Dear John -

I have reviewed the minutes you sent me on 12/19/2007 and am responding in time for the deadline below.

I have several comments about these minutes. I have included them in the attached document using the MS Word comments feature. The details are attached, but can be summarized very generally as follows:

1. It was my understanding that there were no minutes or transcripts of this meeting.
2. There are some statements in the minutes that do not fit my recollection.
3. Some parts of the minutes do not accurately reflect the divergence of opinions expressed at the meeting.
4. Some parts of the minutes do not accurately reflect the details of the deliberations.
5. The overall tone of the minutes makes it seem as if the conclusions represented strong, unanimous, scientific recommendations of the panel, when they really were opinions with varying degrees of enthusiasm from individual panel members, varying degrees of scientific justification, and varying degrees of consensus.

Thank you -

Jim Stein

James H. Stein, M.D.
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>>> "Strony, John" <john.strony@spcorp.com> 12/19/2007 1:59 PM >>>

Here you go.
-----Original Message-----
From: Strony, John
Sent: Wednesday, December 19, 2007 10:53 AM
To: 'jhs@medicine.wisc.edu'
Subject: Experts Panel Minutes
Jim,
Enclosed please find the minutes to the Experts Panel held on November 16 , 2007. Please review and comment by Friday December 21 at noon. If you approve without any change then there will be no need to reply.
Many thanks
John

<<Minutes of proceedings Experts Panel Top Line 20071214 V9.doc>>

ENHANCE Experts Panel Meeting Notes
November 16, 2007

Executive Summary

On August 20, 2007 MSP presented to John Kastelein, M.D., Ph.D. an overview of the findings from the blinded image data base that resides in the Core Echo Laboratories of the Academic Medical Center of Amsterdam, Netherlands. It was concluded from that meeting that there existed a degree of biologically implausible IMT data values that may affect the credibility of the image database. As a result of these findings and by mutual agreement with the Principal Investigator, the Sponsor convened an Independent Expert Panel to discuss the design and management of the protocol, image recording procedures, and data acquisition of the ENHANCE trial and to seek the best path forward with respect to the study-related issues.

The Panel consisted of:

J. Robin Crouse, M.D., Wake Forest University
James Stein, M.D., University of Wisconsin
Michiel Bots, Ph.D., University of Utrecht
Greg Evans, M.S., Wake Forest University
David Orloff, M.D., Med Pace

Other attendees from Merck and Schering-Plough were:

Enrico Veltri, M.D.
John Irvin, M.D.
Tom Musliner, M.D.
Scott Korn, M.D.
Michael Perelman, M.D.
John Strony, M.D.
Andrew Tershakovec, M.D.
Ram Suresh, Ph.D.
Bo Yang, Ph.D.
Michael Stepanavage, Ph.D.
Colin Goddard

The Panel had available to them all materials presented to and reviewed by the Principal Investigator, Professor Kastelein. These materials are attached. Additionally the Panel members were granted unrestricted access to the blinded image data base and were provided statistical services for the purpose of performing blinded analyses of their choosing of the image data base. Any individual analysis requested by a Panel member was shared with all members of the Panel.

The Panel concluded that:

- ENHANCE (single frame) imaging and reading methodologies are suboptimal relative to currently employed methodologies. However the image data and analyses are reportable.

Comment [JS1]: I believe that this sentence is an overstatement. We had approximately 6 hours to work so the number of images we were able to review was limited. They may have been "available" but they could not be reviewed meaningfully because of time constraints. We reviewed, at most 50-75 images and those only were images that the company chose to show us. I recall that I and Dr. Evans added the qualification that our conclusions were based on the images we saw, and they were not a randomly selected set of images, thus they were potentially biased because they were selected by the company to illustrate certain points. Therefore we can't exclude the possibility that we'd have different conclusions if we saw the rest of the images.

Comment [JS2]: The problem here is that we did not vote on these points and had a divergence of opinions on several of them. We reached consensus on most of them, however the tone of these conclusions makes it seem as these were strong, unanimous, scientific recommendations, rather than opinions with varying degrees of enthusiasm from panel members and varying degrees of scientific justification. Indeed, the conclusions were made by the companies, not by us.

Comment [JS3]: We did not say "relative to currently employed methodologies." That is true, but the imaging and reading protocols in ENHANCE were suboptimal even relative to methodologies employed at the time the study commenced and relative to procedures in clinical and epidemiological studies conducted in the 1990's.

Comment [JS4]: We did not state that the data and analyses "are reportable."

- There exists biologically implausible readings defined as >0.1mm difference between the paried baseline and endpoint readings. Similar findings are present in other studies and have been seen in approximately 12%.
- Despite significant methodologic issues, the re-reading of the ENHANCE images is not recommended.
- The common carotid artery (CCA) provides the most reliable and consistent measurements in IMT studies with the least level of missingness or implausible readings. Therefore the CCA is now commonly considered the most reliable endpoint. Thus the CCA should be elevated to become the primary study endpoint.
- Maintain the analysis of all carotid segments (ICA, BCA, CCA) as a secondary endpoint.
- Femoral IMT analysis should be reported, but publication can be after the carotid IMT analysis.

Comment [JS5]: We not define "biologically implausible reading" this way. This contradicts a statement later in the minutes.

Comment [JS6]: This was an estimate from Dr. Bots that Dr. Evans agreed with. It was not a conclusion of the panel.

Comment [JS7]: This was not a conclusion of the meeting. We stated that in regard to this (ENHANCE's) specific data set, with its imaging and measurement problems, the measurements of the CCA are the most valid of the segmental measurements. In this content, "valid" means most likely to *reflect* the scientific truth – the real measurements of the carotid IMT. We said the company could "consider" making the CCA measurements the primary endpoint.

ENHANCE Experts Panel Meeting Notes
November 16, 2007

Minutes to the Experts Panel Meeting

Background and Formation of Experts Panel

Comment [JSB]: It is my recollection that at the beginning of the meeting, Dr. Strony stated that there would be "no minutes" and "no transcripts" so we would speak freely and not be concerned that our individual remarks would "get back to Dr. Kastelein."

On August 20, 2007 a meeting was held with the principle investigator, John Kastelein, M.D., Ph.D. to discuss the status of image data acquisition and its quality. It was concluded that there existed an unacceptable level of biologically implausible IMT measurements within the data base.

The sponsor and PI agreed to convene an independent expert panel to discuss the status of the image data base especially as it relates to the standards by which current and contemporaneous IMT trials are designed and conducted.

The Panel members nominated by Professor Kastelein and who accepted were:

J. Robin Crouse, M.D. – IMT - Wake Forest University, North Carolina
James Stein, M.D. – IMT - University of Wisconsin, Madison
Michiel Bots, Ph.D. – IMT University of Utrecht, Netherlands
Greg Evans, M.S. – Statistics -Wake Forest University, North Carolina
David Orloff, M.D. – Regulatory - Med Pace, Cincinnati

Professor Kastelein recused himself from the proceedings. Likewise it was recommended that anyone connected with the CEL or study operations be excluded from attending and participating in the panel discussion.

The Panel members were given hard copies of the sonographer and reader training manuals, trial overview, and findings presented to Professor Kastelein. They were also granted unrestricted access to the blinded image data base that currently resides in the Core Echo Laboratories, Academic Medical Center, Amsterdam, Netherlands.

A face-to-face meeting was held November 16, 2007 in Washington, D.C. to discuss the ENHANCE protocol design, data findings and to seek a path forward.

Question and Answer Session

Question #1

Based on your examination of the single frame images of ENHANCE and relative to other IMT trials, what is the overall quality of individual images and what is the uniformity of image acquisition?

The panel noted the presence of design limitations including single-frame imaging without video loop backup, limited sonographer instruction on verifying proper transducer positioning, no ECG gating, and limited instruction on the use of internal landmarks. Overall the panel deemed the quality of images acceptable but below the standard of contemporaneous studies.

The panel also noted that when various segments are compared for acquisition quality and longitudinal segment acquisition, the common carotid segment is most reliable of the three segments.

Question #2

Is the current database clean and credible?

The panel expressed a wide array of opinions, including concerns over unreported and later updated data file segments. Given the limitations of the protocol, the panel also expressed concerns over the IMT community accepting the bifurcation and internal carotid data. The panel was unanimous in concluding that the common carotid segment was the cleanest and most interpretable. The panel agreed to the fact that the CCA is a more reliable marker of disease as opposed to the internal and bifurcation, which are less reliable due to the difficulty in acquiring these data. They stated that these findings provide a rationale for restructuring the protocol endpoints to that of the common carotid segment at the conclusion of the study but prior to unblinding without raising integrity questions.

Question #3

Is there a standard upon which outlier IMT measurements are defined?

