

1 opposed to the other two?

2 DR. CHADWICK: Very little. In the eight
3 years that I have been at the University, the IRB
4 has actually found two, possibly three incidences
5 that were not previously captured either by
6 investigators or sponsors. That's three in eight
7 years.

8 PRESIDING OFFICER WOODCOCK: Other
9 questions? Dr. Lepay?

10 MEMBER LEPAY: Gary, one thing I notice
11 you didn't touch on, or at least I do not recall
12 hearing it, was the issue of whether there should
13 be a different level of oversight or a different
14 set of definitions as it pertains to the local site
15 versus remote sites in a multi-centered trial.

16 I was just wondering what your views are
17 on this?

18 DR. CHADWICK: Actually, I did touch upon
19 that. I think they should be the same. And the
20 answer is, IRBs shouldn't review adverse event
21 reports, whether they occur locally or whether they
22 occur in a multi-centered study.

23 IRBs ought to get processed information.
24 They should use it as part of their continuing
25 review and not the part of the continuous review

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1 that is appropriate for studies that ought to be
2 conducted by sponsors and by investigators.

3 PRESIDING OFFICER WOODCOCK: Additional
4 questions?

5 (No response.)

6 PRESIDING OFFICER WOODCOCK: Well, thank
7 you very much. Our next speaker will be Dr. Owen
8 Reese, who is Executive Director of the Western
9 Institutional Review Board.

10 DR. REESE: Thank you very much. Western
11 Institutional Review Board, very much wishes to
12 express its thanks to Commissioner Crawford and to
13 the FDA for allowing us this opportunity to express
14 our opinion on a very important and very
15 frustrating topic.

16 Our experience cooperates that of most of
17 us in the room and the FDA that currently we are
18 not receiving the information necessary to fulfill
19 our mission.

20 And, what we do receive is a process that
21 is very burdensome. We have extensive experience
22 in the review of adverse event reports. We receive
23 12,000 site-generated AEs annually, 14,000 unique
24 sponsor-generated AE reports annually.

25 And -- oops, back one. To review this we

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1 have three full -time staff members who are
2 responsible for entering the information into our
3 information system.

4 We have two medically trained pre -
5 reviewers who seek to identify those that are
6 duplicates or are not unanticipated. And then we
7 have a full -time physician who reviews the work of
8 the previous and makes recommendations to the IRB.

9 This process is plagued with
10 inefficiency. In addition to the 60 reports we
11 receive daily, w e receive 250 to 350 duplicate
12 sponsor reports.

13 Seventy percent of the site -generated
14 reports are told to me not related to the study
15 agent. And, it requires, of course, that all these
16 be reviewed to discover the duplication and the low
17 relevance, and is exceedingly burdensome.

18 Although, CONCEPTUAL FRAMEWORK 312.32
19 charges sponsors to identify in each IND safety
20 report all reports previously filed with the IND
21 concerning similar adverse experiences and analyze
22 the significance of the adverse experience.

23 In light of previous reports, very few
24 sponsors provide this information. Because we are
25 unaware of the total number of subjects at risk, we

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1 are forced to either evaluate the significance of
2 an event in isolation, or spend many hours
3 obtaining additional information from sponsors.

4 Our needle in the haystack occurred a few
5 years ago. We're a central IRB for a large study
6 involving Voltaren. And we discovered gastric
7 perforation as a risk.

8 And that was, at that point, undiscovered
9 by the sponsor. That was a number of years ago.
10 And Gary has two or three. That's the only one
11 that we can point to.

12 I applaud Penn for being able to
13 discovery that Vioxx risk, because we certainly
14 would not have been able to do that with the
15 information we have.

16 These occasions today are exceedingly
17 rare. Commonly, for multi -site studies, the
18 reports we receive that do suggest increased risk
19 have already been massaged.

20 They come accompanied by the consent form
21 changes that are recommended and the protocol
22 revisions. In other words, evaluation of the
23 problem and the determination of the action needed
24 are made independent of input from an IRB.

25 In many cases it's apparent the FDA has

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1 been involved in the process of determining the
2 action to be taken by the sponsor. This really
3 calls into question the utility of having the IRB
4 review these reports at all.

5 In recent months, the well-publicized
6 problems involving Vioxx and natalizuma led to very
7 drastic action. From our perspective, the actions
8 were taken without input or direction from any IRB.

9 And, although we were able to implement
10 subject notification, it would have been a major
11 improvement. Had we received prior notification we
12 could have done a much more coordinated and timely
13 approach.

14 Let me address the three specific
15 questions. What role do IRBs play in the review
16 of adverse events information? And, is there a
17 difference in the role for single site and multi-
18 site trials?

19 WIRB believes strongly that any multi-
20 site trial that involves risk to subjects should be
21 required to constitute a DSMB to monitor adverse
22 events in real time.

23 The DSMB charter must require that
24 significant conclusions be reached and forwarded to
25 the involved IRBs in a timely manner. The IRBs'

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1 role should not be to review the individual adverse
2 events for these studies, but rather evaluate the
3 DSMB findings and recommendations, determine how
4 the subject should be informed, how protocol should
5 be amended or study stopped.

6 For single site research it's important
7 that an independent entity evaluate these in order
8 to provide additional perspective to the
9 relatedness and severity of the events.

10 Sponsors will customarily provide this
11 review. Institutions might provide it. But, in an
12 investigator sponsored research, it may fall to the
13 IRB, especially those of us who are central IRBs.

14 I think that we're willing to accept the
15 role of evaluating all the adverse events of those
16 trials if we can off -load some of the
17 responsibility of the non-site trials.

18 What types of adverse events should IRBs
19 receive information? I think we need to broad
20 reporting to include all events that significantly
21 impact subjects' quality of life.

22 We certainly receive those that are
23 confined to death, life threatening events,
24 inpatient admissions, the usually definition of
25 SAE.

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1 But we're charged with notifying subjects
2 of events that would impact their desire to either
3 participate or remain in a trial. One area that
4 has not been touched on today as of yet, is events
5 occurring as a result of the research , not of the
6 agent.

7 Washout periods are not considered by
8 sponsors to be related to the study agent. And
9 they are related to the information that an IRB
10 needs to tell the subjects.

11 So, I would hope that a broadened
12 definition would include adverse eve nts occurring
13 during placebo run -ins. What should be the
14 approach for providing adverse event information to
15 IRBs?

16 In the case of multi -centered trials, it
17 would require DSMB reports should provide analyzed
18 and summarized information. However, the basi s for
19 any conclusions and recommendations must be evident
20 in the report if we are expected to implement those
21 recommendations.

22 Such reports should be made to the IRB on
23 a routine schedule basis, and whenever data results
24 in a significant recommendation with respect to the
25 protocol, the investigators brochure, or informed

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1 consent.

2 WIRB does not believe that receipt of
3 reports of aggregated data without accompanying
4 interpretation explanation will be of any value.
5 They will, by design, be untimely and will in
6 effect require each IRB to become a DSMB without
7 the benefit of viewing unblinded data.

8 It will promote inconsistency in
9 duplication of effort. It would require each IRB
10 to increase resources in terms of statisticians and
11 software.

12 And I think, while some of us could
13 certainly do that, a number of IRBs would find it
14 unduly burdensome. Events occurring in single site
15 trials must be accompanied by sufficient subject
16 history and findings for the IRB to independently
17 assess the relationship of the event to the studied
18 drug or device.

19 For single site studies, reports should
20 be reviewed in real time in order to respond to
21 significant problems in a timely manner. All
22 reports should be standardized and should include
23 an interpretation of the relevance of the event for
24 other subjects in the study.

25 The sponsor should be responsible for

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1 reporting on multi -site trials. Investigators,
2 with the assistance of sponsor if present, should
3 report on single site trials.

4 The reporting system should be the same
5 for drugs and devices. Thank you.

6 PRESIDING OFFICER WOODCOCK: Thank you.
7 Are there question for the speaker from the panel?

8 Yes, Dr. Rohan?

9 MEMBER ROHAN: When you discuss data
10 safety monitoring board, I wondered if you would
11 care to -- or if you had any thoughts regarding the
12 European proposal , the independent ethics
13 committee.

14 Do you feel that the DSMB should always
15 be independent, sometimes? Is that part of --

16 DR. REESE: I think it should be
17 independent.

18 MEMBER ROHAN: Always?

19 DR. REESE: Always.

20 PRESIDING OFFICER WOODCOCK: Additional
21 questions? Dr. Temple?

22 MEMBER TEMPLE: A large fraction of
23 industry sponsored trials don't have data
24 monitoring committees as now set up. And, in our
25 proposal for DMCs, we don't particularly urge t hem

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1 for relatively short -term studies that are over
2 fairly soon.

3 Would a sponsor analysis substitute in
4 cases where there is no data monitoring committee?
5 What's your view? I mean, you want analyzed data,
6 I understand, not investigation reports.

7 DR. REESE: I think whether you call it a
8 DSMB, an IDMC, a DMC, whatever, it needs to have
9 independent -- be independent of sponsors and it
10 needs to analyze data in real time and present that
11 to IRBs.

12 MEMBER TEMPLE: Okay. That's sort of
13 what I'm asking. The typical, I do not know, pain
14 study or something like that, isn't going to have
15 an independent committee, at least not as currently
16 constituted.

17 So, my question is, in the absence of
18 such a committee, and they don't exist for most
19 symptom trials -- they do for outcome trials, of
20 course -- what's the substitute place to get a sort
21 of organized report? Or do you have one in mind?

22 DR. REESE: I don't think there is a
23 substitute. I think it is to require that
24 committee. If IMRBs are not going to analyze the
25 data, and no one else is going to analyze the data,

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1 if we're going to change the system, it takes some
2 drastic action.

3 MEMBER TEMPLE: Okay. So, every trial
4 has to have a data monitoring committee?

5 DR. REESE: I think so.

6 MEMBER TEMPLE: People would be grateful.

7 PRESIDING OFFICER WOODCOCK: Other
8 questions?

9 (No response.)

10 PRESIDING OFFICER WOODCOCK: Thank you
11 very much.

12 DR. REESE: Thank you.

13 PRESIDING OFFICER WOODCOCK: Our next
14 speaker is Dr. Howard Dickler, who is a Senior
15 Consultant for Research at the Association of
16 American Medical Colleges.

17 DR. DICKLER: Good morning. My name is
18 Howard Dickler. I'm the Senior Consultant for
19 Research at the Association of American Medical
20 Colleges.

21 My background is contained in the written
22 statement. The AAMC represents the Nation's 126
23 medical schools, more than 400 teaching hospitals,
24 and 94 professional societies that represent about
25 105,000 academic medical faculty.

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1 Biomedical and health sciences research
2 involving human subjects takes place at all of
3 these institutions. And all of them have human
4 subjects protection programs in place.

5 In developing our comments and
6 recommendations for this hearing, we have consulted
7 with numerous individuals at these institutions,
8 including directors of human subjects protection
9 programs, research and clinical research deans, and
10 university counsels.

11 Our recommendations have several goals.
12 First, and most important, is to ensure that
13 medically and scientifically relevant data on
14 adverse events are communicated to IRBs in a timely
15 manner that will facilitate their central role in
16 protecting human subjects in clinical trials.

17 Second is to ensure that IRBs remained
18 focused on the task for which they were created to
19 make an ethical determination that risk to human
20 subjects have been minimized to the greatest extent
21 possible, that the risks are reasonable in relation
22 to the anticipated benefits if any, and that the
23 risks, benefits, and alternative options are
24 clearly communicated to the potential participants
25 in the informed consent process.

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1 IRBs were never intended to be either
2 scientific review or data monitoring committees.
3 Third is to propose a process that will promote
4 responsible and effective adverse event reporting
5 during the conduct of multi-centered clinical
6 trials in order to stem the flood of non -
7 aggregated, un-analyzed adverse event reports that
8 currently inundates Human Research Protection
9 Programs.

