

1 take it?

2 MR. BORASKY: I would think so.

3 MEMBER TEMPLE: If it's useful.

4 MR. BORASKY: But I also think that if
5 you've got an event that's so significant that it
6 requires changing the protocol, for example, that
7 the sponsor is going to find out about it
8 regardless.

9 You know, consent forms -- I mean,
10 there's already so much variation in any one multi -
11 site study about what different IRBs are requiring
12 to see in a consent form. But, it's --

13 MEMBER TEMPLE: I thought you were
14 speaking more broadly though. If they're on site
15 and can therefore provide insight into the
16 prominence of that adverse reaction, even if it's
17 to conclude, it probably wasn't the drug.

18 Somebody -- you'd think everybody would
19 want to know that. It sounds like useful
20 information. At least that's the premise that a
21 number of people have spoken to, that because
22 they're there, because they can enquire, they can
23 actually do better than somebody off of the
24 sponsor, maybe sometimes.

25 MR. BORASKY: Because they're being the

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1 IRB? Because the IRB is there?

2 MEMBER TEMPLE: Yes, because they're
3 there, the investigator is there, and they can
4 question him and get more information. I thought
5 that's the premise that you and actually several
6 other people have enunciated.

7 MR. BORASKY: Well, I think the idea --

8 MEMBER TEMPLE: I don't think there's a
9 way to get that information back that's been
10 described.

11 MR. BORASKY: Well, partly. What we've
12 said is that the IRB reserves the right or has the
13 right to ask for more information. Where that
14 information comes from may be the sponsor.

15 It may be a safety committee. It's not
16 necessarily the PI. And, in fact, often may not be
17 if the IRB is asking questions about what's the
18 significance of this event within the greater
19 community of trials of this drug.

20 The local PI is unlikely to know that
21 also.

22 MEMBER TEMPLE: Okay. I thought there
23 were a number of people that had expressed the view
24 that the local IRB can do special things because
25 they're there, they have all the information.

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1 Maybe --

2 MR. BORASKY: Our comments didn't mean to
3 imply that. They just mean to imply that they need
4 to look at the local ones because they've got a
5 responsibility to the subjects at that sight.

6 PRESIDING OFFICER WOODCOCK: Additional
7 questions from the panel?

8 (No response.)

9 PRESIDING OFFICER WOODCOCK: Now, our
10 next speaker, Dr. O'Rourke, is not able to be here.
11 So David Boraski is going to read her statement as
12 well.

13 MR. BORASKY: For those of you who know
14 Pearl, you will know I'm a sorry subject. But
15 Pearl is sick. She sends her regrets and has asked
16 me to read her comments that she submitted as Chair
17 of the Board of Directors of PRIM&R.

18 One behalf of PRIM&R and ARENA we thank
19 you for the opportunity to share thoughts, concerns
20 and suggestions regarding the handling of adverse
21 events in human research.

22 The goals are obviously. Individual
23 research participant s reasonably expect that
24 research is monitored for safety and that they will
25 be informed of all relevant details and risks

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1 during the course of the research.

2 Investigators must clearly understand and
3 fulfill the responsibility for evaluating as well
4 as reporting adverse events. IRBs must feel
5 comfortable that they are in timely receipt of
6 information that may alter risk assessment or
7 require re-contacting participants to ascertain
8 their willingness to continue in the research.

9 The information must be reliable,
10 relevant, useful, and presented in a comprehensive
11 and comprehensible format. But, meeting these
12 goals is difficult.

13 Current regulations are riddled with
14 inconsistent language and inconsistent requirements
15 that foster confusion that can lead to under as
16 well as over-reporting.

17 The system needs improvement, hence this
18 hearing. ARENA has presented comments to the
19 specific questions posted. I would like to add a
20 few bring comments that embellish these responses.

21 First, the need for harmonization. Today
22 the focus is FDA regulated research. But the topic
23 of adverse event reporting does not respect that
24 boundary.

25 Study participants expect the same level

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1 of protection regardless of regulatory assignment
2 to the FDA or the common rule. IRBs should not
3 have to tier the level of protection as a function
4 of specific regulatory construct.

5 Please keep in mind that IRBs can best
6 protect subjects if allowed to implement uniform
7 definitions and rules for all research. Please
8 harmonize, not only between the different centers
9 at FDA, but between the relevant Federal agencies
10 as well.

11 Second, make certain the solution fits
12 today's heterogeneous paradigm. While the
13 challenges of multi-center research with numerous
14 sites, numerous investigators, and numerous IRBs
15 screen for attention, remember single site
16 investigator initiated protocols still exist.

17 Adverse events will occur in all research
18 models. Any solution must respect and be
19 applicable to the entire spectrum. Finally, make
20 proposed solutions achievable.

21 Please consider the logistics and the
22 necessary resources. For example, if more data
23 monitoring committees will be required, consider
24 the fact that, even now, investigators have
25 difficulty identifying people willing to serve on

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1 DSMBs or even to serve in lesser oversight roles.

2 If more independent monitoring is
3 required, how will these people be found, be paid,
4 be vetted as free of conflict of interest. On
5 behalf of PRIM&R and ARENA, we thank you for the
6 opportunity to discuss this with you today.

7 And we welcome the opportunity to work
8 with you in the development of new guidance,
9 policies, or regulations.

10 PRESIDING OFFICER WOODCOCK: Thank you
11 very much. All right. Our next speaker will be
12 Dr. Wendy Stephenson. Dr. Stephenson is t he co -
13 Chair of a CIOMS working group.

14 DR. STEPHENSON: Good afternoon. And
15 thank you to FDA for holding this public hearing on
16 such an important topic, reporting of adverse
17 events to institutional review boards.

18 I'm Wendy Stephenson. I'm currently an
19 independent consultant with 15 years experience as
20 head of safety for multi -national pharmaceutical
21 companies, first for Merck, and most recently for
22 Wyeth.

23 Today I will be presenting on behalf of
24 the CIOMS VI working group for which I served as
25 the industry co-Chair person. My participation on

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1 CIOMS VI was sponsored by Wyeth.

2 CIOMS, or the Council for International
3 Organizations of Medical Sciences, provides a forum
4 under the auspices of the World Health Organization
5 for experts from government, industry, and academia
6 to come together in an unofficial capacity to
7 discuss areas of mutual interest and concern.

8 The CIOMS working group on drug safety
9 have provided a mechanism for regulators and
10 industry to develop proposals with the hope that
11 these proposals will eventually be adopted by
12 national and regional regulators.

13 Previous working groups have been
14 successful in doing just that. For example,
15 recommendations of the CIOMS I working group led to
16 the international harmonization of the criteria,
17 timing, and content of expedited reporting to
18 regulatory authorities, including FDA.

19 Most recently, the CIOMS VI working group
20 addressed the management of safety information from
21 clinical trials. The CIOMS VI working group
22 recommendations are currently in press.

23 As with previous working groups, the
24 CIOMS VI working group included representatives
25 from WHO, from regulatory authorities, and from

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1 industry, as well as research institutions.