A) What are some outlier definitions used?

Comment [JS9]: Lack of application of standardized instrumentation settings

Comment [JS10]: I also expressed concern about the lack of reading standards or at least their inconsistent application.

Comment [JS11]: I do not agree with this. I stated that the image quality was not acceptable. It was below that of contemporaneous studies as well as older studies, as I stated above.

Comment [JS12]: Missing here is the long discussion we had – and the differences of opinions expressed – about whether or not the variability in measurements was similar to that seen in other studies. In aggregate, the progression rates and variability, as well as much of the missingness data – were similar to other studies. But when we looked at images and considered the CIMT values of individual subjects over time, almost all the examples we saw showed measurement errors, biologically implausible measurements, biologically implausible changes in CIMT measurements, and/or failure to adhere to the protocol. It was expressed by Dr. Bots that much of the concern we had would not affect the outcome because they would be randomly distributed between arms. Great concern was expressed that the aggregate values may look reasonable, but that they may not reflect reality. I recall this concern was expressed quite forcefully by myself, Dr. Strony, and the statistician who presented the data, and that Dr. Evans concurred. I recall stating that "this is not a numbers game – it is science, and what we measure must reflect reality, not just work out mathematically" and tha ... [1]

Comment [JS13]: Also missing is the very important discussion we had about the statistician's presentation of the data showing that the SD of the change in CIMT was much smaller than initially expected, thus increasing the chances that that a difference between the groups could be found by chance alone. No conclusion was made after that di ... [2]

Comment [JS14]: The concerns about unreported and later updated file segments were serious. I recall that I and other panel member specifically stated that we could not determine if the database was "clean and credible" based on the information presented.

Comment [JS15]: "probably" is ... We did not state this with certainty because of the issues about data management. Here, our statements about the CCA are out of context. They had to do with imaging and measurement, not data handling.

B) Based on previously conducted IMT studies what percentage of evaluable readings are anticipated?

The panel stated that there is no established standard for identifying IMT outliers. However, it is reasonable to use 2.5-3.0 standard deviations as a threshold. The panel also stated that the study team should evaluate the data by looking at all images to confirm that the images were acquired appropriately and measurement made correctly.

Comment [JS16]: I don't recall this being a conclusion. It is reasonable, but not something we stated. It also contradicts the statement earlier in the minutes about biologically implausible data.

Question #4

With regards to missing data, what is the percentage of images that were disqualified and not replaced from other completed IMT trials?

A) What percentage of patients were impacted by the missingness?

The Panel varied in their opinion on the presence, extent, and impact of missingness on the study. They noted that other trials experience missingness in the range of 4-10% and involves <15% of patients. (ENHANCE had 86% of patients experiencing missingness). Additionally, the bifurcation and internal carotid segments should account for the bulk of missingness. The Panel again reiterated that the study should focus on CCA data, since it is easy to acquire and measure and given the limitations of the protocol the CCA images should have the most complete and reliable data base.

Question #5

Is there a methodology that has been successfully used to identify and address biologically implausible readings?

The Panel agreed that both biologically impausible readings and missing data were bad for the trial. However, they were split as to which was worse. There was no one appropriate direction identified. Suggested remedies presented by the Panel included:

- Reread all data supplemented by a built in adjudication process
- Re-read or outrightly discard any measure that differed by more than 1.5mm from the mean
- Adjudicate each image set including those images comprising the missing cohort
- Do nothing as any adjudication or censuring would potentially increase the missingness to an unacceptable level.

Comment [JS17]: I do not recall this as a suggested remedy.

Question #6

Can this data be cleaned with the current process?

Question not Discussed

Question #7

What is the path forward?
Given that the sponsor is obligated to and will report on the study to the scientific/medical community, what is the path forward?
Extreme choices are:

a. Accept the data as is.
b. Install a new reading and analysis process proactively. Execute and accept risk that the data will not get any better.

The Panel opinions ranged from:

-ENHANCE is a study whose image recording and data acquisition are methodologically limiting and thus the results are meaningless

to

- assess "maximum likelihood analysis" with image re-evaluation and re-reading

to

- there is merit to leaving the data as is; the data are credible and not substantially out of line with earlier IMT studies.

The Panel was unanimous in their opinion to elevate the common carotid to the primary endpoint, especially if missingness in the CCA is 8% or less. (Post meeting note: CCA missingness is approximately 3% in ENHANCE) The Panel agreed that changing the primary endpoint to focus on the CCA is acceptable and doable without bias. The rationale for making the switch is analogous to applying the best available "assay" to answer the question at hand.

Comment [JS18]: This really overstates our recommendation. We did not vote on this. You asked each of us our opinions, the strength of which varied from complete comfort to a lukewarm feeling that it was "reasonable." The tone here implies that we strongly recommended this when in reality, we just advised you on what the scientifically valid approaches would be. It was the decision of the company to change the endpoint.

Comment [JS19]: I do not recall us making this specific statement. I recall us discussing expected rates of missingness.

Additional questions:

Femoral IMT results: *How important* are they? *Is it critical to report the results together with the CIMT results?*

The Panel stated that the femoral IMT data are not crucial to the initial presentation and publication of the results. Such results can be acceptably published at a later date. Efforts should be focused on the carotids.

Re-reading all study images: *If the sponsor decides to do a re-read of the entire image database, including all 6 carotid segments per time-point for all time points and subjects, how long would you estimate this would take in your laboratory?*

The Panel stated that any re-read should be limited to the common carotid segment as that segment is most reliable and clinically appropriate. It would take an estimated 12 months to re-read the CCA.

Comment [JS20]: Again, "most reliable" in the context of this limitations of the study. "Clinically appropriate" was not discussed or stated.

Page 4: [1] Comment [JS12] **James Stein** **12/21/2007 11:43:00 AM**

Missing here is the long discussion we had – and the differences of opinions expressed – about whether or not the variability in measurements was similar to that seen in other studies. In aggregate, the progression rates and variability, as well as much of the missingness data – were similar to other studies. But when we looked at images and considered the CIMT values of individual subjects over time, almost all the examples we saw showed measurement errors, biologically implausible measurements, biologically implausible changes in CIMT measurements, and/or failure to adhere to the protocol. It was expressed by Dr. Bots that much of the concern we had would not affect the outcome because they would be randomly distributed between arms. Great concern was expressed that the aggregate values may look reasonable, but that they may not reflect reality. I recall this concern was expressed quite forcefully by myself, Dr. Strony, and the statistician who presented the data, and that Dr. Evans concurred. I recall stating that "this is not a numbers game – it is science, and what we measure must reflect reality, not just work out mathematically" and that several people agreed with this sentiment.

Page 4: [2] Comment [JS13] **James Stein** **12/21/2007 11:44:00 AM**

Also missing is the very important discussion we had about the statistician's presentation of the data showing that the SD of the change in CIMT was much smaller than initially expected, thus increasing the chances that that a difference between the groups could be found by chance alone. No conclusion was made after that discussion, but serious concerns were expressed by the panel.

From: James Stein [jhs@medicine.wisc.edu]
Sent: Thursday, January 03, 2008 5:59 PM
To: Strony, John
Cc: Stephen DiTullio
Subject: Re: ENHANCE IMT Experts Meeting - comments on revised set of"minutes" (with attachment)
Importance: High
Attachments: JStein comments 01032008 on Minutes of proceedings Experts Panel Top Line 20080103 V13 DO RC MB GE JS.doc

Dear John -

Attached are my comments to the revised minutes from the ENHANCE IMT expert meeting in November and my suggested edits. I have used MS Word's commenting feature and track changes feature to make my points.

The details are attached, but can be summarized, in general, as follows:

1. Since there was no audio or written transcription of the meeting, I still have a hard time calling this document "minutes." They really represent a recollection of what happened. As such, they at best are an incomplete summary of what transpired at the meeting.

2. Although this version is an improvement over the 12-21-07 document that I previously commented on, several of the comments I made on the 12-21-2007 version were not incorporated into this draft.

Given these considerations, I cannot "OK" or "approve" this document.

Thank you -

Jim

James H. Stein, M.D.
Division of Cardiovascular Medicine
G7/341 CSC
600 Highland Avenue, MC 3248
Madison, Wisconsin 53792
Phone: (608) 263-9648 FAX: (608) 263-0405
http://www.cvrc.wisc.edu/airp
http://www.uwhealth.org/heartandvascular

>>> "Strony, John" <john.strony@spcorp.com> 1/3/2008 9:26 AM >>>

Jim,

Enclosed are the revised minutes incorporating everyone's comments. Please review. If OK let me know by 4 PM EST Friday.

