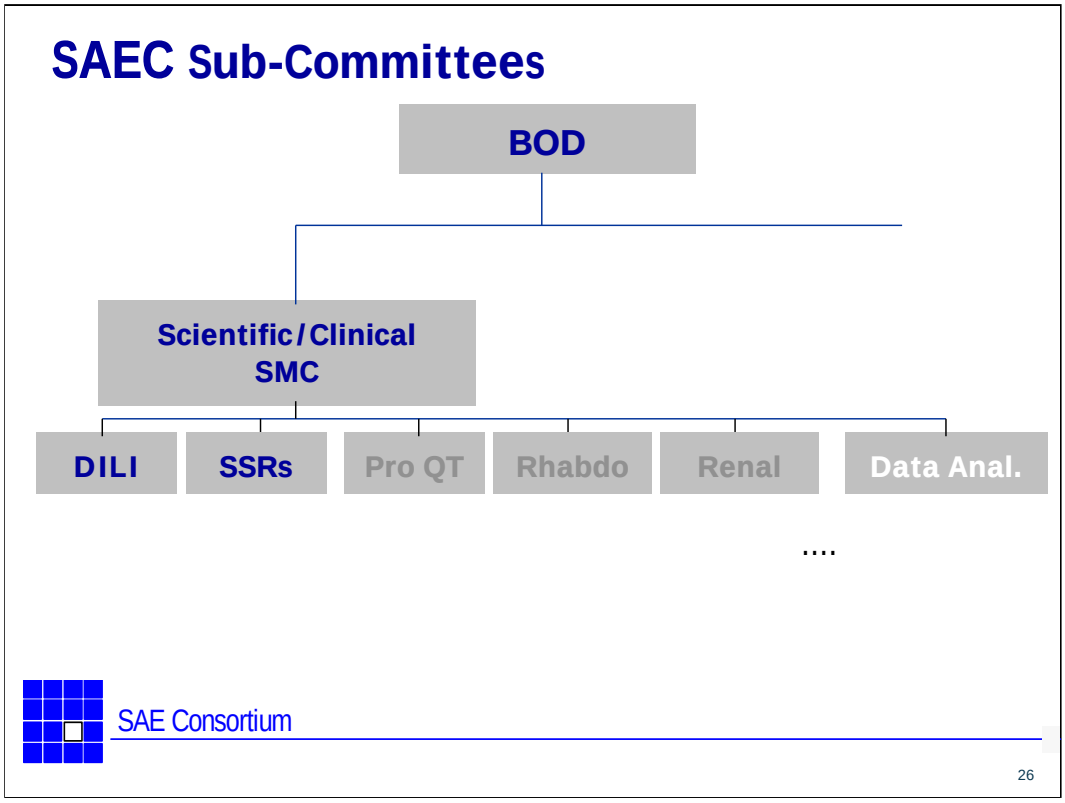
Then the availability of that data will be made through a secure mechanism to the investigators and they'll be able to access it online after they've signed a data use agreement. It's a fairly standard method.



One kind, and then I'm going to talk about the future, kind of how this goes. The organization that's put in place is really completely focused to support the execution of this type of research and evolve it forward.



So even though there's a board of directors and a legal and IP group, they're just staff people trying to facilitate effectively a series of sub-consortia, focused on these different serious adverse events, and the purpose of that infrastructure which is primarily led by me, so we have a head count of one person, trying to do this by design, is to provide as much support to facilitate this research as effectively as we can accomplishing the objectives that we've set out.