10 This massive burden drains resources that
11 could be better used in protecting human subjects.
12 It is inefficient and wasteful because duplicative
13 efforts are undertaken at every site, and can be
14 ineffective essential information and analysis are
15 often absent from these reports.

16 Fourth is to use as much as possible
17 language and existing regulations to construct this
18 process thereby easing and speeding the
19 implementation of changes.

20 Now, if one were to create an ideal
21 approach and process to accomplish these goals,
22 what would the characteristics be? We would
23 suggest the following characteristics.

24 For adverse events that occur at other
25 sites in a multi -centered trial, often referred to

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1 as external adverse events, IRBs should be given
2 summary reports of serious unexpected events that
3 are possibly, probably, or definitely related to
4 the study.

5 These summary reports would contain all
6 available relevant and aggregated information and
7 statistics. On evaluation of that information a
8 determination of whether or not risk was involved,
9 and if risk were involved, a recommendations as to
10 study c hange, whether that be suspension,
11 termination, protocol modification, or a change in
12 the consent.

13 Local event reporting internal adverse
14 events would remain largely unchanged. IRBs would
15 continue to receive and review all individual
16 reports of serious unexpected and related events
17 for local subjects along with the investigator's
18 assessment about whether the event involves risks
19 and necessitates a change in the protocol or
20 consent.

21 Let me clarify for the panel, based on
22 the earlier presentations, that what we really mean
23 there is that, if it's a single site trial, the
24 rules should remain largely unchanged.

25 If you are a local site in a multi -

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1 centered trial, it would go through the same
2 process. The full IRB would continue to focus on
3 the ethical decisions that are its mandate.

4 Four, the process could be accomplished
5 with no or minimal additional expense and without
6 the creation of new and additional committees or
7 entities.

8 The rules would be largely identical for
9 drugs, biologics, and devices. All the responsible
10 parties, the investigators, the sponsor, and the
11 IRBs, would review the summary and the
12 determination of whether risk was involved and
13 whether study changes and full IRB review was
14 needed.

15 And finally, the process would be
16 implemented as soon as possible via the issuance of
17 guidance that builds as much as possible on current
18 regulatory language.

19 Recommendation, we recommend that the
20 sponsor be made responsible for the summary of
21 adverse events reports described above for a number
22 of reasons.

23 First, of all the responsible parties,
24 only the sponsor has study -wide data. Second, the
25 sponsor may in addition be in possession of data

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1 from other trials using the same drug, biologic or
2 device.

3 Third, the sponsor employs individuals
4 with the medical and scientific expertise needed to
5 examine the data and make determinations about
6 risk.

7 Fourth, the language and the existing
8 regulations for medical devices lends itself to
9 this approach. This language requires reporting to
10 the IRB and to the sponsor all unanticipated
11 adverse device effects as soon as possible, but not
12 later than 10 days after the investigator learns of
13 the effect.

14 Then -- and I quote -- sponsors are
15 required to report the results of an evaluation of
16 a reported effect to reviewing IRBs and
17 investigators within ten working days after the
18 sponsor receives notice of the effect, end of
19 quote.

20 We believe that an effective and
21 manageable adverse event reporting process for
22 multi-center trials can be established by issuing
23 guidance and eventually regulations making the
24 following additions and changes to this language.

25 First, this language should be applicable

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1 to all studies of drugs, biologics, and devices.
2 Second, the word evaluation should be precisely
3 defined to mean the preparation of the summary
4 report for all unexpected serious and related
5 adverse events which contains all available
6 relevant and aggregate information and statistics,
7 an evaluation of that information, a determination
8 of whether or not risk was involved, and -- if risk
9 was involved -- a recommendation as to what sort of
10 study change would be required, suspension,
11 termination, protocol modification, or change in
12 the consent.

13 The investigator and the IRB -- and I
14 should clarify that most cases what is meant by the
15 IRB is an executive review by one or a sub-group of
16 clinician investigators who are members of the IRB.

17 They will review the report and
18 recommendation. And, in cases where the sponsor
19 determined that risk was not involved, either the
20 investigator or the executive review of the IRB
21 would have the option of making a different
22 determination.

23 All adverse events determined to involve
24 risk by any of the parties would be rapidly
25 communicated to the full IRB. Those that did not

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1 will be forwarded in a summary fashion at the time
2 of continuing review.

3 All adverse events that do not meet the
4 criteria of serious unexpected and related will be
5 aggregated, analyzed and forwarded to investigators
6 and IRBs for continuing review.

7 We believe that if these recommendations
8 are adopted the goals stated at the beginning of
9 our presentation will be reached. A process will
10 be in place where the full IRB is allowed to focus
11 on its ethical mandate.

12 All the responsible parties will be
13 appropriately involved and multiple lines of
14 protection will exist for human subjects.
15 Additionally, this approach will greatly reduce the
16 flow of paperwork to IRBs and will increase the
17 efficiency and effectiveness of a review of
18 unanticipated serious adverse events.

19 While we feel we have proposed a process
20 that can work well, we must also note that this
21 process is based on trust and is dependent on the
22 sponsor carrying out its role in a complete,
23 honest, and responsible manner.

24 Certain recent events have cast a shadow
25 on that trust. Should future events further erode

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1 the confidence and trust placed in the sponsor,
2 this process will have to be revised.

3 In that situation, it's likely that a new
4 and more costly mechanism will have to be created,
5 either under the FDA itself or its designee to
6 perform these tasks.

7 We thank you for holding this hearing and
8 seeking solutions for a problem that it is an
9 obstacle to strong human subjects protections.

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

12 (No response.)

13 PRESIDING OFFICER WOODCOCK: All right.
14 Well, I thank you very much. Our next speaker will
15 be Paul Covington, Executive Vice President of
16 Development at PPD Development.

17 MR. COVINGTON: An interesting morning so
18 far. A lot of different opinions and solutions.
19 And so, what we would like to present are some
20 potential solutions as well.

21 I'm a boarded internist. I'm currently
22 Executive Vice President of PPD, which is a CRO
23 headquartered in Wilmington, North Carolina. I'm
24 currently responsible for medical and regulatory
25 affairs, including pre and post-marketing safety

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1 surveillance, program management, medical writing,
2 product development, etcetera.

3 I have personal research interest in
4 diabetes, cardiology and critical care, and have
5 been involved with establishing data monitoring
6 processes for patient safety and integrity in
7 complex studies for critical care.

8 I'm today appearing on behalf of ACRO,
9 the Association for Clinical Research
10 Organizations. As you know, CRO's assist the
11 pharmaceutical, biotech, and medical device
12 companies with the conduct of thousands of clinical
13 trials each year.

14 They are a key participant in the
15 development of new drugs and new treatments. ACRO
16 members employ over 40,000 people worldwide and
17 conduct research in about 60 countries currently.

18 ACRO appreciates the opportunity to
19 discuss how IRBs obtain and review information
20 about adverse events and to hear ideas about how to
21 improve the process in order to assure the
22 protection of the rights and welfare of human
23 subjects, and to make sure that the risk to
24 subjects are minimized, quotes.

25 So, on behalf of ACRO, I will lay out two

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1 concrete and related suggestions meant to assist
2 IRBs. First, that the FDA and stakeholders,
3 including sponsors, institutions and all others,
4 move to standardizing the collection of safety data
5 -- standardizing.

6 And second, for all medium to large
7 randomized multi-center trials, the sponsor of the
8 research would be responsible for standardizing
9 tabular analytic summaries of safety data that
10 would be sent to investigators, DMCs, and/or IRBs.

11 Now, our goal here is to protect the
12 safety of human participants and to ensure data
13 integrity. CROs offer a view that's interwoven
14 because we see so many different sponsors.

15 We deal with so many different people.
16 We are part of a process that involves
17 investigators, IRBs, DMCs, regulators, and patients
18 all together.

19 So, we have this cross-cutting view of
20 clinical research. And we bring this perspective
21 to the table. So, based on the experience of our
22 member companies, we are relying on two sources for
23 our suggestions.

24 First is a recent project that was
25 undertaken by the association in response to the

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1 FDA's critical path initiative in which we
2 developed proposed standardized templates for AE
3 and concomitant medication case report forms.

4 And second, we'd like to build further
5 upon the feedback that we submitted to the agency
6 from the association on the March 2003 proposed
7 Safety Reporting Requirements for Human Drug and
8 Biological Products.

9 So let me begin by acknowledging the
10 situation that you've heard all morning. IRBs are
11 ill-equipped to deal effectively with safety
12 information on their own.

13 Far too often they're short -staffed,
14 under-resourced, don't have access to data
15 management sophisticated systems needed to analyze
16 serious adverse events in context.

17 And I'm going to -- instead of focusing
18 my talk on expected, unexpected, serious, etcetera,
19 you're going to see a slightly different view.
20 Today the necessary tools to crunch data, assess
21 causality, and make safety recommendations and
22 decisions, really exist within sponsor companies
23 and their CRO companies and maybe data monitoring
24 committees.

25 IRBs have neither the complete data nor

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1 the analytical resources to make these decisions in
2 isolation. So, let me start. There's
3 extraordinary variability in the structuring
4 content of just this simple adverse collection
5 form.

6 We set up a task a few months ago to try
7 to see within our CRO organizations, members of
8 ACRO, just what we could do. And the variety just
9 within our organizations was profound.

10 We believe that the variability in data
11 collection is unnecessary, introduces inefficiency,
12 and has a potential for error. So the member
13 companies came to believe that an adverse event
14 case report form could be standardized in short
15 order.

16 And, to demonstrate that, we developed
17 it. It was achieved and, in fact, has been -- we
18 have sent it, we have prepared it. And it will be
19 sent and presented to the Agency in the short-term.

20 In developing these standardized forms,
21 especially the adverse event report form, our
22 project team was guided by certain general
23 principals.

24 One, that the format and content of an AE
25 form should facilitate the collection of required

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1 and relevant data and not include unnecessary or
2 extraneous information.

3 Two, that a standardized form should be
4 clear, user friendly, and allow greater use of
5 timely reporting by investigators and sponsors in
6 review by IRBs, DMCs, etcetera.

7 Three, that any proposed standardized AE
8 reporting form should recognize and be consistent
9 with the regulatory requirements such as with ICH,
10 CIOMS, and CDISC, which we'll come back to.

11 And, as you all know, CDISC is the
12 consortium for data standards electronically.
13 We've had contacts with CDISC. And, based on our
14 feedback from CDISC, ACRO believes that almost all
15 stakeholders will recognize the significant
16 advantages to be realized from increased
17 standardization of data collection, transmission,
18 review, and analysis.

19 So we devoted our resources on this and
20 we developed the prototype, AE and CONMED case
21 report form pages. To date, ACRO has not
22 undertaken further work on the standardization of
23 other data collection forms, especially the
24 additional information required by sponsors and
25 submitted to IRBs alike for the processing of

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1 serious adverse events.

2 ACRO strongly urges the Agency to
3 encourage and foster the collaboration of all
4 stakeholders, including IRBs, institutions,
5 sponsors, etcetera to support the proposed AE
6 collection forms and to encourage the development
7 of other standardized forms, especially the SAEs
8 and processes as promptly as possible.

9 Next, I'd like to address how should the
10 safety data be presented to either IRBs, DMC,
11 investigators, or whomever? It is how that
12 presentation that you've heard all morning is
13 driving the problem.

14 Isolated events don't give us data. It
15 gives us data. It doesn't give us information.
16 So, when ACRO commented on the proposed safety
17 reporting rule published by the FDA in March of
18 '03, we expressed concern that the potential
19 outcome of the broadened definition of a suspected
20 adverse drug reaction was the IRBs would be further
21 inundated by written safety reports of serious
22 adverse drug reactions that were unexpected,
23 especially in medium to large multi-center phase
24 three trials.

25 Now, for this large subset of clinical

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1 trials we suggested an approach to SAE reporting
2 and review that would allow IRBs and the FDA as
3 well as other stakeholders to focus on safety
4 trends rather than isolated events.