Several panelists have expressed concerns over the presence of minutes when we had informed everyone that no transcripts would be recorded. The minutes are intended to accurately reflect and summarize in a collective fashion what was discussed by the members while maintaining confidentiality of the individual and his remarks. These minutes are intended for the FDA and are not subject to public access.

ENHANCE Experts Panel Meeting Notes
November 16, 2007

Executive Summary

On August 20, 2007 MSP presented to John Kastelein, M.D., Ph.D. an overview of the findings from the blinded image data base that resides in the Core Echo Laboratories of the Academic Medical Center of Amsterdam, Netherlands. It was concluded from that meeting that there existed a degree of biologically implausible IMT data values that may affect the credibility of the image database. As a result of these findings and by mutual agreement with the Principal Investigator, the Sponsor convened an Independent Expert Panel to discuss the design and management of the protocol, image recording procedures, and data acquisition of the ENHANCE trial and to seek the best path forward with respect to the study-related issues.

The Panel consisted of:

J. Robin Crouse, M.D., Wake Forest University
James Stein, M.D., University of Wisconsin
Michiel Bots, M.D., Ph.D., University of Utrecht
Greg Evans, M.S., Wake Forest University
David Orloff, M.D., Medpace, Inc., Cincinnati

Other attendees from Merck and Schering-Plough were:

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Michael Stepanavage, Ph.D.
Colin Goddard

The Panel had available to them all materials presented to and reviewed by the Principal Investigator, Professor Kastelein. These materials are attached. Additionally the Panel members were granted unrestricted access to the blinded image data base and were provided statistical services for the purpose of performing blinded analyses of their choosing of the image data base. Any individual analysis requested by a Panel member was shared with all members of the Panel.

The Panel provided the following advice:

- ENHANCE (single frame) imaging and reading methodologies are suboptimal relative to currently employed methodologies. However the image data and analyses are

Comment [JS1]: I suggest a footnote stating that the minutes are not transcripts of the proceedings of the meeting, but instead represent a summary constructed afterwards. They are at best an incomplete summary of what transpired at the meeting and the key points we addressed.

Comment [JS2]: It is my recollection that there also were concerns about data management, such as the existence of data files with measurements that either were not entered into the official measurement database or that reflected more "recent" measurements than those in the measurement database. A statement should be inserted here that reflects concerns about the integrity of the data was part of the reason for convening the expert panel. As written, it seems like we were convened only to discuss the biological plausibility of the data findings.

Comment [JS3]: Same concern as stated in my 12/21/2007: "I believe that this sentence is an overstatement. We had approximately 6 hours to work so the number of images we were able to review was limited. They may have been "available" but they could not be reviewed meaningfully because of time constraints. We reviewed, at most 50-75 images and those only were images that the company chose to show us. I recall that I and Dr. Evans added the qualification that our conclusions were based on the images we saw, and they were not a randomly selected set of images, thus they were potentially biased because they were selected by the company to illustrate certain points. Therefore we can't exclude the possibility that we'd have different conclusions if we saw the rest of the images." This will need to be qualified to reflect the above, either here or elsewhere in the minutes.

Comment [JS4]: Same concern as stated in my 12/21/2007 comments: "We did not say "relative to currently employed methodologies." That is true, but the imaging and reading protocols in ENHANCE were suboptimal even relative to methodologies employed at the time the study commenced and relative to procedures in clinical and epidemiological studies conducted in the 1990's." It would be more appropriate to say "suboptimal for achieving the study's prespecified objectives."

reportable~~,~~ ~~although some~~The panelists had widely varying degrees of concern about the quality of the image data.

- There exists biologically implausible readings defined as >0.1mm difference between the paired baseline and endpoint readings. Similar findings are present in other studies, and it was estimated to have been seen in ~~approximately 12~~approximately 12%.
- Despite significant methodologic issues, the re-reading of the ENHANCE images is not recommended, since the assumption is that re-reading will not get rid of the biologically implausible data because these values are mostly a consequence of problems in the ultrasound images.
- The common carotid artery (CCA) provided the most reliable and consistent measurements in ENHANCE with the least level of missingness or implausible readings. Therefore the results based on CCA should be more robust to the sub-optimal image acquisition and reading methodology employed in this trial and are expected to give the most valid (i.e., reflecting the truth) results from the trial. Thus, the sponsor should consider changing the primary study endpoint to measurements of the CCA ~~should considered by the Sponsor as the primary study endpoint.~~
- If the sponsor changes the primary endpoint, they should m~~M~~aintain the analysis of all carotid segments (ICA, Carotid Bifurcation, CCA) as ~~a~~ secondary endpoints.
- Femoral IMT ~~has not been related to~~ is not as strongly predictive of~~the~~ incident ~~of~~ cardiovascular events and has less external validity than Carotid IMT. As it is not a valid alternative for cardiovascular events, the publication of the Carotid ~~IMT should~~IMT should not be delayed pending cleaning of the Femoral IMT data. Femoral IMT analysis should be reported, but publication can be after the carotid IMT analysis.

Comment [JS5]: Same concern as stated in my 12/21/2007 comments: "We did not state that the data and analyses "are reportable.""

Comment [JS6]: Same concern as stated in my 12/21/2007 comments. "We not define "biologically implausible reading" this way." This contradicts the statement on page 5, line 16, and it should be removed.

Comment [JS7]: Same concern as stated in my 12/21/2007 comments: "This was an estimate from Dr. Bots that Dr. Evans agreed with. It was not a conclusion of the panel."

ENHANCE Experts Panel Meeting Notes
November 16, 2007

Minutes to the Experts Panel Meeting

Comment [JS8]: As stated above, I suggest a footnote stating that the minutes are not transcripts of the proceedings of the meeting, but instead represent a summary constructed afterwards. They are at best an incomplete summary of what transpired at the meeting and the key points we addressed.

Background and Formation of Experts Panel

On August 20, 2007 a meeting was held with the principle investigator, John Kastelein, M.D., Ph.D. to discuss the status of image data acquisition and its quality. It was concluded that there existed an unacceptable level of biologically implausible IMT measurements within the data base.

The sponsor and PI agreed to convene an independent expert panel to discuss the status of the image data base especially as it relates to the standards by which current and contemporaneous IMT trials are designed and conducted.

The Panel members nominated by Professor Kastelein and who accepted were:

J. Robin Crouse, M.D. – IMT - Wake Forest University, North Carolina
James Stein, M.D. – IMT - University of Wisconsin, Madison
Michiel Bots, M.D., Ph.D. – IMT-University of Utrecht, Netherlands
Greg Evans, M.S. – IMT ~~and Statistics~~and Statistics -Wake Forest University, North Carolina
David Orloff, M.D. – Regulatory - Med Pace, Cincinnati

Professor Kastelein recused himself from the proceedings. Likewise it was recommended that anyone connected with the CEL or study operations be excluded from attending and participating in the panel discussion.

The Panel members were given hard copies of the sonographer and reader training manuals, trial overview, and findings presented to Professor Kastelein. They were also granted unrestricted access to the blinded image data base that currently resides in the Core Echo Laboratories, Academic Medical Center, Amsterdam, Netherlands.

A face-to-face meeting was held November 16, 2007 in Washington, D.C. to discuss the ENHANCE protocol design, data findings and to seek a path forward.

Question and Answer Session

Question #1

Based on your examination of the single frame images of ENHANCE and relative to other IMT trials, what is the overall quality of individual images and what is the uniformity of image acquisition?

The panel noted the presence of design limitations including single-frame imaging without video loop backup, limited sonographer instruction on verifying proper transducer positioning, no ECG gating, and limited instruction on the use of internal landmarks. Overall the panel deemed the quality of images acceptable but below the standard of contemporaneous studies, although some panelists had varying degrees of ~~concern~~of concern ~~about the~~about the quality of the image data. The key parameters usually reported in CIMT trials, such as reproducibility, aggregated information on completeness of data, baseline CIMT values, standard deviations of progression rates, progression estimates seem comparable to other studies.

The panel also noted that when various segments are compared for acquisition quality and longitudinal segment acquisition, the common carotid segment appeared to be the most reliable of the three segments in ENHANCE. And thus, the analyses based on the CCA IMT measurements will reflect most likely the truth (i.e., give valid results). Results based on the mean max CIMT have a high probability of being spurious because of the high rate of missing values in the calculation of mean max progression rates.

Comment [JS9]: As noted in my 12/21/2007 comments: "Lack of application of standardized instrumentation settings" and "concern about the lack of reading standards or at least their inconsistent application."

Comment [JS10]: As noted in my 12/21/2007 comments: "I do not agree with this. I stated that the image quality was not acceptable. It was below that of contemporaneous studies as well as older studies, as I stated above." The statement that "some panelists had varying degrees of concern about the quality of the image data" does not, in my opinion, accurately reflect the divergence of opinions.