Moving Forward

- Member Development
- Follow on Studies –SSR & DILI [including validation]
- SAE definition consensus conference [*SAEC/Wellcome Trust/PGRN*]
- Additional SAEs/New Cohort Development – Traditional Channels
- Novel, Collaborative Channels

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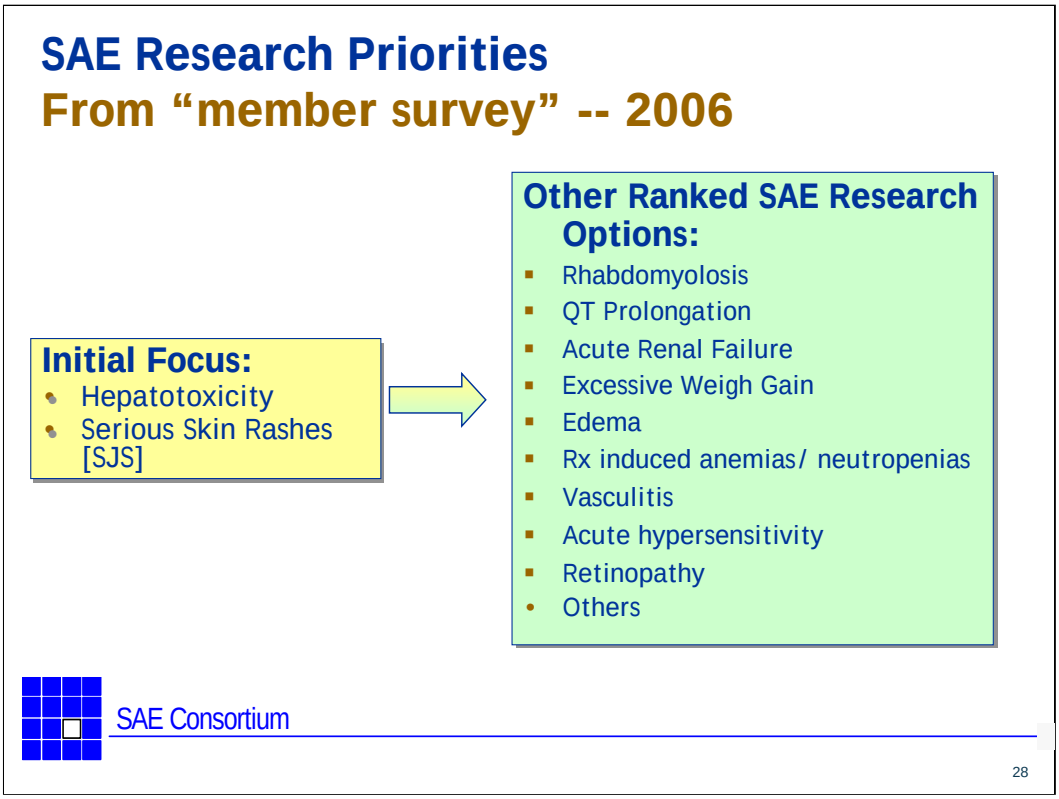
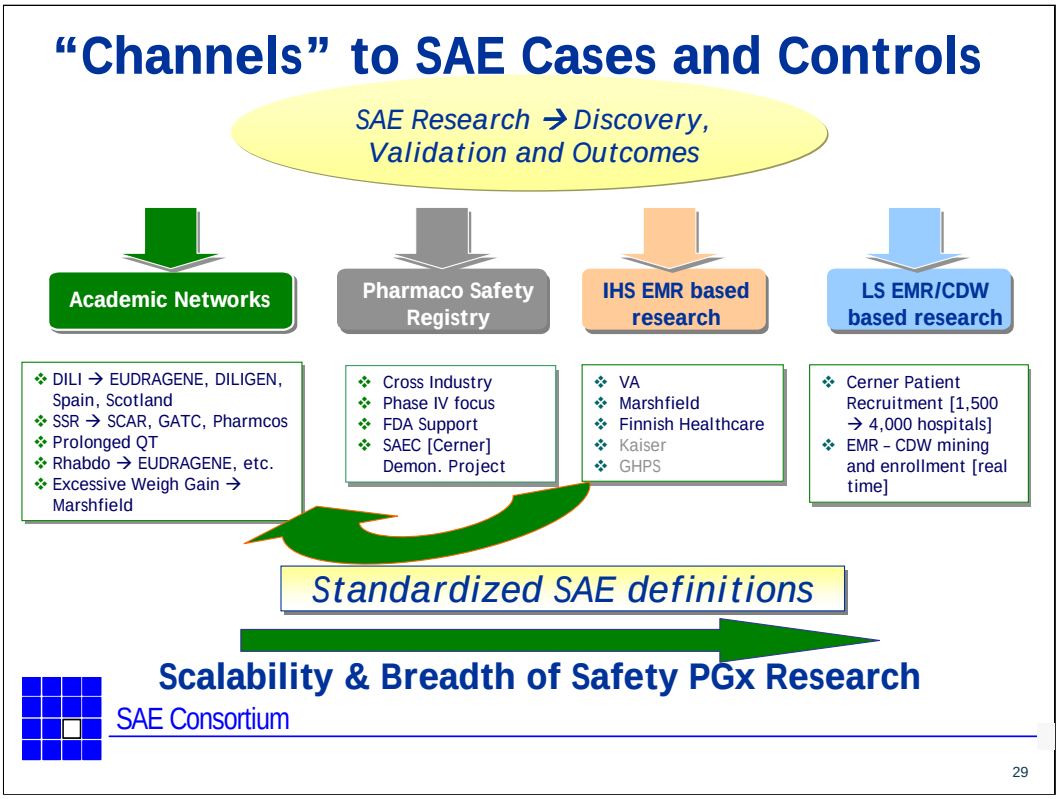
So as we move forward, a couple of comments I'll make. Membership development is very important. That's where our financial resources come. We certainly hope that all companies will participate in this as we move forward, both in terms of in kind contributions as well as financial.