5 Reduce IRB workload while improving IRB
6 decision making and assuring the Agency of adequate
7 IRB oversight. Our proposal would require any
8 sponsor, private or public, commercial, government,
9 etcetera, of medium to large -- and we have vaguely
10 defined that as, say, for example, greater than 150
11 patients, multi-center, randomized studies -- to
12 provide to the investigators, DMCs, reviewing IRBs,
13 regular -- and we've not defined that yet, loosely
14 defined as monthly, bi-monthly, quarterly, you pick
15 a date -- partially blinded -- and I want to come
16 back to that -- partially blinded standardized
17 tabular summaries that have been analyzed of all
18 serious SADRs sorted using standard coding
19 dictionaries.

20 Here, partially blinded tabular summaries
21 implied data assigned to group A, group B, group C,
22 but without specifically identifying treatment
23 assignment for the groups.

24 Sponsors, IRBs, DMCs and others could
25 then make appropriate decisions based on

1 differences between groups without complete
2 unblinding.

3 This suggested approach could also be
4 applied to larger non -randomized trials as well
5 using predictive properties of what's known about
6 the drug already.

7 Under this approach the FDA could still
8 define certain individual events as, quote, always
9 expedited reports, unquote, requiring immediate IRB
10 notification as noted in the March '03 document.

11 Meanwhile, smaller studies, the current
12 safety reporting system would -- we would suggest
13 to be retained. Our suggested approach to safety
14 reporting for medium to large trials would decrease
15 the number of isolated IND safety reports and
16 present more relevant information for decisions
17 processing.

18 It would not address the continued flow
19 of isolated expedited safety reports from smaller
20 single center studies, nor the issue of expedited
21 reports from other sources, such as post -marketing
22 spontaneous reports for products that are being
23 studied that have already been approved.

24 We recognize too that this proposal is
25 not without caveats, such as how will stakeholders

1 respond to partially unblinded information? How
2 often will IRBs respond to summary information by
3 requesting further details, especially complete
4 unblinding in response to minor differences across
5 partially blinded study groups?

6 Will IRBs choose not to act o n this
7 information, and instead requesting all studies to
8 have formal DMCs? How will the current
9 predominantly paper -based SAE system be able to
10 respond rapidly enough to meet the needs of, quote,
11 frequent tabular summary analysis?

12 Or does this approach the dictation of
13 the shift of pure electronic capture of all SAEs?
14 Since its inception, ACRO has advocated uniform
15 subject protection requirements that would apply to
16 all research under Federal oversight, regardless of
17 the source of funding.

18 We believ e that all participants in
19 research enterprise must be fully committed to the
20 protection of research participants. We urge the
21 panel to work with the NIH and other Federal
22 agencies to ensure that safety reporting
23 requirements for investigators, sponsors,
24 institutions, IRBs, and others be harmonized as
25 much as possible.

1 And further, we encourage you to consider
2 our two suggestions for facilitating the reporting
3 of meaningful safety data to IRBs and fostering
4 better safety review.

5 Thanks, and I look forward to the
6 questions.

7 PRESIDING OFFICER WOODCOCK: Thank you
8 Dr. Covington. Are there questions from the panel?
9 Dr. Goldkind?

10 MEMBER GOLDKIND: I just wanted to get
11 further clarification from you as to who would be
12 partially unblinding the data?

13 MR. COVINGTON: If we look at what DMCs
14 historically have asked for, or if you look at
15 protocols that prospectively define it, you see an
16 assignment to a group.

17 And you're asking who would be partially
18 unblinded. The techniques would involve a couple.
19 One could say that the sponsors themselves would
20 also have access to partially unblinded
21 information, group A, group B, group C.

22 But, if you wanted to restrict that, the
23 sponsor then would have to wall -off internal people
24 who would have access to the partial ly unblinded
25 information.

1 And then the partially unblinded
2 information could be submitted either the
3 investigator or to the DMC, or to the IRB. But,
4 ultimately once it gets out, it's going to be out.

5 So, whether you choose to wall it off
6 internally at the sponsor or not is a separate
7 issue. But, the issue is to give relevant
8 partially unblinded information for safety purposes
9 only. Yes, sir?

10 PRESIDING OFFICER WOODCOCK: Go ahead.

11 MEMBER TEMPLE: Do I understand that your
12 reasoning was as follows? You liked the ICH
13 definition of what you could call a lower standard
14 for reporting, that is as long as it can't be ruled
15 out.

16 MR. COVINGTON: right.

17 MEMBER TEMPLE: But, there was anxiety
18 about whether that would produce a flood of stuff.
19 But your remedy to that was to not look at
20 individual reports but to look at an overall
21 assessment.

22 MR. COVINGTON: Right.

23 MEMBER TEMPLE: Which I assume you mean
24 you think --

25 MR. COVINGTON: Yes.

1 MEMBER TEMPLE: -- would not be as
2 profligate.

3 MR. COVINGTON: Okay. So let me comment.
4 The current suggestion and the tone is that adverse
5 events -- serious adverse events -- adverse events
6 can be defined as associated, means you cannot rule
7 out.

8 If you cannot rule out, most physicians,
9 including myself, will probably assign. Because I
10 could come up with every kind of definition of why
11 something is associated.

12 I can make it up. So, for us, trying to
13 go down the expected, the unexpected route, the
14 related, the unrelated route really isn't very
15 productive.

16 Okay, at the end of the day, give me the
17 aggregate data, all serious adverse events sorted
18 by group A, group B, group C, to do a comparison
19 because someone said this morning, well, deaths in
20 oncology study are anticipated.

21 Well, if I've got a two-arm study and the
22 deaths in one arm are greater than the other arm,
23 they may be anticipated with what's going on. If
24 I'm treating hepatitis and I've got hepatitis
25 getting worse in one arm than the other arm, is

1 that drug or is that non drug?

2 So, in our mind -- cannot rule out -- we
3 would support and we would support looking at all
4 SAEs, not trying to select what's related,
5 unrelated, you know, expected, unexpected.

6 MEMBER TEMPLE: But, if I understand you,
7 it's because you're asking people to intelligently
8 look at group data as opposed --

9 MR. COVINGTON: Yes.

10 MEMBER TEMPLE: -- to individual reports.

11 MR. COVINGTON: Yes, that is correct,
12 group data.

13 PRESIDING OFFICER WOODCOCK: Any other
14 questions from the panel?

15 (No response.)

16 MR. COVINGTON: A CRO thanks you for the
17 opportunity.

18 PRESIDING OFFICER WOODCOCK: Thank you
19 very much. Our final speaker this morning will Dr.
20 William Hendee who is a Senior Associate Dean and
21 Vice President at the Medical College of Wisconsin,
22 and I know has been working on this issue a long
23 time.

24 DR. HENDEE: Thank you for this
25 opportunity to meet with you. I came here this

1 morning at the request of the Chairs of the
2 Institutional Review Board at my institution.

3 And I'm here simply to tell you, boy do
4 we need some help for this group. We're dying out
5 there. And we're dying because of SAEs coming to
6 us from everywhere.

7 That's what I want to talk about, so
8 let's get started here. Medical College of
9 Wisconsin is located in Milwaukee. It's a free -
10 standing, private medical college.

11 We have about 1,075 faculty. We're the
12 upper third of academic medical centers in terms of
13 NIH support, largest group practiced in Wisconsin,
14 800 medical students, about 600 graduate students.

15 So we're a substantial organization. And
16 we're private. We do about -- we have about 2,000
17 active clinical research studies involving human
18 participants.

19 We process about 600 new IRB applications
20 per year in our four primary institutional review
21 boards, three of which are focused on o ur adult
22 care hospital, and one of which is focused on our
23 clinics that belong to the college.

24 And then we have four other IRBs that are
25 affiliated with a VA hospital, a mental health

1 complex, the Blood Research Institute, and
2 Children's Hospital.

3 We have three standing DSMBs and we also
4 have DSMBs that are specifically set up for
5 individual studies that don't fall within the
6 framework of our existing DSMBs and pediatrics,
7 cancer, and functional imaging.

8 I'm here to tell you that we recognize in
9 our IRB process the responsibility that we have.
10 And we're certainly prepared to be accountable for
11 any SAEs of unanticipated and significant events
12 that occur as a result of a single site study in
13 our institution.

14 Fine. We're also willing to be and able
15 to be accountable for adverse event reports that
16 are generated in our institution as a result of our
17 participation in a multi-site clinical study.

18 We recognize that and we're prepared to
19 deal with that. But the question is, what are we
20 supposed to do about adverse event reports that
21 come to use from other institutions that are
22 participating in multi-site studies?

23 I'm sure you've been hearing this all
24 morning. I'm just going to reiterate the major
25 part of this problem. We get adverse events from

1 institutions that are participating in multi -
2 institutional trials in which we are participants.

3 But we have no way of judging the
4 significance of these adverse events. We have no
5 context in which they were generated. There's no
6 synthesis of the information that allows us to get
7 some idea as to whether or not these represent
8 actual risk to our own patients.

9 There's no analysis of them. They come
10 to the principal investigator, who sends them to
11 us, asks us to sign off on them. We already have
12 an overworked staff.

13 And this is certainly not helping and is
14 simply an overwhelming volume of data that we
15 really don't know what to do with. For example,
16 for the eight months from July -- and I'll show you
17 a picture of this.

18 Over the eight months from July 200 4
19 through February of 2005, we have an 11 foot high
20 tower of adverse event reports from other
21 institutions than our own that are participating
22 with us in multi-institutional trials.

23 From one study alone we have 17 inches of
24 adverse event reports. These are not limited to
25 serious or unanticipated adverse events. They're

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1 not limited to specific experimental protocols.

2 They're not limited even to adverse event
3 reports. We just get a lot of paper, as you can
4 see. Now, this is the -- what did I tell you it
5 was -- 17 foot high pile of adverse event reports.

6 We pulled them out of our drawers. And I
7 had them stack up. The ceiling wasn't high enough
8 to put on pile, so we had two. If you look in the
9 drawer, you'll see 17 inches of adverse event
10 reports and other data associated with one
11 particular study.

12 What are we supposed to do with these? I
13 asked our IRB staff. I said, well what about these
14 adverse event reports that you're getting from
15 other sites?

16 Are they always relevant? Here are a few
17 of the things that they reported. Events reported
18 that a current study is involving investigational
19 product in a combination with drugs other than
20 those studied at our site.

21 Events reported that occur in a different
22 population than the population participating at our
23 site. Events reported that occurred in a different
24 study for a different medical condition than we're
25 studying at our site.

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1 This list went on for quite a ways. I'll
2 just give you a few examples. The reports received
3 are in follow-up to a previously filed report, but
4 the updated information does not alter the previous
5 reported determination regarding causality and
6 seriousness.

7 Report doesn't contain all the
8 information necessary to understand the impact of
9 the occurrence of the event. Only a portion of the
10 external serious adverse event reports contained
11 enough information regarding the number of reports
12 of that particular event under the IND for the
13 studied drug.

14 These are just examples of information
15 that we just don't have any real way of managing.
16 So, you've asked some questions. Should IRB
17 responsibilities for multi-site trials differ from
18 those for single site trials?

19 The answer is absolutely. For single
20 site trials, we're prepared to manage our
21 responsibility and be accountable. But, for multi-
22 site trials we really can't judge the significance
23 of adverse events reports, from other institutions
24 in which we are -- that are participating in trial
25 with us.

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1 We need help there. Are there
2 circumstances under which IRB should receive
3 information about adverse events that are not both
4 serious and expected?

5 I think so, if they're going to
6 potentially have an impact on the protocol or on
7 the informed consent. If there is some reason why
8 we should know about this, because it's going to
9 impact our participation in the study or how we go
10 about the study, we need to know that.

11 What can be done to provide IRBs adverse
12 event information that will enable them to better
13 assess the implications, reported events for
14 studied subjects when those adverse events come
15 from other institutions?