2 In addition to addressing other very
3 important aspects of the manage ment of safety
4 information from clinical trials, the CIOMS VI
5 working group developed specific proposals for
6 changes to the requirements for reporting adverse
7 events to institutional review boards.

8 The information most relevant to this
9 discussion -- what happened?

10 (Pause.)

11 DR. STEPHENSON: Sorry. Okay, this is
12 where we should be. The information most relevant
13 to this discussion can be found in Chapter 7,
14 regulatory reporting and other communication of
15 safety information in clinical trials.

16 With the growing number of trials that
17 are multi-national and the expanding scope and size
18 of the typical drug development program, what used
19 to entail a couple of hundred subjects now often
20 involved thousands or sometimes tens of thousands
21 of subjects.

22 The resulting increased volume of adverse
23 event reports that investigators and IRBs must deal
24 with can be staggering, as you've already heard.
25 While sponsors have been accustomed to reporting in

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1 an expedited fashion to regulatory authorities
2 based on a well established set of criteria, it is
3 questionable whether it is useful to disseminate
4 the same information to scores and sometimes
5 hundreds of investigators and in turn to IRBs.

6 Sponsors and regulatory authorities
7 generally have computerized databases available for
8 storing, cataloging, coding, and analyzing
9 information.

10 Investigators and IRBs generally do not
11 and are often overwhelmed with the amount of
12 paperwork that comes their way. Even if the
13 resources were available for each investigator to
14 manage, maintain, and analyze the data, the value
15 of such redundancy is questionable.

16 Likewise, while certain IRBs will
17 continue to have the need to receive and review
18 investigation case reports from their own sites,
19 they are ill equipped to manage and interpret the
20 many other case reports originating from other
21 sites, often from other parts of the world, and to
22 place them into their proper perspective.

23 Unfortunately, while based on a well -
24 intentioned desire to improve the protection of
25 human subjects, the system has become a resource -

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1 intensive activity that does not necessarily result
2 in effective communication of useful safety
3 information to those who need to know and to act.

4 The CIOMS VI working group believes that
5 individual case recording should not be considered
6 synonymous with communication of important new
7 safety information.

8 Individual case reports do not always,
9 and often do not include important new safety
10 information. Conversely, important new safety
11 information that is best derived from an overall
12 analysis of reports in aggregate may not be
13 effectively conveyed through individual case
14 reporting.

15 The remaining slides include the specific
16 recommendations and proposals of the CIOMS VI
17 working group as they relate to communication of
18 safety information to IRBs.

19 It should be noted that these are only
20 proposals that would, of course, not supercede
21 existing regulations. The hope is that, like
22 previous recommendations, these proposals will
23 stimulate reconsideration of existing national and
24 international regulations perhaps with the
25 international conferences of harmonization.

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1 The CIOMS VI working group recommends
2 replacing the current practice of sending large
3 numbers of individual case reports to investigators
4 and ethics committees with a more reasona ble
5 approach to communicating important safety
6 information to all who need to know.

7 Such an approach would involve periodic
8 and, at times, adhoc communications to
9 investigators and ethics committees or IRBs that
10 include an update of important safety info rmation,
11 as well as the evolving benefit risk profile.

12 For approved products, the working group
13 recommends a timeframe for periodic reports to --
14 I'm sorry. I'm on the wrong one again. I'm sorry.
15 For unapproved products and in lieu of expedited
16 reports, the CIOMS VI working group recommends
17 periodic reports to investigators and IRBs that
18 include a line listing of unblinded clinical trial
19 cases that were expedited to regulatory authorities
20 since the last reporting period.

21 A copy of the current developm ent core
22 safety information, along with an explanation of
23 any changes to that, and a brief summary of the
24 emerging safety profile.

25 Although it is recommended that the

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1 default would be quarterly updates, there may be
2 circumstances when a more immediate communication
3 would be appropriate.

4 Likewise, there may be circumstances when
5 less frequent updates should be sufficient. For
6 approved products, the timeframe for period reports
7 to investigators and IRBs would depend on the
8 extent to which new indications are being
9 developed.

10 For a product undergoing phase three
11 trials, for a new indication, continuation of the
12 quarterly reports would be advisable. For well
13 established products, less frequent updates would
14 be appropriate.

15 And, at some time, there should only be a
16 need to update investigators and IRBs when there
17 are significant new information to report. When
18 updates are provided by the sponsor to
19 investigators and IRBs, whether for unapproved or
20 approved products, line listings should include
21 only unblinded expedited reports from clinical
22 trials.

23 The line listing should include interval
24 data that is only for cases expedited since the
25 last update. However, the summary of the emerging

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1 safety profile should take into account all of the
2 accumulating data.

3 It is recommended that Me dDRA preferred
4 terms be used. The line listing should generally
5 not include spontaneous reports. Instead,
6 significant issues arising from spontaneous reports
7 can be described in narrative form.

8 For phase four investigators and their
9 associated IRBs, communication of changes to the
10 company's core safety information for the marketed
11 product should be sufficient.

12 And periodic reports or line listing
13 should no longer be necessary. Of course, if there
14 is a significant safety issue, either from an
15 individual case report or review of aggregate data,
16 then the sponsor should issue a prompt notification
17 to all parties, namely regulatory authorities,
18 investigators, and IRBs.

19 And here a significant safety issue might
20 be defined as one that has a significant impact on
21 the course of the clinical trial or program, or
22 warrants immediate update of informed consent.

23 If these proposals are accepted and
24 implemented through regulations, the CIOMS VI
25 working group believes that the result will be a

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1 much more efficient system for managing safety
2 information from clinical trials and most
3 importantly for identifying and communicating
4 important new safety information to all who need to
5 be informed and to take action in a timely manner.

6 Thank you to FDA for the opportunity to
7 present to you today on this very important and
8 timely topic. And thank you all for your
9 attention.

10 PRESIDING OFFICER WOODCOCK: Thank you.
11 Are there questions from the panel?

12 (No response.)

13 PRESIDING OFFICER WOODCOCK: Thank you
14 very much.

15 DR. STEPHENSON: Okay.

16 PRESIDING OFFICER WOODCOCK: Our next
17 speaker is Thomas Adams, President and Chief
18 Executive Officer of the Association of Clinical
19 Research Professionals.

20 MR. ADAMS: Thank you Dr. Woodcock. I am
21 Tom Adams the President and Chief Executive Officer
22 of the Association of Clinical Research
23 Professionals.

24 For those of you who I know and are
25 aware, I'm also a member of the Secretary's

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1 Advisory Committee on Human Research Protections.
2 I did want to clarify today that my remarks are
3 those representing ACRP and not SACHRP.

4 I'm very honored to be here along with my
5 colleague Greg Koski, M.D. to participate in this
6 hearing on behalf of the ACRP membership. I'd like
7 to take just a moment to tell you a little bit
8 about ACRP and our purpose for being here today.

9 ACRP is a global not-for-profit
10 professional association of over 20,000
11 individuals, representing 63 countries on six
12 continents who are engaged and dedicated to
13 clinical research and development.

14 Our mission is to provide global
15 leadership for the clinical research profession by
16 promoting and advancing the highest ethical
17 standards and practices.