Comment [JS11]: As noted in my 12/21/2007 comments: "Missing here is the long discussion we had – and the differences of opinions expressed – about whether or not the variability in measurements was similar to that seen in other studies. In aggregate, the progression rates and variability, as well as much of the missingness data – were similar to other studies. But when we looked at images and considered the CIMT values of individual subjects over time, almost all the examples we saw showed measurement errors, biologically implausible measurements, biologically implausible changes in CIMT measurements, and/or failure to adhere to the protocol. It was expressed by Dr. Bots that much of the concern we had would not affect the outcome because they would be randomly distributed between arms. Great concern was expressed that the aggregate values may look reasonable, but that they may not reflect reality. I recall this concern was expressed quite forcefully by myself, Dr. Strony, and the statistician who presented the data, and that Dr. Evans concurred. I recall stating that "this is not a numbers game – it is science, and what we measure must reflect reality, not just work out mathematically" and that several people agreed with this sentiment."

Question #2

Is the current database clean and credible?

The panel expressed a wide array of opinions, including serious concerns over unreported and later updated data file segments. Given the limitations of the protocol, the panel also expressed concerns over the IMT community accepting the bifurcation and internal carotid data. The panel was unanimous in concluding that the common carotid segment data would likely be the cleanest and most interpretable. The panel agreed to the fact that the CCA is a more reliable marker of disease in the ENHANCE study as opposed to the internal and bifurcation, which are less reliable due to the difficulty in acquiring these data. Thus, results based on the CCA measurements are more likely to be valid than the composite mean max IMT values or those of other segments. In addition, there are several other lipid lowering trials on CIMT progression that have used common CIMT as primary outcome, a change towards ~~CCA - CCA.~~ The panel stated that these findings provide a rationale for restructuring the protocol

endpoints to that of the common carotid segment at the conclusion of the study but prior to unblinding without compromising the integrity of the trial.

There also was discussion about the data showing that the standard deviation of the change in CIMT was much smaller than initially expected, thus increasing the chances that a difference between the groups could be found by chance alone. No conclusion was made after that discussion, but serious concerns were expressed by some members of the panel.

Question #3

Is there a standard upon which outlier IMT measurements are defined?

A) What are some outlier definitions used?

B) Based on previously conducted IMT studies what percentage of evaluable readings are anticipated?

The panel stated that there is no established standard for identifying IMT outliers. The panel also stated that the study team should evaluate the data by looking at all images to confirm that the images were acquired appropriately and measurement made correctly.

Comment [JS12]: This contradicts the statement on page 2, lines 4-6 (second bullet -- that bullet should be removed)

Question #4

With regards to missing data, what is the percentage of images that were disqualified and not replaced from other completed IMT trials?

A) What percentage of patients were impacted by the missingness?

The Panel varied in their opinion on the presence, extent, and impact of missingness on the study. They noted that other trials experience missingness in the range of 4-10% ~~and~~% and involves <15% of patients. (ENHANCE had 86% of patients experiencing missingness). Additionally, the bifurcation and internal carotid segments ~~should~~ likely accounted for the bulk of missingness. This observation supported the~~The~~ Panel's ~~again reiterated that the study~~ suggestion that the sponsor and study team consider changing the primary endpoint to~~should~~ focus on CCA data, since ~~it is easy to acquire and measure and~~, given the limitations of the protocol the CCA images should have the most complete and reliable data base.

Question #5

Is there a methodology that has been successfully used to identify and address biologically implausible readings?

The Panel agreed that both biologically implausible readings and missing data were unfavorable and serious limitations to the overall interpretation of the trial results. However, they were split as to which was worse. There was no one appropriate direction identified. Suggested remedies discussed by the Panel included:

- Reread all data supplemented by a built in adjudication process
- Re-read or outrightly discard any measure that differed by more than 1.5mm from the mean
- Adjudicate each image set including those images comprising the missing cohort
- Do nothing as any adjudication or censuring would potentially increase the missingness to an unacceptable level.

Comment [JS13]: As stated in my 12-21-2007 comments, "I do not recall this as a suggested remedy."

Question #6

Can this data be cleaned with the current process?

Question not Discussed

Question #7

What is the path forward?
Given that the sponsor is obligated to and will report on the study to the scientific/medical community, what is the path forward?
Extreme choices are:

~~a. Accept~~a. Accept the data as is.
b. Install a new reading and analysis process proactively. Execute and accept risk that the data will not get any better.

The Panel opinions ranged from:

-ENHANCE is a study whose image recording and data acquisition ~~are methodologically~~are methodologically limiting and thus the results are meaningless

to

- assess "maximum likelihood analysis" with image re-evaluation and re-reading

to

- there is merit to leaving the data as is; the data are credible and not substantially out of line with earlier IMT studies.

The Panel was unanimous in their opinion that it was ~~appropriate~~ reasonable to elevate the common carotid to the primary endpoint, especially if missingness in the CCA is

Comment [JS14]: As stated in my 12-21-2007 comments, "This really overstates our recommendation. We did not vote on this. You asked each of us our opinions, the strength of which varied from complete comfort to a lukewarm feeling that it was "reasonable." The tone here implies that we strongly recommended this when in reality, we just advised you on what the scientifically valid approaches would be. It was the decision of the company to change the endpoint."

less than other segments. (Post meeting note: CCA missingness is approximately 3% in ENHANCE) The Panel agreed that changing the primary endpoint to focus on the CCA prior to breaking the blind is ~~acceptable~~ reasonable and doable without bias. The rationale for making the switch is analogous to applying the best available "assay" to answer the question at hand.

Comment [JS15]: As stated in my 12-21-2007 comments, "I do not recall us making this specific statement. I recall us discussing expected rates of missingness." I do, however, think this is reasonable.

Additional questions:

Femoral IMT results: *How important* are they? *Is it critical to report the results together with the CIMT results?*

The Panel stated that the Femoral IMT is not at present regarded as a valid alternative to Carotid IMT for prediction of cardiovascular events ~~as compared to Carotid IMT~~. Thus Femoral IMT data are not crucial to the initial presentation and publication of the results. While the ideal would be to present both carotid and femoral results simultaneously, it is more important to release the carotid results when they become available. The femoral results can be acceptably published at a later date. Efforts should be focused on the carotids.

Re-reading all study images: *If the sponsor decides to do a re-read of the entire image database, including all 6 carotid segments per time-point for all time points and subjects, how long would you estimate this would take in your laboratory?*

The Panel stated that any re-read should be limited to the common carotid segment as that segment ~~was~~ should be the most reliable in ENHANCE. It would take an estimated 12 months to re-read the CCA.

ENHANCE Experts Panel Meeting Summary
November 16, 2007

Executive Summary

On August 20, 2007 MSP presented to John Kastelein, M.D., Ph.D. an overview of the findings from the blinded image data base that resides in the Core Echo Laboratories of the Academic Medical Center of Amsterdam, Netherlands. Concerns were expressed during that meeting that there existed a degree of biologically implausible IMT data values that may affect the credibility of the image database. There also were concerns about the data base integrity. As a result of those concerns and by mutual agreement with the Principal Investigator, the Sponsor convened an Independent Expert Panel to discuss the design and management of the protocol, data management, image recording procedures, and data acquisition of the ENHANCE trial and to seek the best path forward with respect to the study-related issues.

The Panel consisted of:

John Robert Crouse, M.D., Wake Forest University
James Stein, M.D., University of Wisconsin
Michiel Bots, M.D., Ph.D., University of Utrecht
Greg Evans, M.S., Wake Forest University
David Orloff, M.D., Medpace, Inc., Cincinnati

Other attendees from Merck and Schering-Plough were:

Enrico Veltri, M.D.
John Irvin, M.D.
Tom Musliner, M.D.
Scott Korn, M.D.
Michael Perelman, M.D.
John Strony, M.D.
Andrew Tershakovec, M.D.
Ram Suresh, Ph.D.
Bo Yang, Ph.D.
Michael Stepanavage, Ph.D.
Colin Goddard
Stanley Petrauskas

The Panel had available to them all materials presented to and reviewed by the Principal Investigator, Professor Kastelein. These materials are attached. Additionally the Panel members were granted unrestricted access to the blinded image data base and were provided statistical services for the purpose of performing blinded analyses of their choosing of the image data base. Any individual analysis requested by a Panel member was shared with all members of the Panel. It is recognized that due to the voluminous nature of the data and time constraints for review, all of the images could not be reviewed

and that the panelists may have arrived at different conclusions if all of the images were reviewed.