Clearly, there are a significant number of follow on studies that need to be designed as we move through both the serious skin rash and the DILI. So we will be working through those.



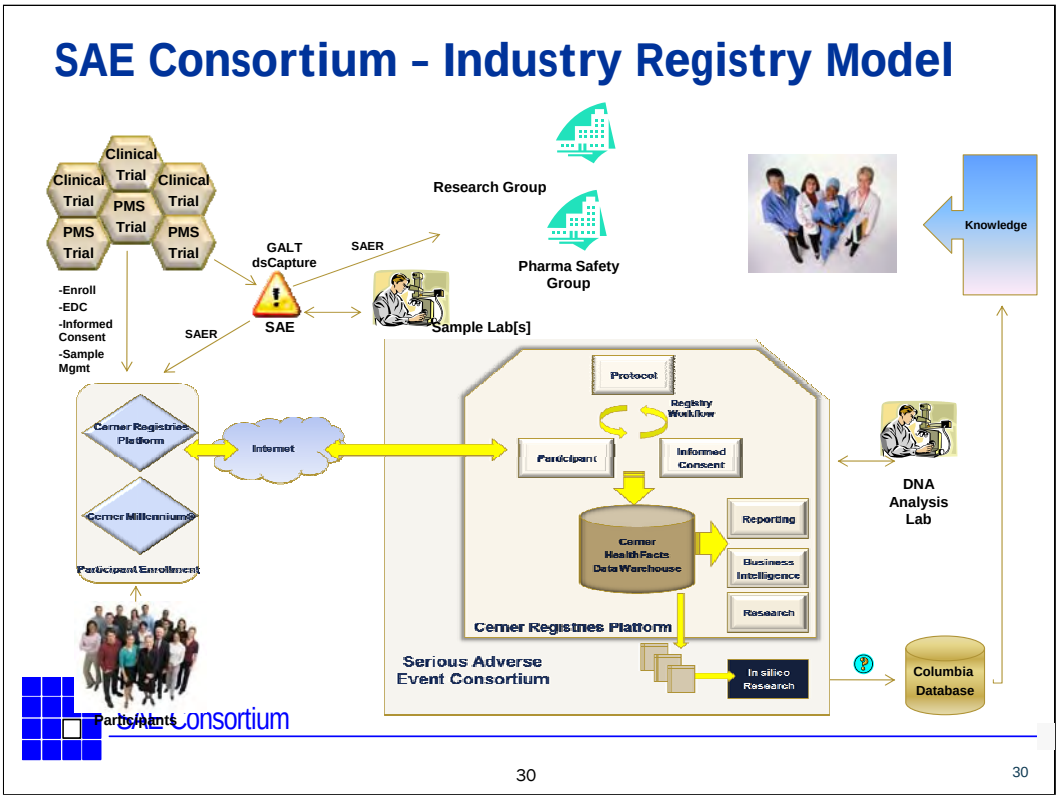
In addition, I can't underscore enough how important it is for this community, whether it's in the DILI area or other areas, to rise to the challenge to standardize the definition of what this condition really is. To me it is unacceptable, if we're going to do good biomedical research, that we don't come together as a community and standardize that definition. Clearly, I know there are a lot of challenges but this research is fundamentally enabled by that type of definition. So in that light, in lack of progress, certainly the DILI area has been one of the gray areas that have moved forward, and I think we're real close to be doing that. There are other areas that aren't as developed. The concept of having a consensus conference, an international consensus conference, where there's preparation beforehand, to standardized definitions and this will be jointly hosted, at least right now by the Consortium, Wellcome Trust, Pharmacogenetics Research Network and the FDA, to try and bring together leading academics and put these definitions in place. If we do that well, that will enable us as I go forward and talk to you about our future focus.