18 ACRP is pleased to participate in
19 discussions on the problem involved with adverse
20 event reporting in working towards solutions that
21 all parties involved in the system benefit from.

22 The development of a logical functioning,
23 pre and post-marketing AE reporting system is most
24 critical, however, for the safety of individuals
25 and those individual using drugs or devices.

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1 While it is certainly important to
2 consider these challenges from the perspective of
3 institutional review boards, ACRP does not believe
4 that appropriate solutions can ignore that IRBs are
5 but one essential component of our system for
6 clinical research and protection of human subjects.

7 Accordingly, we believe that effective
8 solutions to the challenges and problems that have
9 already been discussed here this morning will
10 require a broader systems approach, one that
11 recognizes shared goals, different needs, and often
12 overlapping all of the entities and individuals of
13 what we at ACRP call the clinical research team.

14 Team members include IRBs, investigators,
15 sponsors, coordinators, regulators, and so on.
16 This team represents all the parties involved in
17 the safe and successful operation, validation, and
18 dissemination of information in clinical research.

19 We need an approach that will allow true
20 identification of AEs for ultimately the better
21 protection of human subjects. Adverse event
22 reporting is a systemic problem.

23 And ACRP believes it requires a systemic
24 solution. Like those who have testified earlier,
25 ACRP does agree with the recommendations of the

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1 Secretary's Advisory Committee on Human Research
2 Protections as detailed in the Committee e's letter
3 to Secretary Thompson.

4 In ACRP's opinion, however, the
5 recommendation offered by the advisory committee
6 calling for harmonization of reporting requirements
7 is only one small step -- but a necessary step --
8 toward beginning to address these issues.

9 The problem however, is not just knowing
10 what to report, when and to whom, but what it all
11 means. The problem is we have no effective process
12 for doing so today.

13 On behalf of ACRP, we appreciate the work
14 to be done by this panel. And now Dr. Kos ki will
15 present our testimony regarding possible solutions
16 to what we believe to be a very doable activity.

17 PRESIDING OFFICER WOODCOCK: Thank you.
18 Dr. Koski?

19 DR. KOSKI: Thank you very much Tom. And
20 good afternoon Dr. Woodcock, distinguished members
21 of the panel. My name is Greg Koski. I'm a member
22 of the Board of the Association of Clinical
23 Research Professionals.

24 I also chair its committee on Government
25 Affairs. And, like Tom, on behalf of all of our

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1 colleagues in ACRP, I'd like to thank you for the
2 opportunity to express our thoughts this afternoon
3 on the challenges of trying to appropriately
4 report, analyze, and disseminate in a timely and
5 meaningful manner the information around adverse
6 events related to drugs and medical devices.

7 These are issues with which I have some
8 experience, having been an investigator, an IRB
9 chair, as well as the Director of a Human Research
10 Affairs for a large research -based academic health
11 center, the Partners Healthcare System in Boston
12 Harvard Medical School.

13 And, of course having served as the
14 Director of the Office of Human Research
15 Protections here at the Department of Health and
16 Human Services.

17 The issues that we're talking about today
18 are hardly new. As you all know well, the Office
19 of the Inspector General, the National Bioethics
20 Advisory Commission, the IRB community, the
21 industry, the academic community, and many others
22 have been talking about these issues, expressing
23 their shared concerns about them for a long time.

24 And, even if it has taken far too long to
25 get to the point that we are today, I think that

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1 FDA and HHS really deserve a strong commendation
2 for really beginning to tackle the issues that have
3 been described in the testimony that we've already
4 heard.

5 I think I'm the next to the last speaker,
6 actually. You know, there's always that mixed
7 blessing of being at the end of the program because
8 you've had a change to hear everything that
9 everyone else has already said.

10 But then, on the other hand, everybody
11 else has already heard everything that everybody
12 else has to say. And so, you wonder if there's
13 anything left to say.

14 Let me find something here. We're going
15 to try to focus in these next few minutes not so
16 much on the specifics of the remodeling, the
17 reform, the best practices that we've heard about
18 described so far today, but rather how we enable
19 them, how we support them, how we make them a
20 reality, how we actually bring them about.

21 And I think we've heard this alluded to
22 in several of the remarks that we've heard from
23 other speakers today. And I'm going to try to
24 expand on those just a bit.

25 As Tom said, ACRP believes that what we

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1 need to do now goes beyond simply tweaking the
2 existing system, the current approach, even though
3 that is clearly something that needs to be done in
4 a very serious way.

5 And I think we're well down that road
6 after today's hearing. ACRP believes that there is
7 an urgent need and a compelling justification to
8 create and implement a comprehensive national
9 adverse event reporting system that takes advantage
10 of currently available information technology to
11 address some of these long-standing and ongoing
12 problems that we've heard about from other
13 speakers.

14 Very recently the FDA has expressed its
15 interest in using enhanced information technology
16 and data mining procedures in order to improve,
17 enhance approaches to drug safety.

18 ACRP believes that this is a very
19 important step, a huge step in the right direction.
20 Critical to this effort, however, is a more
21 effective approach to actually reporting and
22 recording the adverse events in a systematic
23 fashion because we believe that the best outcome of
24 these data mining efforts will actually come from
25 mining a comprehensive database of timely reliable

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1 information.

2 And we simply need a more effective
3 system to get the information into that database so
4 that it can be used appropriately. We believe that
5 an adverse representing and analysis system
6 properly designed, should, in fact, must serve many
7 different goals and masters recognizing that not
8 all parties need the same thing.

9 One happens to be at the FDA where one
10 wants to catalogue all of the events that occur in
11 a profile of a given drug. One needs to have every
12 event recorded.

13 That's not the same information that's
14 needed by an institutional review board or an
15 investigator. And so we need, as Dr. O'Rourke said
16 in her comments in absentia, a system that is
17 flexible enough to be able to accommodate the full
18 spectrum of activities that occur in this
19 particular domain.

20 Now, we believe that this system needs to
21 have certain goals, as I said. Among them it
22 should be possible to use it for both recording and
23 characterizing the adverse event protocols for
24 investigational and approved drugs, devices, and
25 biologics.

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1 Second, we believe that it obviously has
2 to serve in the process of protecting, not only
3 research participants, but also patients and the
4 public at large.

5 We believe that it needs to provide a
6 simple registry. A simple uniform registry of
7 clinical trials, as well as the parties who are
8 involved in them.

9 And perhaps most importantly, it needs to
10 serve as a national resource of relevant
11 information that can be used by all of these
12 parties, including investigators, the institutional
13 review boards, data monitoring committees, the
14 sponsors, the regulators, and the public itself.

15 Now, toward this end, we believe that an
16 effective system needs to have certain design
17 features built in. Among these are uniformity.
18 There should be a single set of requirements and
19 guidance for reporting of adverse events in all
20 clinical trials regardless of the source of
21 funding, whether it's public or private, what the
22 principal oversight agency is, whether it's the
23 FDA, the Office for Human Research Protections, or
24 another of the Federal agencies.