Although there was no formal vote, the Panel provided the following general advice:

- ENHANCE (single frame) imaging and reading methodologies are suboptimal for achieving the study's prespecified objectives. The panelists had widely varying degrees of concern about the quality of the image data.
- There exists biologically implausible readings which were arbitrarily defined by the Sponsor as >0.1mm difference between the paired baseline and endpoint readings. Similar findings are present in other studies, and it was estimated by some panel members to have been seen in approximately 12%.
- Despite significant methodologic issues, the re-reading of the ENHANCE images is not recommended, since the assumption is that re-reading will not get rid of the biologically implausible data because these values are mostly a consequence of problems in the ultrasound images.
- The common carotid artery (CCA) provided the most reliable and consistent measurements in ENHANCE with the least level of missingness or implausible readings. Therefore the results based on CCA should be more robust to the sub-optimal image acquisition and reading methodology employed in this trial and are expected to give the most valid (i.e., reflecting the truth) results from the trial. Thus, the sponsor should consider changing the primary study endpoint to measurements of the CCA.
- If the sponsor changes the primary endpoint, they should maintain the analysis of all carotid segments (ICA, Carotid Bifurcation, composite) as secondary endpoints.
- Femoral IMT is not as strongly predictive of incident cardiovascular events and has less external validity than Carotid IMT. As it is not a valid alternative for cardiovascular events, the publication of the Carotid IMT should not be delayed pending cleaning of the Femoral IMT data. Femoral IMT analysis should be reported, but publication can be after the carotid IMT analysis.

ENHANCE Experts Panel Meeting Summary
November 16, 2007

Summary of the Experts Panel Meeting[1]

Background and Formation of Experts Panel

On August 20, 2007 a meeting was held with the principal investigator, John Kastelein, M.D., Ph.D. to discuss the status of image data acquisition and its quality. It was concluded that there existed an unacceptable level of biologically implausible IMT measurements within the data base.

The sponsor and PI agreed to convene an independent expert panel to discuss the status of the image data base especially as it relates to the standards by which current and contemporaneous IMT trials are designed and conducted.

The Panel members nominated by Professor Kastelein and who accepted were:

John Robert Crouse, M.D. – IMT - Wake Forest University, North Carolina
James Stein, M.D. – IMT - University of Wisconsin, Madison
Michiel Bots, M.D., Ph.D. – IMT University of Utrecht, Netherlands
Greg Evans, M.S. – IMT and Statistics -Wake Forest University, North Carolina
David Orloff, M.D. – Regulatory - Med Pace, Cincinnati

Professor Kastelein recused himself from the proceedings. Likewise it was recommended that anyone connected with the CEL or study operations be excluded from attending and participating in the panel discussion.

The Panel members were given hard copies of the sonographer and reader training manuals, trial overview, and findings presented to Professor Kastelein. They were also granted unrestricted access to the blinded image data base that currently resides in the Core Echo Laboratories, Academic Medical Center, Amsterdam, Netherlands. It is recognized that due to the voluminous nature of the data and time constraints for review, all of the images could not be reviewed and that the panelists may have arrived at different conclusions if all of the images were reviewed.

A face-to-face meeting was held November 16, 2007 in Washington, D.C. to discuss the ENHANCE protocol design, data findings and to seek a path forward.

[1] This summary of the ENHANCE Experts Panel Meeting is not intended to constitute a transcript of the proceedings of the meeting or otherwise to capture the full details of the discussions.

Question and Answer Session

Question #1

Based on your examination of the single frame images of ENHANCE and relative to other IMT trials, what is the overall quality of individual images and what is the uniformity of image acquisition?

The panel noted the presence of design limitations including single-frame imaging without video loop backup, limited sonographer instruction on verifying proper transducer positioning, no ECG gating, lack of application of standardized instrument settings, lack of consistently applied reading standards, and limited instruction on the use of internal landmarks. The panelists expressed a range of degrees of concern about the quality of the image data.

The panel discussed whether or not the variability in measurements was similar to that seen in other studies. In the aggregate, the progression rates and variability, as well as much of the missingness data, were similar to other studies. However, the examples the panel reviewed of the CIMT values of individual subjects over time showed measurement errors, biologically implausible measurements, biologically implausible changes in CIMT measurements, and/or failure to adhere to the protocol. At least one panel member expressed the view that these issues would not affect the outcome of the study, because they would be randomly distributed between arms. However, other panel members expressed significant concern that although the aggregate values might look reasonable, they might not reflect biological reality, given the problems noted above.

The panel noted that when various segments are compared for acquisition quality and longitudinal segment acquisition, the common carotid segment appeared to be the most reliable of the three segments in ENHANCE. And thus, the analyses based on the CCA IMT measurements would be more likely to reflect the truth (i.e., give valid results). Results based on the mean max CIMT have a higher probability of being spurious because of the high rate of missing values in the calculation of mean max progression rates.

Question #2

Is the current database clean and credible?

The panel expressed a wide array of opinions, including serious concerns over unreported and later updated data file segments, which may reflect a more widespread

problem with data handling. Given the limitations of the imaging protocol, the panel also expressed concerns over the IMT community accepting the bifurcation and internal carotid data. The panel unanimously agreed that the common carotid segment data would likely be the most reliable. The panel agreed to the fact that the CCA is a more reliable marker of disease in the ENHANCE study as opposed to the internal and bifurcation, which are less reliable due to the difficulty in acquiring these data. Thus, results based on the CCA measurements are more likely to be valid than the composite mean max IMT values or those of other segments. In addition, there are several other lipid lowering trials on CIMT progression that have used change in common CIMT as primary outcome. The panel stated that these findings provide a rationale for restructuring the protocol endpoints to that of the common carotid segment at the conclusion of the study but prior to unblinding without compromising the integrity of the trial. If the sponsor changes the primary endpoint, they should maintain the analysis of all carotid segments (ICA, Carotid Bifurcation, composite) as secondary endpoints.

There also was discussion about the data showing that the standard deviation of the change in CIMT was much smaller than initially expected, thus increasing the chances that a difference between the groups could be found by chance alone. No conclusion was made after that discussion, but serious concerns were expressed by some members of the panel that the final results, if statistically significant, still may be spurious

Question #3

Is there a standard upon which outlier IMT measurements are defined?

A) What are some outlier definitions used?

B) Based on previously conducted IMT studies what percentage of evaluable readings are anticipated?

The panel stated that there is no established standard for identifying IMT outliers. The panel also stated that the study team should evaluate the data by looking at all images to confirm that the images were acquired appropriately and measurement made correctly.

Question #4

With regards to missing data, what is the percentage of images that were disqualified and not replaced from other completed IMT trials?

A) What percentage of patients were impacted by the missingness?

The Panel varied in their opinion on the presence, extent, and impact of missingness on the study. They noted that other trials experience missingness in the range of 4-10% and involves <15% of patients. (ENHANCE had 86% of patients experiencing missingness). Additionally, the bifurcation and internal carotid segments likely accounted for the bulk of missingness. This observation supported the Panel's suggestion that the sponsor and study team consider changing the primary endpoint to focus on CCA data, since, given the limitations of the protocol, the CCA images should have the most complete and reliable data base.

Question #5

Is there a methodology that has been successfully used to identify and address biologically implausible readings?

The Panel agreed that both biologically implausible readings and missing data were unfavorable and serious limitations to the overall interpretation of the trial results. However, they were split as to which was worse. There was no one appropriate direction identified. Suggested remedies discussed by the Panel included:

- Reread all data supplemented by a built in adjudication process
- Re-read or outrightly discard outlier measurements
- Adjudicate each image set including those images comprising the missing cohort
- Do nothing as any adjudication or censuring would potentially increase the missingness to an unacceptable level.

Question #6

Can this data be cleaned with the current process?

Question not Discussed

Question #7

What is the path forward?
Given that the sponsor is obligated to and will report on the study to the scientific/medical community, what is the path forward?
Extreme choices are:

a. Accept the data as is.
b. Install a new reading and analysis process proactively. Execute and accept risk that the data will not get any better.

The panel noted that they may have had different recommendations if they had time to review all of the images from the study, or a random subset of the images.

The Panel opinions ranged from:

-ENHANCE is a study whose image recording and data acquisition are methodologically limiting and thus the results probably are meaningless

to

- assess "maximum likelihood analysis" with image re-evaluation and re-reading

to

- there is merit to leaving the data as is; the data are credible and not substantially out of line with earlier IMT studies.

The Panel was unanimous in their opinion that it would be reasonable for the study team to elevate the common carotid to the primary endpoint, especially if missingness in the CCA is less than other segments.[2] (Post meeting note: CCA missingness is approximately 3% in ENHANCE) The Panel agreed that changing the primary endpoint to focus on the CCA prior to breaking the blind is reasonable and doable without bias. The rationale for making the switch is analogous to applying the best available "assay" to answer the question at hand.