In addition, I will not have time to go through this but there are a variety of areas that we have developed using again academic collaborative networks on an international basis, to look at other areas. For example, rhabdomyolosis, prolonged QT interval. We've got some very nice networks that we've put together to begin to do this type of work.

But I really want to focus and it comes back to kind of what Jack ended on, is where I think the channels, how they need to evolve and would it enable this research, and I think new novel collaborative channels will be important.

So my simplistic way of thinking, there are four avenues that we could use right now to source these patients. There are the clinical and traditional academic networks. We've got committed investigators that have a lot of clinical expertise in this phenomenon to come together to try and develop standard networks to do this research, and there area a variety of examples of those.

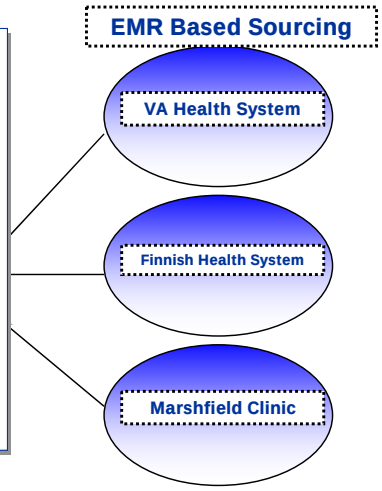


Another opportunity for us is to work as an industry, within the pharmaceutical industry, where we would essentially across the industry develop whether it's in Phase III, whether it's in Phase IV, whether it's in between, that we would develop a standardized web-based platform in order to bring cohorts together to facilitate this type of research and towards that end, we are developing most likely in conjunction with McKinsey and Company, a special project over the next two months to work with the pharmaceutical industry and the regulatory bodies to kind of craft how it is that we would optimally do this, in other words, develop a strong man, and then we could come back and say what's wrong with it, what's right with it, so that we can look at the feasibility of doing this. Obviously FDA's support would be critical in this activity.

The next channel for doing this, I believe is, and I'm not quite as pessimistic at all that you can't develop high quality cases out of integrated healthcare systems. What is really lacking in many cases is not that the information isn't good, historically yes, but if we put together standard definitions of phenotype and provide them to these environments that have both a financial incentive as well as a quality of care incentive, to enable this type of research with an attitude like the Consortium, I think we can yield type all the cases out of it.