25 It needs to have simplicity. The system

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1 should use a simple, common reporting format with a
2 standardized reporting lexicon and a readily
3 searchable, easily managed relational database that
4 facilitates rather than discourages reporting and
5 analysis of this information.

6 It needs to embody both timelines and
7 effectiveness. The system should capture
8 information at the point of origin. It should be
9 taken into the system at the time of entry so that
10 it becomes immediately available.

11 This should be done using technology that
12 eliminates paperwork, eliminates the redundancies
13 that we've seen in the system so far, and makes the
14 information available in real time for use by those
15 that need to have access to it.

16 And it shouldn't make any difference
17 whether it's for the reporter or for those who are
18 actually receiving the reports. The system needs
19 to have the fullest possible connectivity.

20 That is, it should not depend upon any
21 single technology platform. And obviously we have
22 a readily available technology for that, the
23 Internet, the World Wide Web.

24 And we've already seen many such systems
25 in use in other areas. And there's no reason why

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1 it can't be applied in this one. It needs to
2 embody accessibility.

3 The information in this database should
4 be readily available to all appropriate parties in
5 the system. It should allow accessed information
6 in a manner that optimizes the value and the
7 ability to analyze that information while
8 minimizing the likelihood of harm to research
9 participants, patients, and the public.

10 It needs to have sufficient granularity
11 to be able to do the kinds of analyses that are
12 required to produce the reports that we've talked
13 about for different individuals at different parts
14 of the process, because the expectations are
15 different.

16 It needs, of course, to have privacy.
17 All personally identifiable patient information
18 needs to be fully protected. And it needs to be
19 available in identifiable form only on a strict
20 need-to-know basis where the benefits outweigh the
21 risks.

22 It needs to have appropriate security.
23 That security system should include not only
24 password protections and tiered firewalls. And it
25 should be tight security.

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1 But, it will also have appropriate
2 protections for proprietary, legitimate proprietary
3 information, trade secret information, recognizing
4 that such proprietary information should never be
5 allowed to take precedence over the safety and
6 well-being of the research participants or the
7 public.

8 Finally, it needs to embody a work flow
9 management capability that allows, through simple
10 programming, the ability to establish automatically
11 alerts, reports that are disseminated to
12 individuals, all of which, of course, is very easy
13 to do with currently available technology.

14 Many of these design features can be
15 effectively achieved using the readily available
16 secure web-based active server page technologies
17 that capture information through the web and
18 automatically enter it into a defined database with
19 mapping of the elements to appropriate categories,
20 which can be easily defined and can be done a very
21 cost-effective manner.

22 ACRP believes that such a system should
23 be developed as mission-critical, shared
24 infrastructure for designing and conducting
25 clinical research, as well as for protecting the

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1 safety of research subjects, patients, a nd the
2 public.

3 As such, financial support for such a
4 system should be shared by institutional,
5 governmental, and private sponsors of research.
6 One useful and perhaps appropriate model to
7 financing the development and implementation, as
8 well as continuin g operation of the system, could
9 be a user-based national trust fund model analogous
10 to that which today supports the National Air
11 Transportation Safety System.

12 As Dr. Dickler mentioned earlier today,
13 current events have reminded us that, while we
14 certainly need to have a system that monitors
15 safety during clinical trials, we can't ignore the
16 need for better tracking analysis of adverse events
17 after a drug or device has been granted approval
18 for marketing.

19 Others have noted that too often reports
20 of serious but uncommon adverse events only come to
21 light after a drug has been approved for marketing
22 by FDA and has been prescribed to large numbers of
23 patients.

24 Although the existing post -marketing
25 MedWatch system is intended to facilitate tracking

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1 of such events, until recently too few physicians
2 have actually responsibly reported on a regular
3 basis adverse events.

4 And serious safety concerns can easily be
5 overlooked for too long under such an approach.
6 ACRP recommends that, once a comprehensive adverse
7 event reporting system is fully functional, that an
8 educational component tailored to different types
9 of institutions and individuals that would be using
10 the system be also implemented in order to optimize
11 the use of the system.

12 The FDA's recent commitment to
13 strengthening independent oversight of drug and
14 device safety is certainly another step in a
15 positive direction.

16 ACRP believes that the public itself,
17 individual patients and their families should be
18 part of this early warning system for post-market
19 safety surveillance by encouraging private citizens
20 to file their own reports of suspected adverse
21 events related to prescription drugs that they're
22 taking.

23 This capability is already present in the
24 FDA's MedWatch system. But I'm not sure how
25 extensively it's used. Certainly this approach has

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1 worked well in our community Crime Watch program.

2 It's part now of our National Strategy
3 for Protecting Homeland Security and trying to
4 prevent terrorism. There's no reason why it can't
5 work in the area of improving drug safety as well.

6 While we recognize the value in this
7 public reporting, and some have argued for public
8 access to databases of adverse events, it would be,
9 I think, inappropriate not to recognize that there
10 needs to be a certain balance know ing that such
11 systems could be perhaps misunderstood, misused or
12 even abused.

13 And so, there needs to be an appropriate
14 strategy developed for providing access to the
15 system. Now, at first glance one might think that
16 these recommendations represent what IT
17 professionals sarcastically call vaporware.

18 In fact, they are very realistic.
19 Indeed, a prototype system that fulfills most of
20 these criteria has already been developed and
21 implemented through a collaboration of NIH's Office
22 of Biotechnology Affairs and the FDA's Division for
23 Cellular and Gene Therapies.

24 With the leadership of Dr. Amy Patterson
25 and Phil Noguchi, creation of a system which is

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1 called GeMCRIS, which you can all finding by simply
2 Googling on the web, has already been demonstrated
3 to the research community.

4 It has been deployed at NIH supported
5 General Clinical Research Centers across the
6 country. It's used at the NIH clinical center and
7 NCI-supported cancer programs.

8 Although its application is currently
9 limited to these specific programs, it could well
10 serve as the prototype for development of a broad
11 based robust system for adverse event reporting
12 across multiple disciplines.

13 And we believe that an investment of
14 Federal funds to develop and implement such a
15 system in a comprehensive way could yield handsome
16 rewards for all parties to the clinical research
17 enterprise.

18 At the present time Dr. Patterson is
19 charging a trans-federal task force that's actually
20 looking into the possibility of expanding the
21 capacities of GeMCRIS to encompass other areas
22 within medicine, clinical research.

23 I do not know whether or not FDA is
24 actually a part to that activity. I certainly
25 would hope so. The task force is expected to

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1 release its recommendations later on this year, as
2 I understand it.

3 And we certainly hope that FDA will
4 consider them carefully as part of their
5 discussions of what we've heard here today. The
6 clinical research enterprise can no long afford to
7 have several Federal agencies involved in the
8 conduct and oversight of clinical research and
9 safety working in isolation or cross purposes.

10 Instead, we need to seize this
11 opportunity to achieve greater efficiency and
12 effectiveness in the entire human research
13 enterprise while we strengthen our systems for
14 protecting research subjects for the patients and
15 the public. Thank you very much

16 PRESIDING OFFICER WOODCOCK: Thank you
17 Dr. Koski. Are there questions from the panel?
18 Dr. Goldkind?

19 MEMBER GOLDKIND: I know you didn't want
20 to go into too many details. But, what I'm trying
21 to understand is the utility of this database that
22 you're mentioning in light of the fact that we've
23 talked extensively today about not having single
24 individual reports.