16 And the answer, you heard it in the
17 previous speaker. We need a synthesis of that
18 information, and guidance from someone or some
19 group that can provide that synthesis and give us
20 Director.

21 And I have some thoughts as to who that
22 might be. For multi-site studies it is our feeling
23 of eight chairs of IRBs and of the staff of our
24 human research protection office, that there should
25 be a single repository of adverse event reports

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1 that come in from multiple ins titutions
2 participating in a multi-institutional study.

3 And, through the analysis of the
4 information in that repository, a summary or
5 synthesis -- a report, a synthesis should be
6 prepared of serious, unanticipated events.

7 Who could do that? What we'r e trying to
8 do here, by the way, is push back to some agency or
9 some person that can better judge these adverse
10 events than we can.

11 It could the Project Manager, or it could
12 be the project office after example in a Federal
13 multi-institutional trial. It could be the
14 sponsor.

15 In fact, we will not accept a contract
16 with a commercial sponsor to do a drug study or a
17 device study now unless that sponsor will assure us
18 that he or she -- that that organization, that
19 company will synthesize adverse event report s and
20 provide guidance to us.

21 It could be a data safety monitoring
22 board. It could be the principal investigator in a
23 multi-institutional trial in the office of the
24 principal investigator.

25 Who better than that individual to be

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1 able to provide this syn thesis, or somebody else?
2 But not the individual IRBs, not the IRBs at my
3 institution being inundated with adverse event
4 reports that we can't interpret, we can't provide
5 any context for.

6 And yet, we're supposed to somehow review
7 these, sign off on them , and act as though we
8 really know what we're doing. And we don't. So,
9 I'm simply recommending -- making this
10 recommendation to you on behalf of all of our IRBs
11 in my one institution.

12 But I suspect that what problem we have
13 is a problem that's shared b y institutions across
14 the country. Heavier workloads, more compliance
15 activities, increased cost of doing business -- we
16 need to get rid of some of the unessential aspects
17 of this so that we can do a better job in our IRBs
18 of really protecting participant s in research.
19 Thank you for this opportunity.

20 PRESIDING OFFICER WOODCOCK: Thank you
21 very much. Are there questions by the panel for
22 the speaker? Dr. Less?

23 MEMBER LESS: I was just wondering, you
24 said that for commercial drug and device sponsors
25 that you aren't accepting them doing research at

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1 your institution unless they agree to do that
2 analysis of the adverse events.

3 Is that working for you? Because, what
4 I've heard from some people during the break is
5 that, even though the device regs to require some
6 type of evaluation, a lot of the companies aren't
7 doing that.

8 They're just following the drug regs and
9 trying to get by with that. And I was wondering
10 what your success rate is.

11 DR. HENDEE: Well, our success rate is
12 100 percent because we won't accept the contract
13 unless they do it. Now, if you asked me, have we
14 refused contracts?

15 Yes we have. Some companies simply say
16 well, we're not going to take that responsibility
17 on. That's the responsibility of the individual
18 IRBs.

19 And we say, I'm sorry, we can't do that.
20 So I think, how often does that happen? I do not
21 know the percentage. I would guess one out of
22 every four or five contracts was never consummated
23 because of that.

24 MEMBER LESS: And the evaluations you get
25 from those that you do consummate are adequate?

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1 They're doing a full evaluation, making
2 recommendations?

3 Or do you still need to go back and ask
4 them for additional information.

5 DR. HENDEE: It varies. Some are pretty
6 responsible. Others we have to go back and ask for
7 additional clarification on what they're telling
8 us.

9 MEMBER LESS: Okay.

10 DR. HENDEE: But I think it's getting
11 better, actually. I'm hopeful that if enough
12 organizations push back, it certainly will get
13 better.

14 MEMBER LESS: Right.

15 DR. HENDEE: Good question.

16 PRESIDING OFFICER WOODCOCK: Dr. Temple?

17 MEMBER TEMPLE: You were very clear on
18 not reviewing cases from afar without detailed
19 analysis. In considering the same thing, Gary
20 Chadwick sort of also applied that to the case
21 reports that occur at the local institution.

22 He said IRBs are not really in the
23 business of doing this. But, your view was that
24 they should. Now, is that because you believe it's
25 useful, or because you believe it's not that big a

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1 deal?

2 DR. HENDEE: It's a pretty big deal. But
3 I think it's not only useful, I think it's a
4 responsibility that we have. Adverse events that
5 arise in our own institution, whether it's a single
6 site study or a multi -institutional site study
7 where we're the headquarters organization, or if it
8 just happens to occur in our institution, then I
9 think our IRBs -- and our IRBs would agree with us
10 -- would feel that they have that responsibility
11 and they must be accountable because it occurred in
12 our institution with our faculty and our
13 participants, our human participants.

14 So, we will certainly accept that
15 responsibility.

16 MEMBER TEMPLE: You might think though
17 that in a multi -center trial your little slice of
18 it isn't exactly very informative on what's all
19 going on.

20 DR. HENDEE: That's true. So, that's why
21 we need somebody to look at the overall. We're
22 looking at our part of it. But we also need a
23 synthesis of what's happening in the other
24 institutions to provide some context for what we're
25 seeing.

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1 MEMBER TEMPLE: Yes, I understand the
2 second part. But you still believe that it's very
3 important for you to look at the individual ones.
4 There was some difference in what people said.

5 DR. HENDEE: We would feel that -- we
6 would accept that responsibility, yes.

7 PRESIDING OFFICER WOODCOCK : Other
8 questions? Yes, Dr. Lepay?

9 MEMBER LEPAY: Just getting back to your
10 issue of synthesized information, is there a fair
11 amount of latitude in what you are defining as
12 synthesized information or as accepting, I mean
13 data monitoring committee?

14 Are you still accepting synthesized
15 information on a broad range of adverse events, not
16 just serious and unexpected adverse events? I
17 mean, do you narrow this down as you're talking
18 about synthesized information?

19 DR. HENDEE: What we want is guidance
20 from some central source that's reviewing all this
21 information. We want guidance as to whether or not
22 patients that we're studying or individuals that
23 are participating in our studies are in any way at
24 risk.

25 Has the risk benefit changed. Do we need

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1 to change anything in our protocol? That's what
2 we're looking for. However they want to provide
3 that guidance is fine, as long as it's timely.

4 That's the other part of this. It has to
5 be timely because we don't want to be caught with a
6 problem that has been occurring at other
7 institutions.

8 And then there's been a big delay in
9 getting the word out to us.

10 MEMBER LEPAY: And also, do you use
11 clinical investigators or principal investigators
12 in the process as we've heard this morning of
13 additional review or triaging whatever you're
14 getting as far as synthesized information from the
15 sponsor?

16 Or, does this flow from sponsor to the
17 IRB?

18 DR. HENDEE: It flows from sponsor to the
19 principal investigator who then transmits that
20 usually -- in most cases directly to our human
21 research protection office.

22 And yes, we're pretty dependent upon that
23 principal investigator for guidance because that's
24 the individual who is most expert in our
25 institution about the patients and about the study

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1 that he or she is engaged in.

2 So, we're dependent upon that individual
3 and also sometimes colleagues of that individual
4 within that particular division or department. And
5 we certainly seek that advice if we need it.

6 PRESIDING OFFICER WOODCOCK: Other
7 questions? Thank you very much.

8 DR. HENDEE: Thank you.

9 PRESIDING OFFICER WOODCOCK: This
10 concludes the morning portion of our hearing. We
11 will reconvene promptly at one o'clock and have the
12 remaining speakers.

13 (Whereupon, at 12:18 p.m. the above -
14 entitled matter recessed for lunch.)

15

1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 1:07 p.m.

3 PRESIDING OFFICER WOODCOCK: All right,
4 if everyone could please take their seats, I think
5 our panel has returned, generally speaking. We
6 again have a full agenda of speakers for this
7 afternoon.

8 So, we will keep proceeding under the
9 same rules. And then, if at the end we have extra
10 time, we'll open it up to anyone else who would
11 like to make a presentation.

12 Our next speaker is Dr. Vish Watkins, who
13 is Project Leader Eli Lilly & Company.

14 DR. WATKINS: Thank you very much. And
15 thanks to the FDA for convening this, the public
16 hearing, and getting input on this really important
17 issue.

18 I'm a physician with Eli Lilly & Company.
19 And I've worked in different areas, in academics,
20 in -- with the NIH, with the CDC, in private
21 practice.

22 And I've been with Lilly for the last ten
23 years. And the last year of that I spent in our
24 Pharmacovigilance Product Safety Section. And so,
25 that and in the oncology infectious disease part.

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1 And oncology, I think, is o ne of the
2 areas where many serious adverse events occur that
3 sometimes is seen as a burden by IRBs. Given that
4 the drugs are often cytotoxic, patients are very
5 sick.

6 And, in the early stages, most of the
7 events are unexpected until we actually experienc e
8 them. So, clearly, what I would -- I'm going to
9 skip to my last three slides because many of my
10 previous slides I think have been already addressed
11 by the other speakers.

12 I would want to say a couple of things.
13 I think one of the things I've noted is that we've
14 really lacked a principal individual investigator
15 at this conference.

16 And I think it would be important to hear
17 their perspective. And they may as well have
18 experience that the IRBs have said in talking to
19 them, being overburdened by data, not information.

20 But, of course, they would have to speak
21 for themselves. And I think it would be important
22 to hear from them as well. I'm going to go ahead.
23 I think our goal is to try to help find a solution.

24 And we think that that solution can be
25 found in the framework of CIOM VI Working Group

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1 report. And the next slide -- and, in a sense, I
2 think there are two factors, both of which have
3 been discussed this morning.

4 The first is making available periodic
5 aggregated analytic reports of serious adverse
6 events to all parties to whom patient subject
7 safety is very important, the FDA, the IRBs, the
8 investigators, and the sponsors.

9 And clearly, as sponsors, we get the
10 primary data from the investigators. We are in a
11 position to do this. And I think it makes sense
12 for us to put that together.

13 And the CIOM VI suggests that we do this
14 on a periodic, probably quarterly basis. And also,
15 not just by clinical trial, but by compound so
16 that, even if it's not the same multi-centered
17 trial.

18 If there are five trials going and every
19 quarter we analyze, we aggregate those, and we can
20 even provide it in the format that's user friendly,
21 for instance, as MedDRA according to the organ
22 systems, and then broken down by the numbers.

23 And that would, I think, be very helpful
24 for, again, all of our customers to look at. The
25 second point I think that was raised was individual

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1 alert reports, which are really, I think, the crux
2 of the problem that we're discussing here today,
3 what to do with these.

4 Someone has to make a decision as to what
5 is important and what is not. And I would, again,
6 suggest that, as for CIOMS VI responses, we get the
7 data and we can then alert.

8 We continue to send expedited reports or
9 SUSARs to the regulatory agencies. But, to
10 investigators and IRBs we could select those that,
11 according to clinical judgment, seriousness of the
12 event, strength of the evidence for causality, and
13 impact on safety, provide these as single reports.

14 Usually this will have an impact on
15 either the protocol, stoppi ng the study, or
16 changing the informed consent. An example would be
17 serious hepatotoxicity.

18 This is, I think in the CIOMS book or the
19 CIOMS VI chapter that's going to come out. But
20 there are others. I think aplastic anemia, fatal
21 or life-threatening anaphylaxis perhaps torsade de
22 pointes.

23 Those, I think are the easy ones. Now,
24 there are others where there is medical judgment
25 involved. And, if those would change the informed

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1 consent, then we would report them.

2 If not, everyone would see them on a
3 quarterly basis in the line listings. And if
4 there's interest in IRBs, individual reports, case
5 report forms that are important to be seen, we
6 could supply those.

7 So, a suggested approach that we have is
8 that we provide periodic quarterly summary reports,
9 perhaps less frequently the studies are -- if there
10 aren't as many studies and reports, we would
11 provide a line listing.