Sourcing SAEC cases via IHS/EMR
Phase 1 Feasibility Project -- Overview

- 2008-09 Feasibility Projects
- Focus: Using EMR and associated research systems to determine the feasibility of yielding high quality SAE cases.
- SAEC targets/3/collaboration [*of joint interest*] → Hepatotoxicity, Rhabdomyolosis, Prolonged QT, and Excessive Weigh Gain [*initial targets*]
- Standardized definitions for each SAEs
- Dedicated medicines safety fellow /project manager funded by SAEC



SAE Consortium

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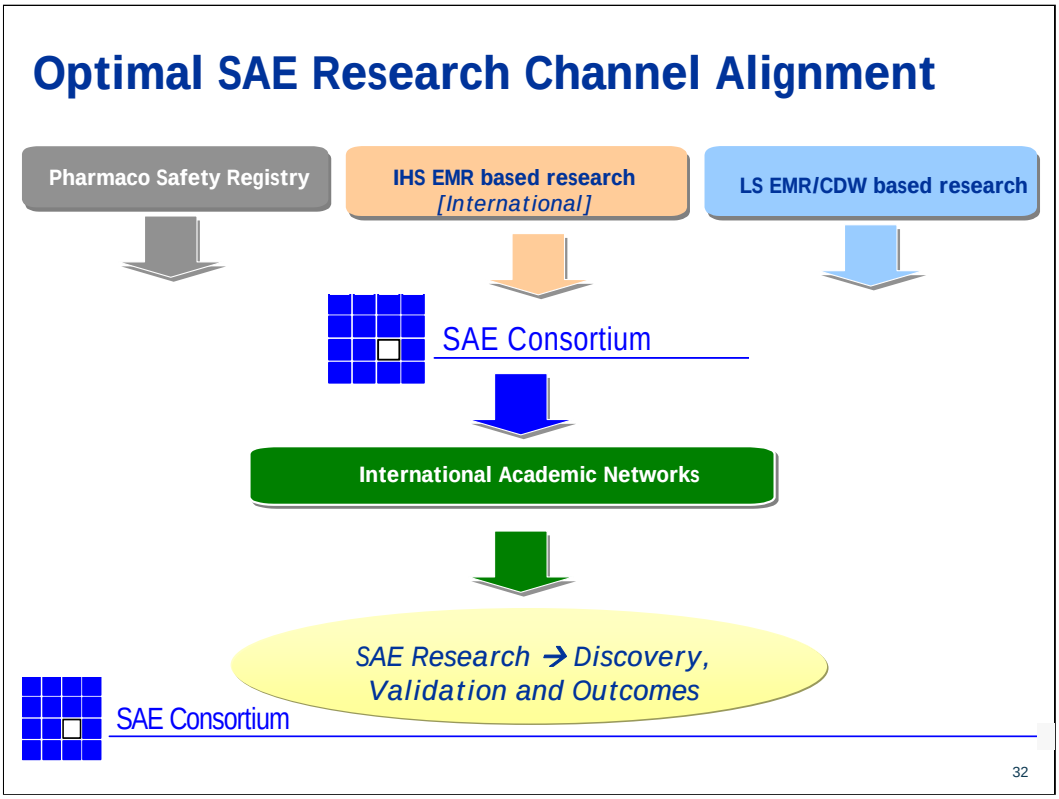
So right now we're structuring three pilots, again using a number of different models, one with the VA, one with Marshfield Clinic in Northern Wisconsin and then with the country of Finland, three different environments that have a well-developed electronic medical record with a good clinical data warehouse where we can pilot against the standard definition, how well could we yield these cases.



And then lastly, and I won't spend a lot of time on this but as we follow, as more and more entities put in electronic medical record environments and they have reasonable clinical data warehouses, then the concept of, through the providers, such as Cerner or others, access to 50 to 60 million patients, then you could potentially use those channels.

So the scalability and breadth are what you can pull together from a subject and related information point of view, I believe gets greater as you move out on this continuum. What it is critically dependent on is proper definitions that are standardized as much as possible in order to enable this type of framework.