Additional questions:

Femoral IMT results: *How important* are they? *Is it critical to report the results together with the CIMT results?*

The Panel stated that the Femoral IMT is not at present regarded as a valid alternative to Carotid IMT for prediction of cardiovascular events.. Thus Femoral IMT data are not crucial to the initial presentation and publication of the results. While the ideal would be to present both carotid and femoral results simultaneously, it is more important to release the carotid results when they become available. The femoral results can be acceptably published at a later date. Efforts should be focused on the carotids.

Re-reading all study images: *If the sponsor decides to do a re-read of the entire image database, including all 6 carotid segments per time-point for all time points and subjects, how long would you estimate this would take in your laboratory?*

The Panel stated that any re-read should be limited to the common carotid segment as that segment should be the most reliable in ENHANCE. It would take an estimated 12 months to re-read the CCA.

ENHANCE EXPERTS PANEL
Washington, DC

Friday 16 November, 2007

ENHANCE Experts Panel

Friday, November 16, 2007

Omni Shoreham

Washington, DC

Thursday November 15, 2007

7:00 PM - Dinner (optional) Private Dining Room

Friday November 16, 2007

7:30 – 9:00 AM Breakfast – Embassy Room

9:00 – 3:00 PM Panel Session – Capitol Room

Welcome and Introduction – Rick Veltri

Overview of Study and Reading Processes – John Strony

Review of Core Laboratory readings – Ram Suresh / Bo Yang

Discussion – Panel

12:00 PM - *Lunch* - Embassy Room

Review of Questions – Panel

3:00 PM – Adjourn

ENHANCE

- Randomized, double blind, multicenter, international
  - 2 year active study period

- 1:1 randomization eze/simva 10/80 mg or simva 80mg
- n = 720 pts
  - Age 30-70 years old
  - Previous on-going treatment with high dose statins for a prolonged period of time
  - Heterozygous FH determined by genetic documentation or established clinical criteria
  - Visits after randomization every 3 months
  - IMT measurements at baseline and at 6, 12, 18, 24 months

ENHANCE

Primary Endpoint

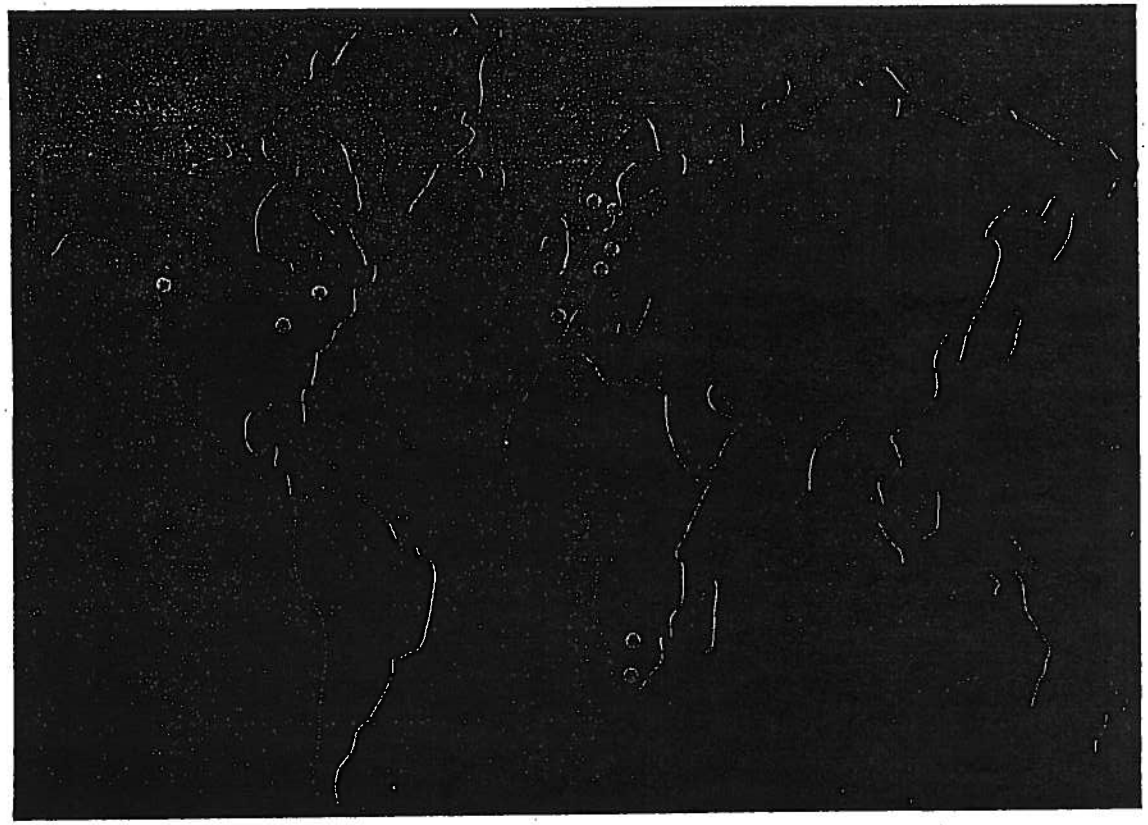
- Change from baseline to endpoint (2 years) in mean IMT (measured as the average far wall IMT of the right and left common carotid, carotid bulb, and internal carotid arteries on a per subject basis) between the two randomized groups.

ENHANCE

Key Secondary Endpoints

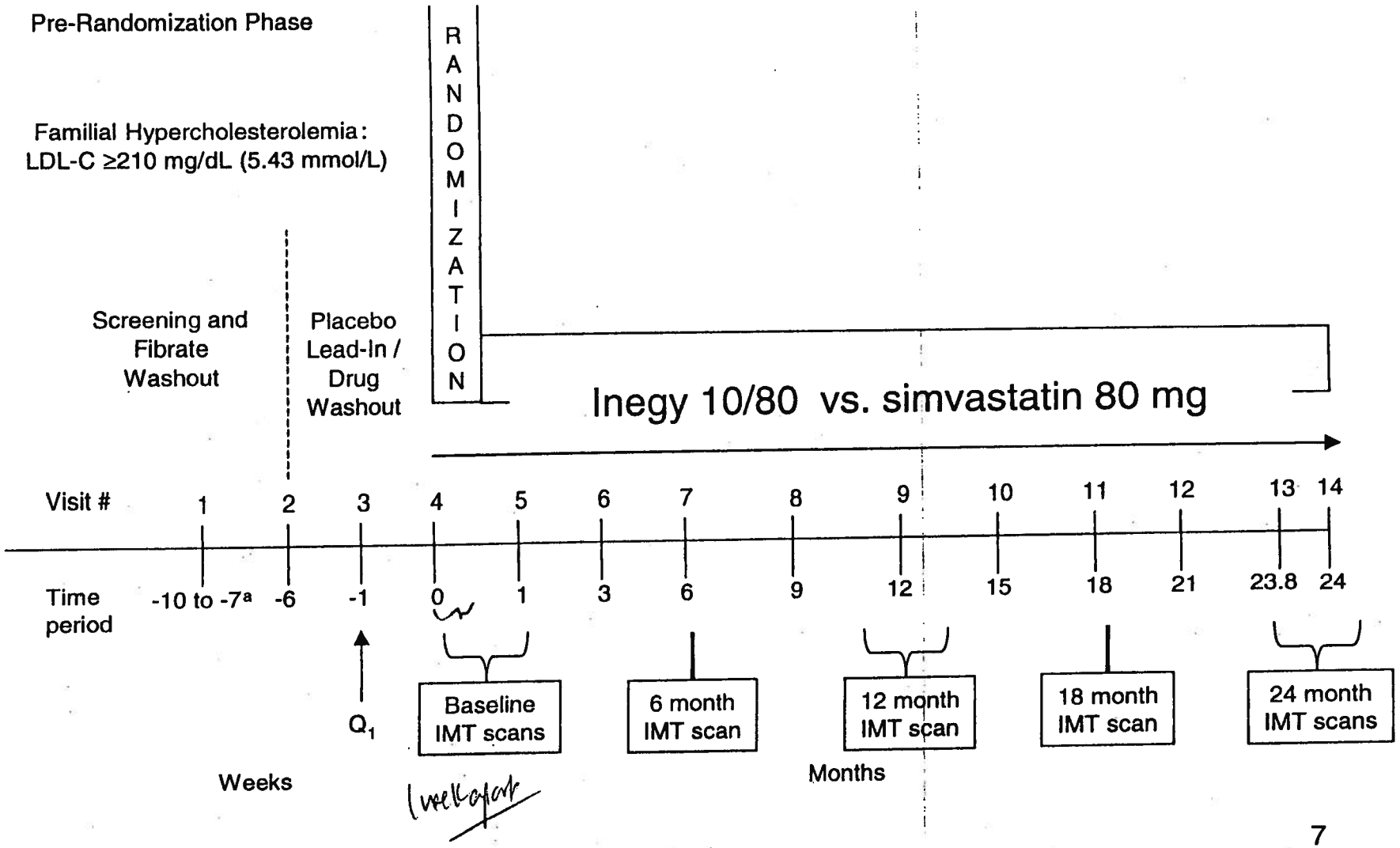
- Proportion of subjects manifesting a reduction in carotid IMT between baseline and endpoint
- Change in maximum carotid IMT between baseline and endpoint
- Proportion of subjects developing new carotid artery plaques (>1.3mm)
- Change in carotid plus common femoral artery IMT