12 It would include expedited reports from
13 clinical trials and a summary assessment of the
14 safety profile of the drug based on that
15 information.

16 In the interim between these reports, if
17 a significant safety finding is discovered, either
18 on an individual case basis, or if the companies --
19 if we're doing monthly surveillance, for instance,
20 and we come across something, then we would inform
21 everyone.

22 I think I'm going to stop there in the
23 interest of time and take questions.

24 PRESIDING OFFICER WOODCOCK: Thank you
25 very much. Are there questions from the panel? Dr.

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1 Temple?

2 MEMBER TEMPLE: Do you think -- I guess
3 for some things a line listing is informative. But
4 I guess I wonder whether you need a little
5 description of the more interesting ones. Or, have
6 you thought about that?

7 DR. WATKINS: I think in the summary
8 report we should address those that are of
9 interest. But there could be a problem if we say,
10 okay, we don't know.

11 It's not enough to list 50 adverse events
12 for informed consent if it's not helpful to anyone.

13 MEMBER TEMPLE: Right.

14 DR. WATKINS: But we'll keep an eye on
15 this. If there are more, we'll discuss with the
16 FDA. We'll bring it to attention, etcetera.

17 MEMBER TEMPLE: So, there'd be some
18 judgment involved in which pull out of the line
19 listing?

20 DR. WATKINS: Yes, and I think we come
21 back to that there is ultimately medical clinical
22 judgment and who should make that judgment.

23 MEMBER TEMPLE: Too bad, that's so hard.

24 DR. WATKINS: Right.

25 PRESIDING OFFICER WOODCOCK: I have a

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1 question. Would these types of reports then be
2 submitted to the regulatory agencies as well in the
3 sense of this is just a common summary report, the
4 same report everyone would see?

5 DR. WATKINS: I think we should submit
6 the reports to the regulatory agencies.

7 PRESIDING OFFICER WOODCOCK: Are there
8 any other questions?

9 (No response.)

10 PRESIDING OFFICER WOODCOCK: Thank you
11 very much.

12 DR. WATKINS: Thank you.

13 PRESIDING OFFICER WOODCOCK: All right.
14 Our next speaker is John Isidor from Schulman
15 Associates IRB, Incorporate. I hope I pronounced
16 your name correctly, representing the Consortium of
17 Independent Review Boards.

18 MR. ISIDOR: See, I always maintain that
19 lawyers should not mess with PowerPoint slides. In
20 the old days, Jim, we never had slides at
21 presentations.

22 Thank you Vish for such a succinct
23 presentation. I'm still trying to digest my lunch.
24 It brought me back to my high school teaching days
25 when I had 32 minutes to eat.

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1 And so, -- and I also was talking to my
2 colleague Jean-Louis about the pronunciation about
3 *déjà vu* because, if you look at my presentation I
4 think you'll understand why we were discussing t hat
5 particular topic.

6 And Jean -Louis says it's important for
7 Anglo-Saxons to pronounce -- at least Americans --
8 to pronounce it correctly. And I'm not -- I'm
9 proving him correct, I'm sure.

10 Anyway, I am the -- it's John Isidor, by
11 the way. And I'm the President of the Consortium
12 of Independent Review Boards. We have some slides
13 and a written presentation that I'm going to read
14 from with respect to this particular issue.

15 And I really do appreciate the
16 opportunity to be able to present to you on this
17 very significant topic. I think that the 11 people
18 that presented before me today have done a very
19 fine job.

20 I think there's been sort of a consistent
21 theme that we've identified a significant problem.
22 I think there's been slight variations on the the me
23 with respect to particularly what we call external
24 versus internal reports and the importance of those
25 reports. So, I will go ahead with my remarks.

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1 The Consortium of Independent Review
2 Boards is pleased to provide comments on the issues
3 raised in th e FDA's notice. The organization
4 appreciates the Agency's recognition of the
5 problems associated with the current system and
6 this important initiative.

7 Now, to advance I just left -click? Oh,
8 the arrow. Okay. CIRB is a consortium of
9 independent IRBs lo cated in the United States and
10 Canada.

11 And we have a central mission of
12 promoting the protection of rights of human
13 research subjects while providing an understanding
14 of how independent IRBs support this goal.

15 We estimate approximately 40 percent of
16 clinical research in the U.S. is conducted in
17 academic settings. And that's probably increasing.
18 And independent IRBs review a majority of this
19 research.

20 Thus, as an organization of IRBs, CIRB
21 has a significant interest in this matter. And FDA
22 has asked for comments on the IRBs' role in
23 reviewing adverse events.

24 Okay. The IRBs' primary regulatory
25 responsibility in clinical research is to assure

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1 the protection of rights and welfare of human
2 subjects participating in research through the
3 review of proposed research and the continuing
4 review of approved research.

5 The review of reports of adverse drug and
6 device reactions associated with IRB approved
7 clinical trials is a component associated with to
8 of the IRBs' regulatory functions associated with
9 clinical review.

10 To be beneficial, the IRBs' review of the
11 reports must be used first to assess the ongoing
12 risk/benefit ratio of the study, and secondly to
13 assess the need to inform participants of
14 significant new findings that might affect their
15 continued participation and the research.

16 Regrettably, due to the inherent
17 limitations associated with the current system of
18 adverse event reporting, the expansion of the large
19 multi-center studies, and the differences FDA
20 definitions associated with reportable events, IRBs
21 often lack access to critical information that
22 would allow for a more meaningful review of
23 reported events.

24 Usually, IRBs randomly receive reports
25 about isolated single events. In connection with

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1 drug studies, IRBs usually can tell from these
2 reports whether the adverse event involves an event
3 on placebo study drug or a comparator.

4 With multi -site studies, except at the
5 time of continual review, IRBs do not know at any
6 given time how many sites or participants are
7 enrolled in a study or how many have experienced a
8 similar adverse event.

9 They lack important data available to the
10 sponsor that track events across multiple studies,
11 including earlier studies, studies conducted
12 overseas and studies conducted over the oversight
13 of different local and central IRBs.

14 As a result, IRBs are hampered in their
15 ability to assess the significance of adverse
16 events in the overall study with respect to human
17 subject risk.

18 Now I'm going to get to our
19 recommendations. And, in the spirit of Vish, I'm
20 going to kick this succinct, which I think is a
21 good spirit for this afternoon.

22 With these limitations in mind, CIRB
23 believes that several steps can be taken to enhance
24 the current system of reporting adverse events to
25 IRBs.

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1 I think this is critically important. I
2 know we've talked about the definitions. And we've
3 talked about the lack of uniformity. But a lot of
4 people in this world live and die on definitions.

5 And they are wedded to definitions. So I
6 think harmony in these definitions is not an
7 insignificant issue. Definitions in FDA drug,
8 device, and IRB regulation should be clarified and
9 harmonized to require investigators subject to the
10 IRBs' jurisdiction to promptly report to the IRB
11 complete information about adverse events at their
12 site that are serious, unexpected, and related to
13 the study product.

14 Such reporting is essential to assure the
15 IRB has up to date information on the status of the
16 study at the individual site where the event
17 occurred.

18 Two, sponsor reports -- sponsor periodic
19 reports to the IRB, a protocol level aggregated
20 safety data in a summarized form, would
21 significantly enhance the IRBs' ability to perform
22 its human subject protection function as it relates
23 to the review of adverse events.

24 The frequency of sponsor reports should
25 be consistent with the degree of study risk. CIRB

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1 believes the level of report detail should either
2 be consistent with the level of safety information
3 detail contained in the sponsor's annual report or
4 that called for in CIOMS working group VI proposal
5 in reporting drug safety data from clinical trials.

6 And we've heard a number of comments on
7 the CIOMS proposal. CIRB does not believe that IRB
8 receipt of additional critical information from the
9 investigator in connection with individual adverse
10 event reports would result in efficient use of IRB
11 resources in the protection of human subjects.

12 If such information is not analyzed by
13 the sponsor first and then provided to the IRB in
14 the form of aggregated reports, IRBs would be
15 required to devote massive resources in the form of
16 manpower and infrastructure to the analysis of such
17 data, possibly to the detriment of other critical
18 IRB functions.

19 Moreover, such detail, an IRB review of
20 adverse event information would present an
21 unnecessary redundancy given that sponsors already
22 have systems in place, either internally or
23 externally through DSMBs to adequately evaluate the
24 significance of individual adverse event reports
25 with respect to the safety of human subjects.

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1 When -- let me back up. When DMBs are
2 associated with a research subject study, a summary
3 of the findings of each DSMB meeting, including the
4 DSMB conclusion, should be sent to the IRB without
5 modification.

6 Conclusion, CIRB believes that the
7 implementation of these three proposals will
8 improve the IRBs' ability to conduct meaningful
9 review of adverse event information placing it in a
10 better position to determine the need to take
11 action, whether that be to require changes to the
12 consent, the protocol, or to change the approval
13 status of the study.

14 CIRBs' written comments will provide
15 additional detail concerning these recommendations.
16 On behalf of the organization I thank FDA. I thank
17 all the speakers for the opportunity to present
18 CIRBs' collective comments on this critical issue.
19 Thank you.

20 PRESIDING OFFICER WOODCOCK: Thank you,
21 Mr. Isidor. Are there questions for the speaker?
22 Dr. Temple?

23 MEMBER TEMPLE: Could you just clarify
24 the first recommendation? That, I take it, refers
25 only to reports to the IRB of things that happened

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1 within their study at that study site?

2 MR. ISIDOR: I didn't wear my glasses
3 here. That was a big mistake. Okay, Dr. Temple,
4 go back.

5 MEMBER TEMPLE: The first recommendation
6 says that the investigator is supposed to report to
7 the IRB complete information ab out adverse events
8 that occur at that site.

9 MR. ISIDOR: Yes.

10 MEMBER TEMPLE: Okay. So, that's sort of
11 the -- other people have said that reporting
12 adverse reactions to the site are not necessarily
13 good. But you mean to say they should?

14 MR. ISIDOR: That the investigators
15 should report serious and unexpected adverse --

16 MEMBER TEMPLE: At that site only.

17 MR. ISIDOR: Correct.

18 MEMBER TEMPLE: And then, for everything
19 else that comes, would have been called external,
20 you think those should be summarized?

21 MR. ISIDOR: That is correct.

22 MEMBER TEMPLE: Okay.

23 MR. ISIDOR: But, I think it's important
24 that any serious adverse event report. And this is
25 me personally now. It needs context. I mean, I

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1 don't care whether it's one site, one IRB.

2 Without some sort of context analysis by
3 the clinical investigator, if that's the only
4 person who is managing that particular trial and
5 conducting that trial, it needs context.

6 Because, I think Gary said it best. When
7 the regulatory structure was established, it's
8 clear to me that the crafters of those regulations
9 did not envision the IRB to take the role of a
10 safety monitoring committee.

11 And if so, then they should have written
12 those regulations dramatically different. And they
13 should have required the necessary components of
14 people that would have that expertise to be able to
15 perform that function.

16 MEMBER TEMPLE: The reason I'm asking you
17 is that your view here doesn't seem to be the same
18 as Garry's. That's why I'm asking you. You want
19 those to go to the IRB, presumably because they can
20 review it. And I just want to find out why you --

21 MR. ISIDOR: No, it's somewhat
22 inconsistent. I agree with Gary's view.

23 MEMBER TEMPLE: Okay. The other thing is
24 it says related to the study article. Do you have
25 some level of relationship? Is that possibly,

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1 probably, definitely?

2 MR. ISIDOR: I think it should be
3 probably or definitely. But, you know, one of the
4 things I think you have identified today Dr. Temple
5 is we have a very risk adverse society.

6 So, however we craft that definition, it
7 appears to me that people are going to push the
8 envelope to over -report because there's a
9 tremendous fear in this society that if we're
10 guilty of under -reporting, we're going to be
11 penalized in the worst possible way.