25 So I'm wondering if you could describe

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1 for me what this database would look like and how
2 it would provide information in context that would
3 differ from just sort of individual reports.

4 DR. KOSKI: The system -- of course,
5 developing the architecture for the system would
6 allow for, for instance, reregistering an
7 individual multi-center clinical trial.

8 At the time of registration, also put
9 into the database would be the individual sites
10 that are participating, the IRBs of record, sponsor
11 information, data monitoring committee information.

12 All the contact information has been
13 built in t here as well. Having a single, web -
14 based, uniform reporting mechanism that would then
15 allow capture in a very easy way all of those
16 adverse events and putting them into this database
17 where it can be used, for instance, by the DSMBs to
18 actually do an analy sis of the events that have
19 occurred, not only within that particular multi -
20 center trial, but perhaps across multiple trials
21 going on using similar classes of -- or the same
22 class of agents with slight differences.

23 Those types of analyses are exactly the
24 kind of data mining that the FDA I currently
25 looking at in terms of trying to identify early

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1 trends that would suggest there might be a safety
2 problem.

3 And this can be done very effectively if
4 we have the database available. The beauty of a
5 system like this is that it not only actually
6 standardizes and creates a uniform, easy mechanism
7 for getting the data, but also creates a warehouse
8 of information that can serve as a real resource to
9 all of the parties that need it.

10 And it includes the capabilities , for
11 instance, if there is an emergency alert that needs
12 to go out to all the participants in a given trial,
13 the DSMB says, we need to stop this trial today.

14 It can be done because the data is there.
15 They compose the alert, hit one button, and
16 automatically send that information to every
17 appropriate participant in the trial, and perhaps
18 even alert others who are doing experiments with
19 similar classes of drugs.

20 So, the ultimate way in which the system
21 is built depends upon what the regulatory agencies
22 and the IRBs, the institutions ultimately agree to
23 is the most appropriate process.

24 But, given that the tools are easily
25 available, it could be done, I think, very quickly.

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1 MEMBER GOLDKIND: So all adverse events
2 would be part of this database, not just serious
3 and unexpected?

4 DR. KOSKI: Exactly. In the database,
5 again, one needs to capture all of the information
6 so that then, upon analysis and review, there would
7 be opportunities at the time of entry of the
8 information, that is when an adverse event is
9 reported, exactly the kind of information that we
10 currently capture.

11 Is this, you know, a simple adverse
12 event, a serious adverse event, an unexpected
13 problem with the research? That can be
14 characterized at the same time so that those flags
15 that can be used through a relational search of the
16 database in order to much, much more efficiently
17 identify where there are, you know, likely to be
18 problems than one could otherwise do it with a 17
19 foot stack of paper reports.

20 MEMBER GOLDKIND: But there would still
21 need to be groups that are analyzing these adverse
22 events. So, beyond the data monitoring committee
23 that you mentioned, who do you see as the groups?

24 DR. KOSKI: Well, one would presume that
25 if the guidance and the rules that are established

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1 by FDA were to -- or NIH -- and, again, I would
2 urge that they be uniform across all of the
3 agencies.

4 If they say that for every multi -center
5 trial we're going to have review by the sponsor and
6 a data monitoring committee on an ongoing basis,
7 that information is immediately available to those
8 bodies for review to support their function.

9 They then would be the ones to do the
10 analysis that we've talked about that would prepare
11 the reports that could go to the IRBs or to
12 individual investigators after the analysis is done
13 so that, instead of just sending a collection of
14 meaningless reports that we've heard too much about
15 today already, the IRBs are given the information
16 that they need in order to exercise their function.

17 So, it's a matter of taking in as much
18 information as you can to enable all of the
19 functions for which it has to be used, but then
20 analyzing it and doling it out, disseminating it in
21 a way that gives it the greatest value for the
22 others that have to use it.

23 A system like this, of course, can also
24 be used to set certain threshold levels of certain
25 adverse events within a trial for instance. Let's

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1 say Dr. Temple said, I need to know when
2 anaphylactic reactions occur in more than, you
3 know, five percent of patients.

4 Well, or it could be set a and send an
5 email to Dr. Temple when that threshold has been
6 met. I just use that as a trivial example for how
7 the system can be used all using currently
8 available technologies.

9 And, as more advanced approaches toward
10 what we might call artificial intelligence are used
11 or developed, they could be applied similarly to
12 the data.

13 PRESIDING OFFICER WOODCOCK: Other
14 questions? Dr. Temple.

15 MEMBER TEMPLE: Do these approaches
16 presume that you can be smart enough to say
17 everything you want to know and fill i n boxes? Or
18 is there room for narratives, and descriptions, and
19 time course, and all that stuff?

20 DR. KOSKI: With the technologies
21 available today using, you know, text -based
22 searches is very realistic. So, the ability to put
23 in textual information and then be able to search
24 on that is very easy to do so that, again, it all
25 depends upon how the system is built.

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1 I have not been allowed access to the
2 most recent GeMCRIS deployment because I'm not
3 doing that kind of research. But, I do not know
4 how that currently stands.

5 But, originally, most of the information
6 was in a two -tiered reporting form that had a top
7 level information that characterized the nature of
8 the event, the timing of the event, the relation to
9 the specific protocol, and then gave much more
10 detail in a second tier so that you, again, achieve
11 multiple levels of granularity to basically say
12 what you need to do with it.

13 Building in as much flexibility as
14 possible allows you to do more things with it in
15 the future that may not have been anticipated when
16 the information was actually collected?

17 PRESIDING OFFICER WOODCOCK: Other
18 questions from the panel? Yes?

19 MEMBER ROHAN: Regarding the reporting
20 uses, including spontaneous reporting, would it be
21 required reporting? Because I guess I'm having
22 trouble understanding if people choose to report,
23 how do you know how many people have been exposed,
24 that sort of thing?

25 DR. KOSKI: This system would be there to

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1 enable and support the rules that would be
2 established by the regulatory agencies, you know,
3 whether it's through the actual regulation or
4 through guidance.

5 So, whatever FDA, OHRP, all the agencies
6 working with the stakeholders choose to do, what
7 they want to require, when, to whom, so on, that
8 can all be supported through a system like this.

9 In fact, it's not only supported, it is
10 facilitated because the single most important thing
11 to do is to use it as a way to achieve the
12 harmonization, the simplicity, the uniformity that
13 we've heard so many people call for here today.

14 So, whatever rules you establish for
15 reporting, this is when you have to do it. This
16 makes it easier to do that and totally eliminate
17 the paper, the redundancy of multiple reporting in
18 multiple places because everybody can simply look
19 at the database and there it is.

20 You know, access to that information can
21 be based on a given individual or a group's need
22 to-know. So, if you're a data monitoring
23 committee, you might have one level of access.

24 If you're actually with the FDA, you
25 might have access to look across multiple companies

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1 who are doing experiments with the same kinds of
2 drugs.