THE ENHANCE TRIAL STUDY SITES



Netherlands (5)
Canada (4)
South Africa (3)
Spain (2)
Denmark (1)
Norway (1)
Sweden (1)
USA (1)

Clinical Trial Design Diagram



Operational Processes

- **Standardization** of ultrasound equipment
  - Accuson equipment with fully digitized recording and storing images
  - Single frame image technology
  - No video backup

- **Training** of sonographers
  - Intensive training and certification program with refresher training at study mid point
  - Feedback via sonographer training updates

- **Imaging**
  - Carotid: 6 segments at each visit
    - Total 42 images per patient
    - >24,000 images to be read independently
  - Femoral: 2 segments at each visit
    - >>10,000 images to be read

Reading Process

- Images in ENHANCE were batch read at end of study
  - Sonographer performance could no longer be altered

- ***Pilot Study - Background***
  - Purpose - Test the ability of the Echo Core Laboratory readers to accurately and consistently read single frame images without video loop support.
  - First 218 completed patients
  - Images were masked and shuffled
  - Reader blinded as to patient, time point, and segment.
  - Ability to read the same geographic region of a given artery segment in more than 24,000 recorded images rested solely on the sonographer's recording.

Pilot Reading

Independent Analysis of Single Frame Imaging

- ***Results of the Pilot Data Acquisition***
  - Between scan variations in transducer angle/patient positioning and other sources of intra- and intersonographer variability caused considerable differences in IMT measurements.
  - Inconsistency in reader identified anatomic landmarks and interfaces
  - Blinded random independent reading of each image resulted in analyses with different measured lengths of the interfaces along the arterial walls of a segment.
  - Outlier reading frequency
    - defined as a $\geq$ 50% difference between the two baseline or endpoint visits,
    - Up to 18% for each segment.
    - Overall outlier readings involved 146 of the 218 patients (67%)

Synchronous Reading

- Images in ENHANCE were patient batch read at end of study
  - Sonographer performance could no longer be altered
  - Every effort needed to be taken to reduce image analysis variability
- Reading Methodology Background
  - Efficacy analysis and data acquisition performed in a per segment fashion
  - **A single file folder created for each segment in each patient**
    - **All 7 images of an identified arterial segment from a single subject were placed in that single folder**
    - visits 3 and 4 (baseline), visit 7 (6 month),visit 9 (12 month), visit 11 (18 month), visits 13 and 14 (endpoint)
  - Images masked and blinded as to, subject name and identification, study center, sonographer, and **timepoint**, and then **shuffled**

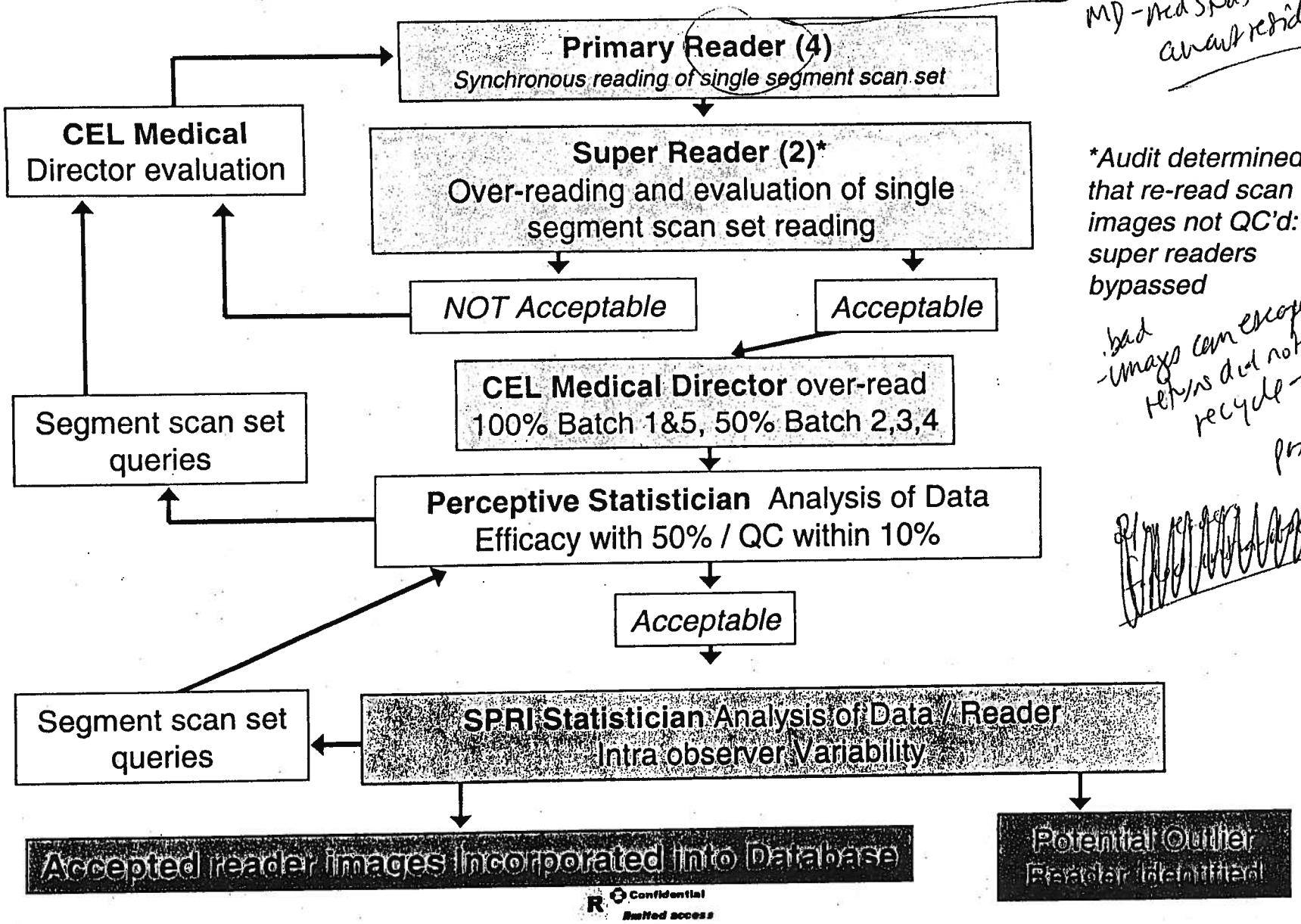
Synchronous Reading

- Synchronous Reading Methodology
  - Allowed the reader to compare the 7 timepoint visit images of a single arterial wall segment synchronously
  - The reader was to evaluate the images side-by-side and at the same time conduct an image assessment
- Qualitative analysis was conducted on each image set
  - Since a radial assessment was not performed AND
  - There was no video background
  - Qualitative analysis performed with special consideration given to
    - arterial wall segment identification
    - correct landmark identification (exactness ensured)
    - consistency (symmetry of location) of the cursor placement along the wall
    - horizontal assessment of the wall
    - presence of image noise
    - transmit zone

Synchronous Reading

- Images evaluated according to the ability to successfully perform measurements of approximately 10 mm arterial lengths and to conduct measurements between the sonographer placed anatomic cursors.
- Focus was on the ability to consistently identify the same interfaces.
- Quantitative Measurements
  - Region of interest needed to be identified in a consistent manner
  - Emphasis on the identification of key segment landmarks with concordant geographic region
  - Traced and measured segments were evaluated synchronously
    - cursor placement
    - consistent length of the measurement