12 And I think the Agency has seen that
13 itself this year.

14 (Laughter.)

15 MEMBER TEMPLE: That's another
16 discussion.

17 (Laughter.)

18 PRESIDING OFFICER WOODCOCK: Other
19 questions from the panelists?

20 (No response.)

21 PRESIDING OFFICER WOODCOCK: Thank y ou
22 very much.

23 MR. ISIDOR: Thank you.

24 PRESIDING OFFICER WOODCOCK: Our next
25 speaker is Dr. Jean -Louis Saillet form Schering -

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1 Plough. And he's representing PhRMA.

2 DR. SAILLOT: Thank you, Dr. Woodcock.
3 Another *déjà vu*. It would fair for anyone here to
4 challenge my accent in English. I'm Dr. Jean -Louis
5 Saillot.

6 I'm head of Global Pharmacovigilance at
7 the Schering -Plough Research Institute. And I'm
8 happy to represent PhRMA's point for consideration
9 to this very important discussion and would like to
10 praise the FDA for putting this workshop, public
11 hearing together.

12 I'm also a member of the PhRMA's clinical
13 research technical group and Pharmacovigilance, an
14 epidemiology technical group. In terms of the
15 issues associated with the current practice, I
16 think in the interest of time, these issues were
17 very well covered with all the different
18 presentations throughout the morning and into the
19 afternoon.

20 The point that we would like to emphasize
21 is that these issues are recognized by PhRMA
22 companies and we are really looking forward to
23 participating in finding a solution that would be
24 agreeable to everyone.

25 And we praise the FDA for organizing the

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1 dialogue around these issues. Some of the drivers
2 behind the current situation are related to the
3 current regulatory framework and guidance
4 documents, including both the FDA IND regulation,
5 as well as ICH Guidance on Good Clinical Practice,
6 which drives the submission of expedited reports
7 with the definition of any report that is serious,
8 unexpected, and at least possibly related to the
9 product under investigation.

10 I think that part of this definition
11 there are points that are very straightforward and
12 points that are a bit more ambiguous. The serious
13 definition is pretty straightforward.

14 Expected, usually whether it's mentioned
15 in a protocol or in the investigative brochure is
16 also pretty straightforward. I think a lot of the
17 controversy that we have heard this morning
18 throughout the morning in terms of relevance of the
19 reports come back to the association of the adverse
20 events to the product under investigation.

21 And definitely the environment throughout
22 PhRMA company is to take a very conservative
23 approach in case report. And that is a hallmark
24 throughout the industry.

25 And I just wanted to highlight this.

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1 These reports have to be submitted to the
2 regulatory health authorities, as well as the
3 investigators, in most situations within 15
4 calendar days from the receipt of the information
5 by the sponsor.

6 It is in turn the responsibility of the
7 investigators to inform the IRBs. However, I think
8 it has been mentioned throughout the morning that
9 the sponsors do indeed put a lot of weight in
10 pushing the investigators to send this information
11 to the IRBs.

12 And, throughout the monitoring activities
13 of the sponsors, they actually verify that the
14 investigators do fulfill this expectation and take
15 action as needed to reinforce this.

16 So, the entire dynamic is really to push
17 for more data. I'm withholding on the term
18 information for the present time. More data is
19 being sent to the IRBs.

20 I think there's also important
21 information in the context of this discussion.
22 There are a number of changes in the current
23 framework that are currently ongoing.

24 I think that we covered examples from the
25 European Clinical Trial Directive, including the

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1 SUSUAR, suspected unexpected serious adverse
2 reactions.

3 It's difficult to anyone to go and say
4 this. They are to be submitted by sponsors to both
5 investigator and ethics committee -- this is
6 something new in Europe -- in addition to their
7 submission by the sponsors to the regulatory health
8 authorities.

9 It also, the clinical trial directive,
10 introduces new reporting requirements that may be
11 very relevant to the discussion and the potential
12 solutions to the current issue.

13 The quarterly line listing, which are in
14 a summary fashion to communicate the information to
15 both the investigators and independent ethics
16 committee as well as the annual safety report.

17 And on this one I will probably come
18 back. A very important aspect of this annual
19 safety report, it is more than just data. It
20 requires an evaluation, a statement being made by
21 the sponsor of the continuing risk benefit, if I
22 could use the word benefit in clinical trials.

23 But, the amount of risk associated with
24 the product. I think that all of the presentations
25 throughout the day and the morning basically point

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1 towards the fact that there's a broad recognition
2 of the issues associated with the current reporting
3 process for the individual case reports.

4 And, the example of the recent CIOMS VI
5 working group recommendation is a good example of
6 that broad recognition. I will not go over the
7 details of the CIOMS VI report.

8 Some parts were already mentioned this
9 morning. And I know that Dr. Wendy Stephenson will
10 also go into more details later on. I think there
11 are a couple of key words, part of this summary
12 taken out of the current -- the most recent CIOMS
13 VI report, is a periodic reporting and adhoc
14 communication.

15 But, the update of important information,
16 as well as the evolving benefit risk profile of the
17 product is critical, going back to some of the
18 points that were -- I liked it in terms of
19 synthesis of information, evaluation, providing
20 information as opposed to data.

21 So, these are critical elements for
22 consideration. What I would like to do is to go
23 over a couple of slides with regard to points for
24 the FDA to consider as these issues are being
25 discussed.

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1 This point mainly addresses FDA question
2 number three, but provide the elements that are
3 relevant to question number two as well. The first
4 bullet talks about the information being provided
5 to the IRB should be complete, timely, and
6 meaningful.

7 I think it is clear that the current
8 process ensures timeliness but does not best
9 address the completeness or the meaningful units.
10 So, one of the conceptual points.

11 And I think that although many different
12 solutions or recommendations were given throughout
13 the morning and into the afternoon, it points
14 towards synthesized aggregate information, I think,
15 came as a recurrent theme.

16 So, one of the points for consideration
17 is to ensure that aggregate safety information is
18 provided at periodic intervals together with an
19 evaluation of the evolving safety profile of the
20 product under investigation, very consistent with
21 CIOMS VI.

22 I think that the interpretation aspect is
23 critical to underline under that point. Well, this
24 periodic reporting would not be the entire picture.
25 They would also -- and we believe that there will

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1 always be a need for adhoc communication on
2 meaningful safety information as this becomes
3 available independent from the periodic reporting.

4 But, in order to move away from the
5 current, almost automatic sending of information,
6 would be to emphasize that meaningful single
7 reports would be communicated.

8 Here the definition -- PhRMA did not come
9 up with a definition that can be readily used.
10 But, we will try to do so in our written comments,
11 that is providing a little bit more information as
12 to what would be the criteria.

13 I think that the criteria fo r that
14 identification as to what is meaningful is going to
15 be the most interesting challenge of any guidance
16 creation that the Agency would like to go forth
17 with.

18 Some of the elements -- at least
19 conceptually -- mention that, if the events due to
20 the nature bring significant new safety information
21 which has implication on the conduct of the trial.

22 There were some examples of a serious,
23 severe, actually, as well, adverse reactions, such
24 as hepatotoxicity or aplastic anemia, or other type
25 of events, would be good examples to put these type

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1 of reports in context.

2 However, in most cases, at least in my
3 experience, modifications to a clinical trial or an
4 informed consent, or a clinical program are usually
5 not driven by single cases.

6 They are driven by a series of cases
7 which come to a threshold that is now seen as
8 impacting the risk of the ongoing trial. So, in
9 such cases the sponsor should, as soon as they
10 identify, this new risk, basically communicate that
11 in an expedited fashion.

12 I think that IND re gulations are already
13 very clear in terms of providing results from
14 aggregate results, for example, from pre -clinical
15 toxicology studies.

16 So, that would basically be very
17 consistent with the current regulations.
18 Additional important elements for conside ration,
19 one of the things that came clear is that, although
20 the discussion is really centered on providing
21 IRBs, Institutional Review Boards, with relevant
22 information, the same challenge of providing
23 investigators with relevant information is present.

24 So, we would like to highlight that the
25 CIOM -- consistent with the CIOM VI, a solution to

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1 also address the data versus information syndrome
2 that we are currently facing should be addressed
3 for investigators as well.

4 So, the focus on only providing relevant
5 reports with periodic evaluation should also help
6 the investigators in fulfilling their obligation of
7 the oversight of the trials at their site.

8 And, obviously, the current expedited
9 reporting to regulatory health authorities, whom
10 are much more poised to make aggregate evaluations
11 because of their databases and infrastructure would
12 remain unchanged.

13 Additional comments or elements for
14 consideration, as the FDA re-evaluates the process
15 of reporting safety information to IRB, PhRMA urges
16 the Agency to also evaluate the value of more
17 meaningful reporting to investigators.

18 Again, this is very much in line with the
19 current CIOMS VI proposal. One point which PhRMA
20 usually pushes pretty hard on and would like the
21 FDA to consider is these activities, obviously, you
22 know, clinical research nowadays is conducted
23 throughout the globe.

24 And, to that point, the CIOMS VI or any
25 further ICH guidance would be greatly appreciated

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1 by the industry. Conclusions, PhRMA company
2 recognize the issue identified by the I RB community
3 and agree that the current system for notification
4 of safety information to IRBs can and should be
5 improved.

6 PhRMA companies recognize that more
7 meaningful information -- and again, here the key
8 operating word is information -- to the IRBs w ill
9 help their role to protect the public, thereby
10 improving the overall clinical research process.

11 And PhRMA urges FDA to take the
12 opportunity of this review to also address the
13 issue of individual cases reporting to
14 investigators. Thank you very much. That's my
15 last slide.

16 PRESIDING OFFICER WOODCOCK: Thank you.
17 Are there questions from the panel? Kate?

18 MEMBER COOK: You talked about new
19 reporting going to the IRBs. Would that be coming
20 from sponsors?

21 DR. SAILLOT: Are you referring to the
22 European Clinical Trial Directive?

23 MEMBER COOK: A new model where there
24 might be periodic reports to the IRBs. Would those
25 be from the sponsors --

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1 DR. SAILLOT: Yes.

2 MEMBER COOK: -- to the IRB?

3 DR. SAILLOT: Yes. These would be from
4 the sponsor. I know that this morning there were
5 discussions as to DSMB versus sponsors. Sponsors
6 cannot be taken out of the equation.

7 This is their role, to look at the
8 evolving profile. And, yes, that would be coming
9 from the sponsors.

10 MEMBER COOK: One of our speakers this
11 morning talked about in her institution's view it
12 was important that reports go to the clinical
13 investigators and from the investigators to the
14 IRBs.

15 And I wondered if you had any comments on
16 that model and whether you would support
17 maintaining that model or changing it.

18 DR. SAILLOT: I would support maintaining
19 that model. What the point is that the information
20 that would be sent to both the investigators and
21 the IRBs, either together or in -- first to the
22 investigators and then forwarding this information
23 to the IRB, would be more meaningful information as
24 opposed to the current, you know, volume of un -
25 aggregated individual case reports.

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1 MEMBER COOK: And I suppose I thought --
2 one thought that I was hearing this morning was
3 that the investigators would actually play a role
4 maybe as assistance to the IRBs in their assessment
5 of that data.

6 Do you see that as a continued role? Or
7 do you see it being more important that the
8 information actually go to the investigators for
9 their own purposes rather than to assist the IRB?

10 DR. SAILLOT: Well, I think that both are
11 extremely valuable. The investigators need to have
12 this information for their -- the oversight of the
13 patients under their direct care, as well as
14 providing any input or guidance to the local IRB.

15 So, I would not separate the two needs.
16 I mean, they are two different needs. But both are
17 important.

18 PRESIDING OFFICER WOODCOCK: Other
19 questions? Dr. Lepay.

20 MEMBER LEPAY: I was just wondering
21 whether the PhRMA group has discussed the role of
22 data monitoring committees and the interaction of
23 data monitoring committees with IRBs in the process
24 of your deliberations.