3 So, all of those things are possible.
4 And we're limited primarily by our creativity in
5 figuring out how to best use a system like this in
6 order to support what we're trying to achieve.
7 Yes?

8 MEMBER ROHAN: And then I guess I had
9 another somewhat related question. You also
10 discuss that there would be sort of a spectrum of
11 individuals, organizations that might be interested
12 in this data, ranging from governmental to
13 commercial interest, to individual consumers.

14 And, maybe I didn't understand. Did you
15 also envision that perhaps individual consumers
16 will be reporting to this database as well or they
17 would have access to look at the data?

18 Or were you also envisioning that the y
19 would be reporting to this?

20 DR. KOSKI: Well, certainly reporting to
21 it is a function that FDA currently supports. I
22 have not seen a lot of active encouragement of
23 that.

24 But you can go to www.fda.gov and there's
25 the box there for consumer reporting . And this is

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1 in the MedWatch system so that that part of it is
2 something that we already do.

3 It's something that we probably don't use
4 effectively. If we were to use it effectively, we
5 may find that the current deficiencies in the post -
6 marketing arena where physicians and others do not
7 reliably report in a timely fashion, could be
8 greatly enhanced, particularly given the current
9 awareness that's stemmed unfortunately from the
10 unfortunate events that we've had.

11 So, certainly reporting is something that
12 could be very valuable because sometimes, you know,
13 the most sensitive observers are those who are
14 taking care of mom and see how mom responds, you
15 know, to this new drug that she's being prescribed
16 by her physician.

17 So, that part of it, I think, is really
18 non-controversial. Realizing that data that comes
19 in from that pathway will not have the same level
20 of sophistication that we might see from a
21 physician or a pharmacist who is reporting.

22 But, nevertheless, that information can
23 be easily managed and screened through a system
24 like this through technologies that can augment the
25 human capability rather than simply relying on an

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1 individual to go through each one.

2 The question of public access to the
3 adverse event database itself is a much thornier
4 issue because, you know, some would immediately
5 say, well, you know, the trial lawyers will be
6 surfing the database in order to look for targets.

7 Well, that could well happen. At the
8 same time, individual consumers could be looking
9 through the database to see, is this really safe
10 enough for me to participate in the clinical trial.

11 That's an area that is not well charted
12 and would have to be given very careful
13 consideration. But, you know, if we were able to
14 define what types of information were appropriately
15 accessed by the public and what time, such as
16 having the adverse events from a trial after its
17 completion, or after a drug has been approved.

18 You know, those are things that we have
19 to explore and work out. But, I do not have any
20 preconceived ideas about that except that there's a
21 growing desire out in the real world of the public
22 wanting to know more, wanting to take a greater
23 role in all of this.

24 And we may well find if we do it properly
25 that the public would not only then become better

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1 informed about the clinical research process, but
2 might at the same time develop a greater degree of
3 trust and confidence that would allow them to
4 participate in that process more than they do
5 today.

6 MEMBER ROHAN: So, I guess this will be
7 my final question. Do you see that there would be
8 a distinction between data that was reported from
9 perspective clinical trials versus data that was
10 reported to --

11 DR. KOSKI: Oh, absolutely. All of the
12 data that would be coming in would obviously be
13 characterized according to its source of origin so
14 that it could be again utilized.

15 But, the flexibility in the technology
16 available today, the capability is so great that
17 that becomes in a sense a trivial sort of
18 programming problem.

19 It's just a question of which file you
20 choose to put that information in. But, having
21 that information, may actually be a way to -- if
22 you pick up something in a clinical trial for drug
23 that's under study and you want to say well gee,
24 you know, does this portend something bad about a
25 drug we approved two years ago.

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1 One might be able to go back and look at
2 the drug, look at the reports that came in from the
3 public and say, we should look at this further
4 because, in fact, it looks like there might be a
5 signal there that we can call out of the noise.

6 And it's this ability to fine tune the
7 signal-to-noise ratio to look at patterns to sort
8 of discover things that might not otherwise jump
9 out and particular can't even be found today when
10 you have stuff scattered.

11 You know, the problem of having a n
12 individual institution or IRB, or even sometimes an
13 individual company, recognize a serious
14 complication or problem because they don't have
15 access to a full set of information is a very real
16 problem.

17 And much of that could be really
18 alleviated going forward with a system, as long as
19 it gets that information into it and you have the
20 ability to analyze it in an effective way.

21 PRESIDING OFFICER WOODCOCK: Other
22 questions from panel members?

23 (No response.)

24 PRESIDING OFFICER WOODCOCK: No? Thank
25 you very much Dr. Koski. Okay. Our final speaker

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1 today is Dr. Sorell Schwartz, who is the Chair of
2 the IRB sub -committee on Adverse Events at
3 Georgetown University Medical Center.

4 DR. SCHWARTZ: You can imagine the
5 pressure on me being the last speaker on a day like
6 this to say something interesting. So I thought
7 I'd like to open the discussion as to which of the
8 16 teams in the NCA tournament you think will reach
9 the final four.

10 (Laughter.)

11 DR. SCHWARTZ: I appreciate the previous
12 speaker's enthusiasm for a broad encompassing
13 program. There is an old Yiddish expression that
14 translates from your lips to God's years.

15 But, at the moment, I think we're going
16 to have to be a little bit more incremental. I'm
17 the Chairman of the sub -committee on Adverse Events
18 for IRB, or IRBs, we have four of them.

19 And I'm also Director of the Division of
20 Research Information and Assessment in the Office
21 of Regulatory Affairs. Now, the reason I give you
22 those titles is not out of immodesty, but to bring
23 out the fact that at Georgetown we made a decision
24 some time ago that while we were waiting for some
25 type of global assessment and help in assessing AEs

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1 that we were going to have to commit our own
2 resources to the very special problem of AEs
3 without burdening each individual member of the
4 IRB.

5 So, we developed a -- what we call the
6 Computerized Adverse Event Reporting System. And,
7 as you can see, it is designed to allow us to
8 respond to the regulatory requirements for -- to
9 assess AE reporting to facilitate both the internal
10 and external event reporting to serve the IRBs'
11 role -- we consider it a pivotal role -- in
12 reviewing adverse events, and to provide a central
13 repository of all adverse events on all clinical
14 trials at Georgetown.

15 And, again, the Georgetown orbit includes
16 Georgetown University Hospital and the entire
17 MedStar health system as far as oncology goes,
18 which consists of nine hospitals in the Washington
19 and Baltimore area.

20 And it will allow us ultimately to have
21 the data there to do cross trial analysis and
22 further search. It involves an electronic
23 submission of new and follow-up internal-external
24 adverse event reports.

25 It works by -- there is -- we archive all

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1 exchanges between the investigator and the IRB by
2 an amendment function. We also have an algorithm
3 to help on the internal events to help the
4 investigator assess causality.

5 And it in itself will assess and remind
6 the investigator they are ready for completeness.
7 And its features include the ability to do various
8 trend analyses.

9 It works by an email notification system.
10 It's a web-based wizard system where we have one
11 adverse event report an external one, for example,
12 that may cover a number of different protocols.