SAEC – Collaborator Support Capabilities

- SAE research funding [via sponsored research agreements] for network development and translational studies
- Experience and legal capabilities to quickly and effectively assemble international collaborative SAE networks
- Ability to leverage, free of charge, a fully established a genetic characterization and analysis pipeline
- Assess to leading industrial and academic collaborators
- Full breadth of research options → discovery, validation, and translational outcome studies
- Freedom to publish, as long as proper recognition is provided & adherence to SAEC data release policy
- Ability to create public awareness of your research → notoriety
- Ability to better compete in the research arena → faster time to SAE research results, with larger cohorts, less hassle and more resources

SAE Consortium

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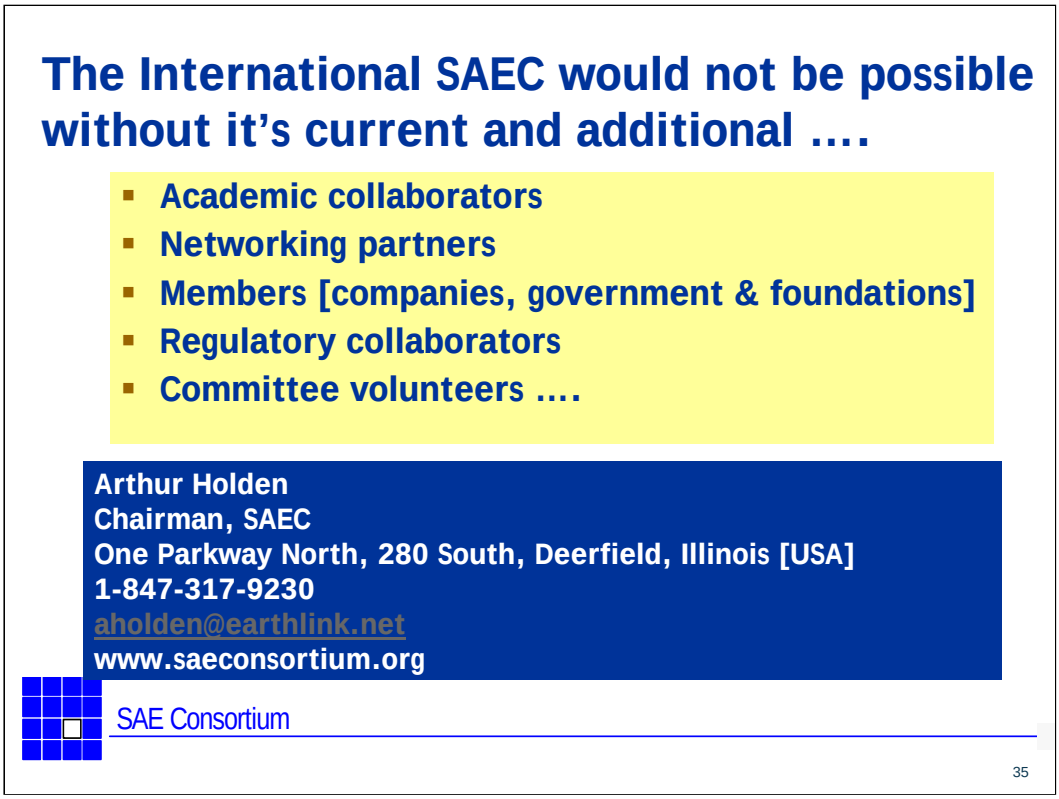
My red light is flashing. So I will leave you with the -- this is a construct of how we would do the registry from an IT point of view, a very simple thing to do IT-wise. The real issue is standardizing the definitions and other aspects.



My vision of how this research paradigm will evolve, at least kind of from a genetic point of view initially is that our expertise is really in these small industrial and academic pockets. In order to do the full range of discovery, validation and outcomes research, they're not ideally suited. We need to feed them and the way to feed them is to put these different channels together through an entity like the Consortium where you can have significant numbers of cases that are obtained in a highly efficient and effective way that we can then be able to do a whole variety of studies off of. And so part of the vision and evolution here is in order to do both discovery, validation and outcomes research, the focus of the Consortium has to be to explore, to evaluate and develop these other channels, and with that, I'll stop.

(Applause.)