25 DR. SAILLOT: We have not have as in

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1 depth discussion that we probably need to have.
2 And, based on some of the input this morning, we
3 will definitely go back and look at this.

4 The -- one of the things that is present
5 in the proposal from the IRB Sponsor Roundtable,
6 and I think would be supported by PhRMA is it is a
7 current best practice to inform IRBs of the outcome
8 of DSMB reviews.

9 But this is not automatically done by
10 every sponsor. So, being able to provide this
11 input I think is extremely valuable like the all
12 the IRBs, you know, whom have been able to interact
13 with, would greatly appreciate even knowing that a
14 DSMB has met and that their conclusions were that
15 the trial could continue unchanged.

16 That information is not always provided.
17 I think that, you know, either guidance or best
18 practice -- implementation of best practices would
19 go a long way for that.

20 PRESIDING OFFICER WOODCOCK: Additional
21 questions? Dr. Less?

22 MEMBER LESS: You had mentioned in one of
23 your considerations that pre-clinical study results
24 would qualify as an expedited adverse event and go
25 directly to the IRB.

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1 In the device regs right now that would
2 normally come to FDA first we would evaluate it,
3 comment on it, and then decide whether or not it
4 should go to the IRB.

5 So you are advocating it would go
6 directly to the IRB or would it come to FDA first
7 and have some discussion s of the relevance of it
8 and seriousness?

9 DR. SAILLOT: What the important point
10 was around this is that there's multiple elements
11 that need to be taken into consideration for a good
12 monitoring of the safety profile of an
13 investigational product.

14 This is obviously information coming from
15 the trial in question, coming from other trials in
16 different indications. And these elements cannot
17 be disregarded.

18 Information from toxicology or pre -
19 clinical studies is also very relevant. The
20 clarification that I would like to give is that it
21 would not be, again, automatic.

22 It is when there is something which is of
23 medical or scientific relevance that this
24 information would be summarized, put in context and
25 provided to all the key players, which include the

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1 investigators.

2 And, again, whether it's going just to
3 the investigators and from the investigators to the
4 IRB or directly in parallel to both, you know,
5 players, is not as important, I think.

6 Or at least we have not gone through
7 within the PhRMA working group gauging whether this
8 parallel reporting is better than the current
9 situation, which is to send the information to the
10 IRB -- to the investigator, I apologize -- and then
11 from the investigator to the IRB.

12 The important point though is that
13 aggregate synthesized relevant information would be
14 provided to all occupiers. I'm not sure I answered
15 your question with that long tirade.

16 MEMBER LESS: I guess normally when I
17 think of pre-clinical study results I don't think
18 of those as an adverse event. And we would see
19 those coming into FDA, I think, first, before they
20 would go to the investigators and to the IRB so
21 that we could take a look at it, decide -- work
22 with you, decide, you know, whether all the IRBs do
23 need to be notified in a way whether there' d be a
24 change to a protocol, the informed consent , as
25 opposed to sending it out to 15 IRBs and then come

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1 back and saying what do you want us to do with
2 this?

3 DR. SAILLOT: Well, first of all, they
4 are -- whether you label them adverse events or
5 not, maybe just semantics. But they are very
6 relevant pre-clinical findings that are important
7 for the entire investigator community or IRB.

8 And although, yes, I think you're right,
9 there would be a lot of interaction with the FDA in
10 terms of discussion as to what is meaningful,
11 clearly the IND regulation mandates the sponsor to
12 send this information to the FDA.

13 But, if I read the regulations correctly,
14 this type of information is also to be sent to the
15 investigators. There is also the fact that studies
16 performed outside of the United States would also
17 benefit from this information.

18 So, there may be a communication that
19 goes directly to the investigators independent of a
20 discussion with the FDA.

21 PRESIDING OFFICER WOODCOCK: Dr. Temple?

22 MEMBER TEMPLE: Your description of
23 reporting of pre-clinical is correct. It can be a
24 serious unexpected adverse event. I just want to
25 be clear.

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1 You have not reached a conclusion yet as
2 to whether you think any or all of these reports
3 ought to go directly both to the investigator and
4 to the IRB.

5 Current rules don't require anything to
6 go from the sponsor to the IRB. And you haven't
7 decided yet?

8 DR. SAILLOT: No, we have not decided
9 that.

10 MEMBER TEMPLE: Okay. Might you address
11 that in your subsequent remarks?

12 DR. SAILLOT: We will try to, yes, in the
13 written comments.

14 PRESIDING OFFICER WOODCOCK: Other
15 questions?

16 (No response.)

17 PRESIDING OFFICER WOODCOCK: Thank you
18 very much Dr. Saillot.

19 DR. SAILLOT: Thank you very much.

20 PRESIDING OFFICER WOODCOCK: Our next
21 speaker is David Borasky, who is the immediate past
22 President of Applied Research Ethics National
23 Association, or ARENA.

24 MR. BORASKY: Well, thank you Dr.
25 Woodcock. And thanks to the other panel members

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1 and presenters for what's been an interesting day
2 so far.

3 My name is David Borasky. I'm the
4 immediate past President of the Applied Research
5 Ethics National Association, or ARENA. And I'm
6 presenting comments today on behalf of ARENA.

7 We appreciate this opportunity to comment
8 on adverse event reporting to IRBs. ARENA is the
9 membership division of Public Responsibility and
10 Medicine and Research, or PRIM&R.

11 PRIM&R is an educational organization
12 dedicated to creating, implementing, and advancing
13 the highest ethical standards in the conduct of
14 research.

15 ARENA's mission is to enhance human and
16 animal research protection and the responsible
17 conduct of research through the educational and
18 professional development of its members.

19 Our 2,000 plus members represent a
20 diversity of institutions throughout the world
21 whose research efforts vary substantially. The
22 membership includes a range of professionals from
23 research administrators, government officials and
24 academic deans, to members and chairs of
25 institutional review boards, institutional animal

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1 care and use committees, and institutional bio -
2 safety committees.

3 And we have the following comments to
4 offer in response to the FDA's questions. What
5 role should IRBs play in the review of adverse
6 events information from an ongoing clinical trial?

7 The role of the IRB is to ensure that the
8 rights and welfare of research subjects are
9 protected. The review of all adverse events in an
10 ongoing clinical trial by a scientifically founded
11 body is extremely important providing knowledgeable
12 protection for subject safety and welfare.

13 To do this, the IRB needs substantive,
14 meaningful data throughout the conduct of all
15 clinical trials. For all ongoing clinical trials,
16 the role of the IRB should be to ensure that there
17 is an adequate data safety monitoring plan in place
18 at the time of initial review and confirm that the
19 plan is working at all continuing reviews.

20 The Federal Regulations state that,
21 quote, where appropriate the research plan makes
22 adequate provision for monitoring these data
23 collected to ensure the safety of subject, end
24 quote.

25 In addition, NIH policy consistently

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1 recommends that all clinical trials include a data
2 and safety monitoring plan. And NIH further
3 indicates that the monitoring pledge should be
4 tailored to the nature, size, and complexity of the
5 clinical trial.

6 The role of the IRB should be to review
7 the data safety monitoring plan to ensure that
8 there is communication between the principal
9 investigator, the sponsor, and the IRB.

10 This plan would set the stage for the
11 local IRB to manage adverse and unanticipated
12 events. The plan should describe the monitoring
13 system, which typically is centralized across
14 research sites and includes procedures for
15 assessing risk to research subjects and
16 recommending actions as needed.

17 The plan should specify who will do the
18 evaluations, the data that will be evaluated, the
19 frequency of the evaluations, stopping rules, and
20 the process for communicating the results of the
21 evaluation to the IRB.

22 The role of the IRB in reviewing
23 unanticipated events should be no different than
24 the review of any piece of information that impacts
25 the rights and welfare of subjects.

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1 At the initial review of a protocol, the
2 IRB expects the principal investigator to include
3 procedures for subject safety, provisions to
4 minimize risks, and methods for data analysis that
5 can be presented in a usable format to the IRB.

6 Only then can the IRB make sound
7 judgments about whether the research procedures
8 meet the federally mandated criteria for approval.
9 As the IRB provides continuing procedures --
10 continuing oversight of the research, it needs to
11 similarly receive complete and useful information
12 that can be used for ongoing risk assessment.

13 This information must include a summary
14 report of adverse events with a description of how
15 these were handled since the last IRB review of the
16 research.

17 Obviously it would continue to be the
18 responsibility of the investigator or sponsor to
19 immediately notify IRBs should immediate action be
20 required to protect subject safety.

21 The IRB should receive complete analyzed
22 information with a recommended plan to minimize the
23 risks associated with the events reported and an
24 indication of whether subjects should be provided
25 additional information that may impact their

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1 willingness to participate, the timing for
2 receiving these reports -- immediate, quarterly, or
3 at the time of continuing review -- should be
4 described in the data safety monitoring plan.

5 In order to review unanticipated or
6 adverse events, the data safety monitoring
7 committee must evaluate the following. What was
8 the level of severity?

9 Was the event unanticipated? Has this
10 event occurred before? And if so, how often? What
11 is the end for individuals receiving the
12 intervention?

13 Was the event related to the protocol or
14 procedures. The IRB should receive only reports of
15 those events that have been determined to have a
16 potential negative impact on subject safety.

17 Therefore, the focus should be on the
18 serious, unanticipated events that are reasonably
19 related to the study procedure. IRBs have a
20 greater responsibility and ability to evaluate
21 adverse events at the sites over which they have
22 purview, which I think we've been calling internal
23 sites or local sites throughout the morning.

24 They're in a position to require
25 immediate action to safeguard subjects at their own

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1 sites. For the review of internal adverse events
2 for which the local IRB has purview, the principal
3 investigator is initially responsible for
4 evaluating the impact of the event, describing any
5 necessary steps to preven t or minimize the
6 occurrence of that event in the future, and
7 reporting his or her findings to the local IRB.

8 If the local researcher does not submit
9 complete information to his -- to the IRB, that IRB
10 has the authority to require additional information
11 that will facilitate an assessment of the impact of
12 that event on the safety and welfare of the
13 subjects participating at the local site.

14 In contrast, IRBs have limited knowledge
15 of the principal investigator and the local context
16 for external events or for external sites and
17 events at those external sites.

18 In order to assess external adverse
19 events, the IRB needs complete information about
20 the context of the event, and an analysis of its
21 relevance and importance to the ongoing study.

22 Rather than rece iving numerous free -
23 floating individual external adverse event reports,
24 an IRB should receive an aggregate report with an
25 analysis and conclusion at intervals appropriate to

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1 the level of risk.

2 The role of the IRBs, therefore, should
3 not include the review of individual reports from
4 external sites. The role of IRBs should be limited
5 to fully examining and acting upon local events
6 where the principal investigator has done the
7 initial evaluation, proposed procedures to minimize
8 the risk, and has provided complete information for
9 consideration, allowing the IRB to act in an
10 informed manner.

11 As we have previously suggested and
12 reiterate below, review of data from an external
13 event should be performed in accordance with an
14 appropriate plan involving one or more persons or a
15 study-specific panel such as a data monitoring
16 committee or a data and safety monitoring board
17 established by the protocol sponsor or the
18 investigator.

19 How does that role differ from the
20 current role of IRBs? This approach differs
21 because the focus of the IRBs will switch to
22 ensuring the implementation of an appropriate data
23 safety and monitoring plan at the time of initial
24 review rather than the ongoing review of individual
25 external adverse or unanticipated events.

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1 This approach would improve human subject
2 protections. The role of IRB review of external
3 events should be quite different. The IRB should
4 only receive a review of aggregate analyzed reports
5 of external adverse events and be able to review
6 them in the context of implementin g changes
7 required to protect human subjects enrolled in that
8 research protocol.

9 This would require central review of all
10 events. Currently IRBs are receiving information
11 of limited value in determining how best to protect
12 the rights and welfare of subjects.