13 We just have one report that applies to
14 all the protocol. It uses a MedDR A of vocabulary
15 and it is HIPPA compliant, HL7 messaging compliant,
16 and all of the words.

17 This is just an abbreviated view. It
18 allows for internal AE reports, external unexpected
19 AE reports and expected external reports, expected
20 report being one that is included where the AE is
21 included in the ICF.

22 There are also reporting modules where
23 the reports can be searched either by canned
24 processes or by a specific inquiries. This is just
25 an abbreviated and attenuated version of a report.

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1 It covers all of the information that is
2 required in MedWatch and the like. It, as I said,
3 involves MedDRA terms. In the cases of external
4 reports, it includes the relationships, the
5 causality relationships established by the -- both
6 the sponsor and the investigator who is reporting.

7 There is a series of questions as to what
8 action we think that the investigator thinks ought
9 to be taken, whether a protocol modification is
10 necessary, whether it is necessary to change the
11 ICF.

12 The amendment function -- all the report
13 is amended and the information -- there may be
14 questions asked, there may be instructions as to
15 revising the ICF.

16 This is a particular display of an
17 exchange that occurred back and forth having to do
18 with a concern about a cardiac arrhythmia.
19 Everything is archived.

20 So there are no separate emails sent.
21 All messages go back and forth. And all of that is
22 recorded and archived on the report. And that
23 pretty much sums up what the report says.

24 But, again, we have an algorithm which
25 can be seen here. The reproductions that are in

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1 the handouts aren't good. But, I assume when they
2 eventually get on the web they'll be better.

3 But, this is four -axis assessment of
4 causation where finally the investigator has a
5 recommended inference level for causation. We
6 began beta testing this in April of 2003 and
7 incrementally rolled it out to Georgetown and non -
8 Georgetown departments.

9 Then on November 1st of last year we had
10 full rollout paper based AE reporting forms no
11 longer accepted. So, comments just on the
12 questions related today, as the FDA recorded in its
13 notice of the hearing, it says it is, quote, aware
14 of concerns that the AE reporting process is
15 burdensome, inefficient and not as effective as it
16 should be in providing IRBs the information they
17 need, close quote.

18 It would be inimical to the IRB function
19 to protect the welfare of human research subjects
20 if this acknowledgement was taken as an opportunity
21 to lessen the burden by truncating AE reporting.

22 The need is to define what can and cannot
23 be accomplished by the current AE reporting rules.
24 The hollowness of the regulatory guidelines is
25 exemplified in part A of 21 CONCEPTUAL FRAMEWORK

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1 312.32.1(a).

2 Quote, associated with the use of a drug
3 -- this is a definition -- there is a reasonable
4 possibility t hat the experience may have been
5 caused by the drug.

6 Now, think about that for a moment,
7 undefined reasonable and a metaphysical use of the
8 word may leaves the statement logically up in the
9 air and provides no guidance at all.

10 But, what guidance can be provided by two
11 IRBs such that they can act in an efficacious
12 manner? And that can be achieved in a more
13 effective form of information processing.

14 We've already heard the major one. And
15 that is the need for more DSMB in a processing of
16 AEs. It is -- DSMB, whether DSMB is or is not
17 operative is too haphazard right now.

18 We need a lot more regulation that really
19 assigns the need to the sponsor for DSMB. It has
20 been emphasized many times today. And, being on
21 the working front of this, I can't empha size -- it
22 can't be emphasized enough.

23 There's also a tendency to look at
24 individual SAE case reports as unworthy of
25 burdening the IRBs. That is that they don't

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1 contain enough information.

2 The fact of the matter is that these SAEs
3 require action. The individual reports require
4 action. And they're going to be with us for a
5 while.

6 And we might as well learn to act on
7 them. What we can ask is, especially for the
8 external ones, is that individual investigators
9 make a try at making some assessment, not what's
10 more likely than not the cause, but what is a cause
11 more likely than another.

12 For example, it's very common with
13 diseases of high morbidity and mortality like AIDS
14 and cancer for an SAE to be reported by something
15 that is likely progression of disease.

16 We need investigators to say, is this
17 more likely progression of disease or more likely
18 caused by the drug. It doesn't have to say this is
19 etched in granite, that it's more likely than not.

20 We just need some assessment from the
21 investigator. Someone did mention latigiaphobia.
22 I won't emphasize that other than the fact that
23 that can lead to so many AEs listed in an ICF it
24 desensitizes the patient.

25 Whether an SAE is expected or unexpected

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1 should not be the sine qua non of whether it is
2 discussed or is handled by the IRB. The fact of
3 the matter is it may be an expected AE.

4 But with care, we actually count the
5 number of times this expected AE has occurred
6 because it may have occurred much more than we
7 expected it to occur.

8 So, don't think that is a particularly
9 cogent distinction that should be made. I should -
10 - I'll end this because just about everything that
11 I had written down to say has been said.

12 There's no use repeating it. What I
13 would like to say is that the -- we disagree, or I
14 disagree or take exception to the idea that the IRB
15 should not be -- have the responsibility for
16 assessing AEs.

17 I do not see at this particular any other
18 choice than for IRBs to assess AEs, to be able to
19 reconsider or re-evaluate the risk profile of what
20 the patients under which jurisdiction are
21 experiencing. Thank you.

22 PRESIDING OFFICER WOODCOCK: Thank you,
23 Dr. Schwartz. Are there questions from the panel?
24 Dr. Temple?

25 MEMBER TEMPLE: Do you feel that way both

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1 about the adverse events that occur in the
2 institution and all others?

3 DR. SCHWARTZ: Yes, sir.

4 MEMBER TEMPLE: So, not to -- but we've
5 got 100 -site multi-center study. They should get
6 not only all of the serious unexpected adverse
7 events, but, as you just pointed out, all of the
8 expected ones also that are serious and review
9 them?

10 DR. SCHWARTZ: Yes. Our CAER system
11 actually allows for the expected to be abbreviated.
12 So, it doesn't take a lot of filling out to do.
13 But it does allow us to record them.

14 And, if we wanted to go back and search
15 for incidents and numbers, we can. But, it's not a
16 burden to them. We recognize if it's already in
17 the ICF.

18 We look at -- the major action we're
19 likely to take is to require a modification of an
20 ICF. If an event is already expected, it's already
21 in the ICF, then the most -- the action we're most
22 likely to take has already occurred.

23 So what we want to do now is just keep
24 track of how often this event is occurring.

25 MEMBER TEMPLE: Well, everyone agreed

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1 that there need to be periodic report s of, you
2 know, heart attacks and other expected things.

3 DR. SCHWARTZ: Right.

4 MEMBER TEMPLE: But you're saying that
5 the local IRB should each do -- each local IRB
6 actually should be doing this. I just want to be -
7 - I think that's somewhat at odds with what other
8 people have said.

9 And I just want to be sure to point that
10 out.

11 DR. SCHWARTZ: We are -- yes, we are
12 recording all expected external AEs. And, if they
13 require -- if we require any follow-up we will tell
14 them. But, for the most part.

15 MEMBER TEMPLE: How do you get them?

16 DR. SCHWARTZ: By reported through the
17 CAER system. You mean, how does the investigator
18 get them? They get them from the sponsor. We
19 require --

20 MEMBER TEMPLE: The sponsor doesn't pass
21 on expected adverse reactions.

22 DR. SCHWARTZ: Oh, you don't think so?

23 MEMBER TEMPLE: Absolutely. They don't
24 have to.

25 DR. SCHWARTZ: I wish you were correct.

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1 We absolutely get expected AEs.

2 PRESIDING OFFICER WOODCOCK: Do your
3 investigators have to data enter each one o f these
4 external AEs into your system?

5 DR. SCHWARTZ: Yes, they enter them. But
6 they enter it in an abbreviated form. In other
7 words, the protocol and the MedDRA term is -- the
8 protocol number and the MedDRA term is entered.
9 That's it. No other information.

10 PRESIDING OFFICER WOODCOCK: Other
11 questions for Dr. Schwartz?

12 (No response.)

13 PRESIDING OFFICER WOODCOCK: All right.
14 At this point the registered speakers have all
15 completed their information. If there is any other
16 member of the public wh o would like to give
17 remarks, we are now open at this time.

18 Okay, if you could please come up to the
19 podium and introduce yourself.

20 DR. GOEBEL: Thank you. I'm Paul Goebel,
21 Vice President with Chesapeake Research Review,
22 Columbia Maryland and an IRB. I have previously
23 been with OHRP and FDA.

24 First I want to strongly endorse Gary
25 Chadwick's analysis of the situation. As far as

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1 local versus non -local, it seems to me that this
2 may not be the way we want to look at this.

3 Rather than a local analysis of one site
4 of a multi -site study, it doesn't seem like that's
5 particularly useful. It seems like it would be
6 better to, when we say local, mean a single site
7 study.

8 And, even the event occurred at your site
9 but is part of a 100 site study, it seems tha t the
10 best information lies with a sponsor to evaluate
11 the significance of that event.

12 So, barring a train wreck , I would
13 suggest that the local IRB defer their action until
14 the sponsor has had a chance to give input as to
15 what this means.

16 I'm going to take a look at this from
17 another standpoint. And that is from the IRBs'
18 point of view. And the authority of the IRB --
19 there really is not too many things the IRB can do.

20 They can suspend or terminate study
21 approval. They can change the consent form. Or
22 they can change the study plan, the protocol. And
23 that's about it.

24 So, what the IRB needs from either the
25 sponsor or the investigator, they need to know --

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1 they need to have an analysis and have a
2 determination should the protocol be changed,
3 should the informed consent be changed, or should
4 the study be stopped.

5 They need to know these three things.
6 And, if you're throwing this out at the IRB and not
7 giving them any background information, the be
8 prepared for them to say this study should be
9 stopped.

10 Because we have this serious -looking
11 adverse event and we don't have any evidence from
12 you saying it shouldn't be stopped. I think IRBs
13 right now are operating under the default position
14 that we should continue this until we have positive
15 proof that there's a problem.

16 Maybe they should be looking at it from,
17 unless we get evidence, we know there's a problem.
18 Unless they get evidence from the sponsor saying
19 it's all right to continue, maybe the default
20 position should be let's stop the study.

21 I imagine if that happened a few times
22 that all of a sudden the IRBs would get a lot more
23 timely information along with these adverse events.
24 To me the regulations, the IND and IDE regulations
25 clearly state that the sponsor should analyze the

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1 significance of the adverse experience and provide
2 this information to the clinical investigators and
3 in the case device regulators to the sponsors.

4 Maybe they don't mean what they so
5 clearly say. But that's my read of what they say.
6 One thing that really is hard for me to get over, I
7 think the serious and unexpected is not a high
8 hurdle.

9 I think that's all right. The thing that
10 seems wide open is the statement in 56.108(b) that
11 any unanticipated problem should be reported to the
12 IRB.

13 To me that is a global term, anything.
14 Then the IRB has to do something with it. So, if
15 the terms in 108, 56.108 could be made consistent
16 with the terms in the IND IDE regulations I think
17 that would help a lot. Thank you very much

18 PRESIDING OFFICER WOODCOCK: Thank you,
19 Dr. Goebel. Are there questions from the panel?

20 (No response.)

21 PRESIDING OFFICER WOODCOCK: No. Thank
22 you. Are there any other members of the public who
23 would like to present? Please come to the podium
24 and identify yourself.

25 DR. COHEN: I'm Jeffrey Cohen. I'm an

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1 independent consultant in Human Research Protection
2 formerly with OHRP. People here -- I know I
3 wouldn't be able to sit without saying something.

4 But what I have to say is not something I
5 expected say before I came here today. I want to
6 commend FDA for its previous inaction. Because FDA
7 has not taken action on this serious problem in the
8 past, the research community in tackling the
9 problem has come up with some very good analyses
10 and some very good solutions.

11 Had the FDA and OHRP and the other
12 agencies put out guidance, put out regulations five
13 years ago, I do not know if those regulations or
14 guidance would have been as well informed.

15 And, the fact that we've waited -- we've
16 had to deal with this problem, the research
17 community has risen to the task. I've heard some
18 very brilliant analyses today.

19 And some really good ideas and good plans
20 and good models. So I really want to commend FDA
21 for its inaction.

22 (Laughter.)

23 PRESIDING OFFICER WOODCOCK: Thank you
24 Dr. Cohen. Are there questions from the panel?

25 (No response.)

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1 PRESIDING OFFICER WOODCOCK: There was
2 another party who wished to say something. If you
3 could please identify yourself.

4 MR. DIXON: I'm Dennis Dixon. I work at
5 the NIH. And I just wanted to ask to be sure th at
6 there was attention paid to a distinction which
7 came through in a couple of the presentations today
8 on what type of material should be forwarded from
9 data monitoring committee reviews to IRBs.

10 I believe that when this first came up
11 Dr. Alfano was very careful to say that it's the
12 recommendations from the DSMBs, not all of the
13 reports and data analyses and data summaries and so
14 on.

15 Other speakers seem to be referring more
16 to the detailed data summaries. And I think, as
17 someone who has worked with bot h IRBs and DSMBs, I
18 think it's the recommendations that are the
19 critical bit of information that the IRBs need.

20 PRESIDING OFFICER WOODCOCK: Thank you.
21 Questions from the panel?

22 (No response.)

23 PRESIDING OFFICER WOODCOCK: Thank you
24 very much. Are there other individuals who would
25 like to speak at this time?

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1 (No response.)

2 PRESIDING OFFICER WOODCOCK: All right.

3 Then I declare this hearing closed. Thank you very
4 much.

5 (Whereupon, at 3:22 p.m. the above
6 entitled matter was concluded.)

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CERTIFICATE

This is to certify that the foregoing transcript in the
matter of: Part 15 Hearing

Before: DHHS/FDA

Date: March 21, 2005

Place: Rockville, MD

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.

A handwritten signature in black ink, written over a horizontal line. The signature is cursive and appears to be "K. M. [unclear]".