13 Multiple reports of the same events are
14 often received with little or no reference on the
15 implementation and therapies that were associated
16 with the event.

17 Reports are submitted that do not clearly
18 define how the investigational agent was
19 administered, what concomitant therapies were
20 administered, whether the participant was receiving
21 a placebo, whether underlying conditions were
22 present, and a variety of other pieces of
23 information that must be available for an IRB to
24 make an informed analysis.

25 Should IRB responsibilities for multi -

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1 site trials differ from those for single site
2 trials? Yes. A summary of the multi -site clinical
3 trials adverse unanticipated events should be
4 prepared by a centralized group with the scientific
5 expertise and the charge to evaluate all
6 information regarding reported events.

7 Issues such as stopping a study, changing
8 a procedure, eliminating an agent, or providing
9 additional information to subjects, should be the
10 responsibility of this review group in
11 collaboration with the sponsor investigator.

12 The FDA and local IRBs should receive the
13 aggregate report with guidance on how to apply that
14 information to their local populations. The role
15 of IRB should be to evaluate the impact of
16 aggregate information provided to them , apply that
17 information to the local populations, and take
18 whatever actions are deemed necessary.

19 What types of adverse events should an
20 IRB receive information about and what types of
21 information need not be provided to IRBs? The
22 reason IRBs exist is for the protection of research
23 subjects, particularly those at the local research
24 site.

25 Therefore, the IRB should be primarily

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1 concerned with, and only receive reports of
2 individual adverse events that occur at the
3 institution for which the IRB is the IR B of record,
4 and then only when the event meets one or more of
5 the following conditions.

6 The event is serious and unanticipated.
7 The event indicates an increase in the potential
8 risk to subjects. The event requires revision of
9 the protocol consent docu ments or the
10 investigator's brochure.

11 The IRB should be provided with external
12 reports such as those produced by a data and safety
13 monitoring board or from a sponsor's medical
14 monitor.

15 In addition, the IRB should receive only
16 those adverse event report s from non -local sites
17 when the report indicates a revision of the
18 protocol consent documents or the investigator's
19 brochure, or when the report identifies
20 unanticipated problems that may affect subjects
21 enrolled at the local site.

22 All reports of adverse events should be
23 accompanied by an analysis that describes the
24 nature of the events and the presumed reason why it
25 occurred, a review of actions taken as a result of

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1 the event and recommendations for actions, if any
2 that are necessary as a result of the event.

3 In all cases, the IRBs should have the
4 authority to require additional information and/or
5 analysis of the reports. Are there circumstances
6 under which the IRBs should receive information
7 about adverse events that are both -- not both
8 serious and unexpected?

9 That information should be provided at
10 the time of continuum review for each protocol. It
11 should be provided in aggregate form with an
12 appropriate -- with appropriate numerators and
13 denominators so that the IRB can make an informed
14 determination about whether the protocol consent
15 process or investigator's brochure should be
16 modified.

17 In a multi -center study, should the
18 criteria for reporting differ depending on whether
19 the events occur at the site or another site? Yes,
20 the criteria for reporting adverse events to an IRB
21 should differ depending on whether the event occurs
22 at the IRB site or at an external site.

23 When a study has multiple sites, the
24 process for reporting and review of adverse events
25 should include central reporting of all ev ents to

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1 the sponsor.

2 The reports should undergo analysis by an
3 appropriately established committee. An aggregated
4 summary report of that analysis should be sent to
5 all reviewing IRBs.

6 Local events that meet the criteria
7 presented above should still be reported to the
8 local IRBs so that they may -- the IRB may take
9 necessary action at the local level.

10 What can be done to provide IRBs adverse
11 event information that will enable IRBs to better
12 assess the implications of reported events? The
13 current system of submitting all AEs from all sites
14 to all investigators and the respective IRBs is
15 inefficient and inundates investigators and IRBs.

16 These reports currently undergo redundant
17 reviews by multiple IRBs, often without sufficient
18 data or the expertise of a data monitoring
19 committee.

20 ARENA proposes that all multi-center
21 clinical trials have an appropriate data and safety
22 monitoring plan and that IRBs receive only relevant
23 data that will enhance the protection of research
24 subjects.

25 The ideal plan would establish a

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1 committee comprised of experts in the disease or
2 condition under investigation. Such a committee
3 would be responsible for a review of any serious
4 unanticipated problems in any adverse events or any
5 anticipated adverse events that exceed the severity
6 or magnitude expected in the targeted research
7 population.

8 A DMC's analysis might determine that an
9 AE requires prompt notification to all
10 participating investigators. This might be due to
11 increased risk or new information that may impact
12 subjects' present or future health.

13 The DMC would also provide guidance
14 regarding the recommended actions that should be
15 taken by the investigator. These recommendations
16 should include specific language that describes the
17 adverse event in clear and non-technical terms,
18 modification of the protocol, treatment, or
19 procedures within a designated timeframe, guidance
20 for the revision of consent documents for currently
21 enrolled and future study subjects, notification of
22 those who have completed the study treatment of the
23 new risks and, of course, notification of the IRB.

24 We propose that aggregate AE data
25 regarding events that DMC's determined do not

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1 increase the risk to subjects be made available to
2 investigators as part of an annual program report.

3 This report should comprise a summary of
4 the DMC general assessment and recommendations
5 relevant to continuing the study. Finally, we
6 propose that investigators receive only serious,
7 unanticipated, and reasonably related AE reports
8 that the DMC concludes are needed to protect
9 clinical trial subjects.

10 Under this system, PIs would have the
11 information needed to take immediate action to
12 protect research subjects. This focused
13 notification of only meaningful AEs would be more
14 efficient and effective than the system currently
15 in place because it would eliminate redundant
16 review of AEs by multiple IRBs and would better
17 protect research subjects in clinical trials.

18 Who should provide reports? The DMC
19 should provide the adverse event reports to the PI.
20 And the PI should provide them to the IRB. Should
21 the approach to providing adverse event reports be
22 the same for drugs and devices?

23 Yes, the approach to adverse event
24 reports for drugs and devices should be identical.

25 Thank you again, on behalf of ARENA for the

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1 opportunity to share these comments.

2 PRESIDING OFFICER WOODCOCK: Thank you
3 very much. Are there questions on this
4 presentation from the panel? Yes?

5 MEMBER ROHAN: You discuss the use of a
6 centralized group to review information from multi -
7 site trials. And it seems like there might be some
8 overlap between the roles or responsibilities, or
9 even actions of an individual IRB which might be
10 doing the same sort of thing.

11 How would you coordinate or distinguish?
12 Perhaps one IRB would make a decision based on
13 their local information and/or data in conjunction
14 with the overall aggregate data they have.

15 They may make a decision. Would that
16 thing go up to the centralized group and then be
17 communicated to the other IRBs? How would you
18 envision that happening?

19 MR. BORASKY: I think the way we envision
20 that happening would be that -- sort of one of the
21 underlying themes that we had was that the IRB is
22 primarily responsible for the subjects at its site.

23 And, any events that occurred at the
24 local site that implied a need for immediate action
25 shouldn't wait to go to a central review committee

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1 and come back so that they would be able to take
2 immediate action for participant safety.

3 But that wouldn't eliminate the need to
4 also send it to the central IRB. So, I take your
5 point that there's the potential for sort of --
6 either two groups working in parallel or coming to
7 conflicting conclusions.

8 But, our overriding concern was that the
9 IRBs be able to exercise what they thought were
10 appropriate measures at the site and , you know,
11 with the understanding that information that went
12 to the central review board and came back may
13 further inform them as the study continues forward.

14 MEMBER ROHAN: I guess I was just
15 thinking in the case that a particular IRB made a
16 decision to stop the study, change the consent,
17 change the procedures, how then would other IRBs --
18 they might not even know.

19 They might know the same data, but not
20 the detail of that local IRB. How would they be
21 informed? Or what if they came to a different --
22 how would you see that?

23 MR. BORASKY: It's a good question. I
24 think it would be hard to construct a system where
25 one IRB would somehow know to report its

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1 information to all of the other reviewing IRBs for
2 a particular study.

3 Often they don't know who the other
4 reviewing IRBs are necessarily. Given that, I
5 think that that is where the centralized review of
6 the information comes into play because, even if an
7 IRB is acting independently at the local level,
8 presumably the information is still going to the
9 central committee that would still be charged with
10 making recommendations as to what to do with that
11 information.

12 In the mean time, tying the IRBs' hands I
13 think would be unwise and probably resisted by IRBs
14 to some extent. And I think that would -- I do not
15 have a good answer other than that.

16 They would have to be allowed to work
17 independently, but with the assumption that all the
18 other IRBs would hear from the central committee
19 that an event of significance had come up.

20 MEMBER ROHAN: At least the actions that
21 had been taken by other IRBs in the multi -centered
22 studies. I guess I was just concerned because it
23 seemed like the focus is on the adverse events and
24 the agreement data and analyses.

25 But yet, if some IRB decided to take a

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1 particular action, it doesn't seem like there's a
2 lot of focus on if a particular action is now
3 taken, that information should also be communicated
4 to the other IRBs that are involved in that study
5 or for that particular product.

6 MR. BORASKY: Potentially I think it
7 could be clumsy. One of the shortcomings that's
8 already been noted is that, you know, an IRB may
9 receive a safety report from a site that may be
10 using the same drug but in an entirely different
11 context.

12 So, actions taken at the local level may
13 not apply to all sites, even if they're using the
14 same drug or device.

15 PRESIDING OFFICER WOODCOCK: Dr.
16 Goldkind?

17 MEMBER GOLDKIND: I'm just still trying
18 to follow along that discussion about the
19 centralized review group. And, from what I
20 understand you saying, it's in distinction to the
21 sponsor and in distinction to a centralized IRB.

22 It's a review group that's looking at the
23 adverse event reports. How would its
24 responsibility differ from the responsibility of
25 the sponsor in reviewing the adverse event reports?

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1 And how would it be comprised that would
2 give it value added compared to the sponsor?

3 MR. BORASKY: Okay, let me -- first I'll
4 try to re -state my case. But I realized all the
5 jargon that we're using today -- DMCs, data
6 monitoring plans.

7 I think stripping that away, in the
8 comments from ARENA what you have is that every
9 study should have a data safety plan. The
10 mechanism indicated by that plan that would fulfill
11 this need for safety oversight is not limited to
12 simply a data monitoring committee or DSMB.

13 It could be that the sponsor is going to
14 do safety review of data and do that centrally and
15 send it back to IRBs. And I certainly wasn't
16 talking about, you know, a central IRB for a multi -
17 center study, but more of having a monitoring plan
18 that the IRB approves in advance of the study, and
19 that that plan is clear about who it is that's
20 going to see the information and analyze it and how
21 it's going to be communicated back to the IRB in a
22 useable format.

23 MEMBER GOLDKIND: So, other than the
24 scientific experts that you mentioned on that
25 centralized group, who else does ARENA envision

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1 would be on that group to help analyze these
2 adverse event reports?

3 MR. BORASKY: I think in putting together
4 our comments we didn't go to that level of
5 recommendation. It is something we could address
6 in our written comments.

7 We didn't go to that level of detail in
8 our preparing of these comments.

9 PRESIDING OFFICER WOODCOCK: Dr. Temple?

10 MEMBER TEMPLE: Just one thing that comes
11 up -- and it may have come up before, but I must
12 say I didn't notice it. If the local IRB, because
13 it's on site and can ask pertinent questions, has a
14 special responsibility for evaluating the events
15 that happen there, one question you can ask is how
16 that evaluation gets back to anybody.

17 Or do they just make a decision locally?
18 I don't think that's really been very well
19 addressed. Maybe it's something the investigator
20 is supposed to forward to the sponsor and comes
21 under the generating of evaluating the adverse
22 event further.

23 Maybe. But I don't think we've actually
24 thought of it that way one way or the other. But,
25 you would think that needs to get to somebody, I

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