Quality Control Process



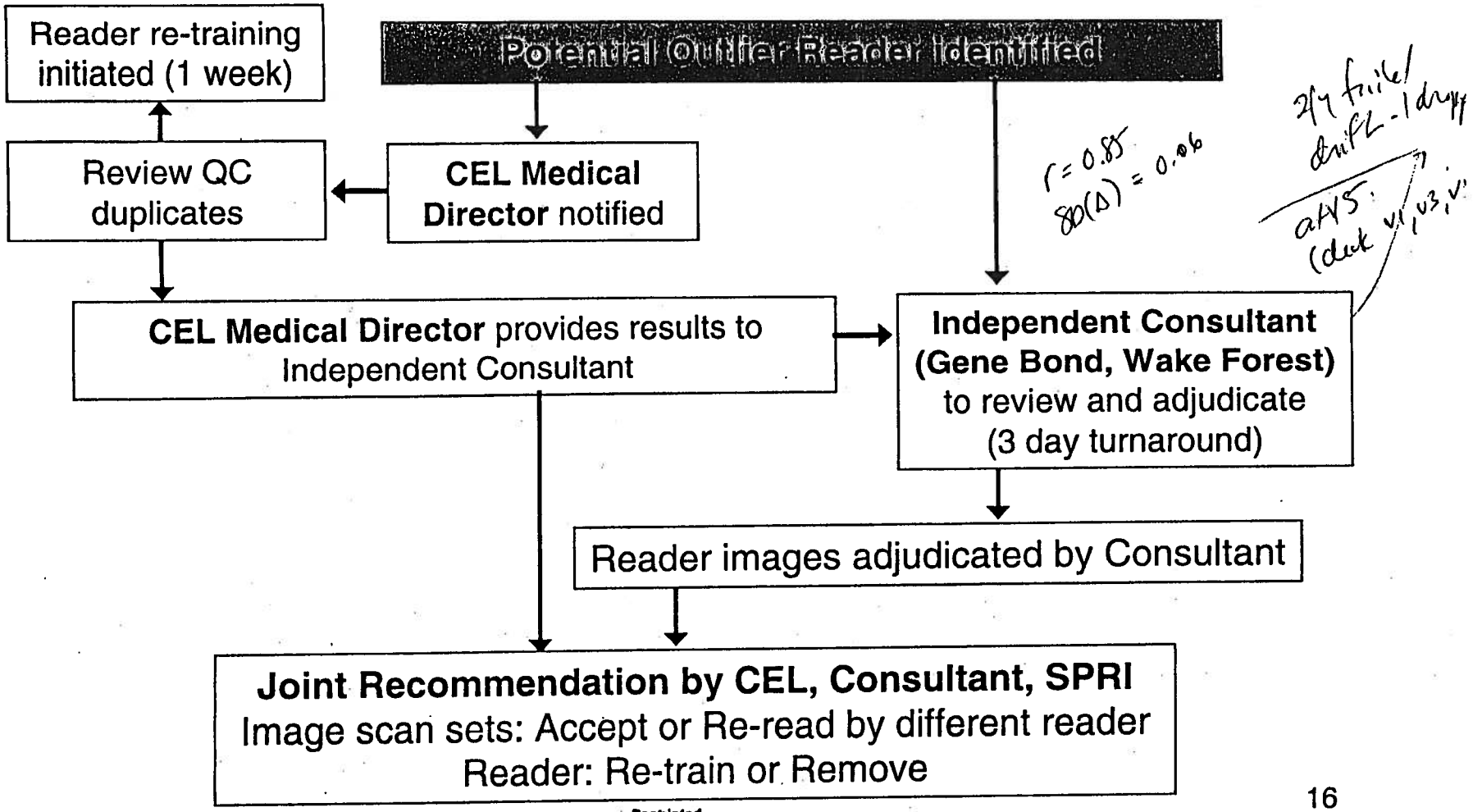
MD - med stud
await residency

*Audit determined that re-read scan images not QC'd: super readers bypassed

bad images can escape loop - techs did not recycle
possible

MSPP 00202

Reader Remediation Plan



ENHANCE

Primary Endpoints

- Change from baseline to endpoint (2 years) in mean IMT (measured as the average far wall IMT of the right and left common carotid, carotid bulb, and internal carotid arteries on a per subject basis) between the two randomized groups.

Sample Size / Power

- With 650 evaluable subjects at this sample size, a difference of 0.05 mm or more IMT change from baseline to endpoint can be detected between the two treatment groups, with 90% power and a significance level of 0.05 (two-tailed), assuming a pooled standard deviation of 0.20 mm.

Status of IMT Data

- Total number of subjects having IMT: 719
- Subjects with evaluable endpoint: 640 (89%)
  - CBA: 85%; CCA: 92%; CIA: 84%
- Subjects with evaluable 24 m IMT: 575 (80%)
  - CBA: 82%; CCA: 86%; CIA: 80%
- Subjects with no missing segment at both baseline and 24-month: 155 (22%)

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Baseline Characteristics

	ENHANCE (n=720)	ASAP (n=325)	RADIANCE 1 (n=904)
Age	45.8 (9.3)	48.5 (10.5)	45.1 (12.5)
Female Gender(%)	48.7%	60%	50.1%
Postmenopausal %	23.6%	16%	
Smoking % Current %	54.3% 28.6%	55% 30%	 20%
DM %	1.8%	1.8%	3.4%
Previous statin High dose	81% 45%	71%	

Baseline Characteristics

	ENHANCE		ASAP		RADIANCE 1	
	Mean	SD	Mean	SD	Mean	SD
Mean IMT	0.69	0.14	0.92	0.19		
CBA	0.79	0.25	1.08	0.29		
CCA	0.67	0.17	0.87	0.17	0.71	0.14
CIA	0.62	0.19	0.83	0.33		
LDL-C (mg/dL)	318	65.5	316	74.6		

-lower- more & / better digital image / analysis ? higher freq

Current View of Database

- Fully "cleaned" data received from CEL
  - After queries of baseline and endpoint pairs (~ 10%)
  - Audit discovery of more than 128 new IMT data points
- Existing data is not statistically analyzable
  - Existence of unacceptable number of biologically implausible IMT values
  - Existence of many missing values, and current processes to query missing values have increased implausible IMT values
  - Statistical issues in analyzing this data

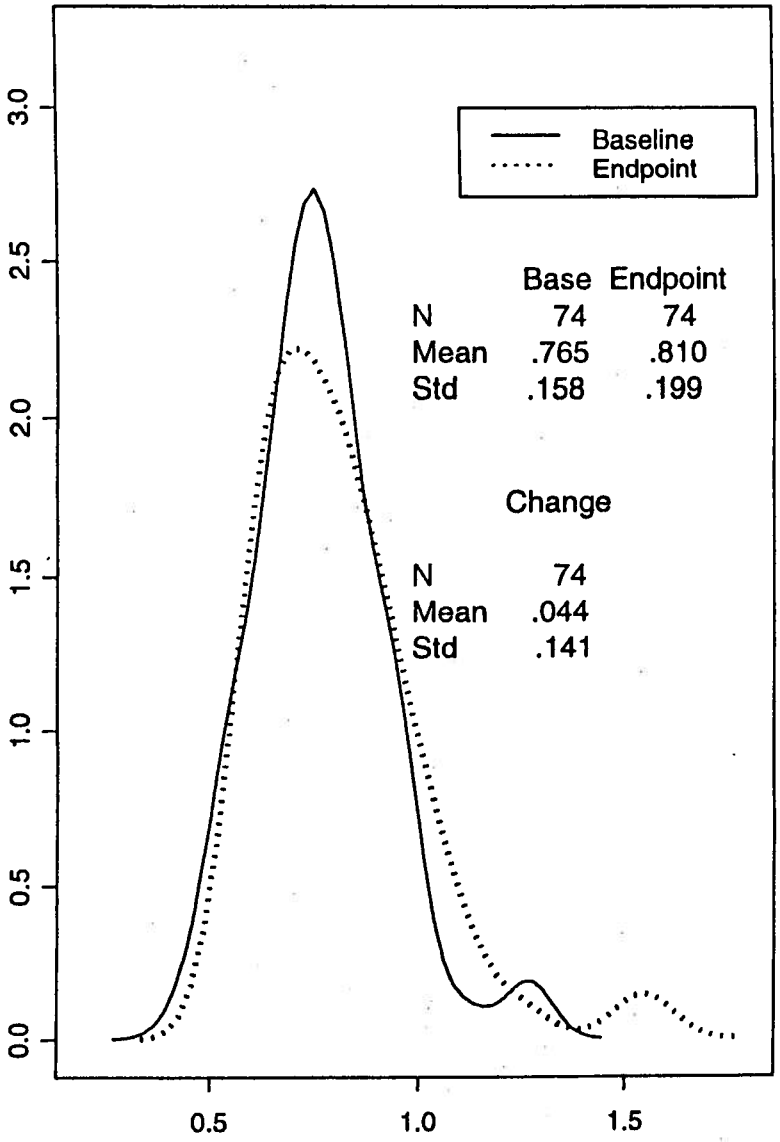
are there other data?

Biologically Implausible Data

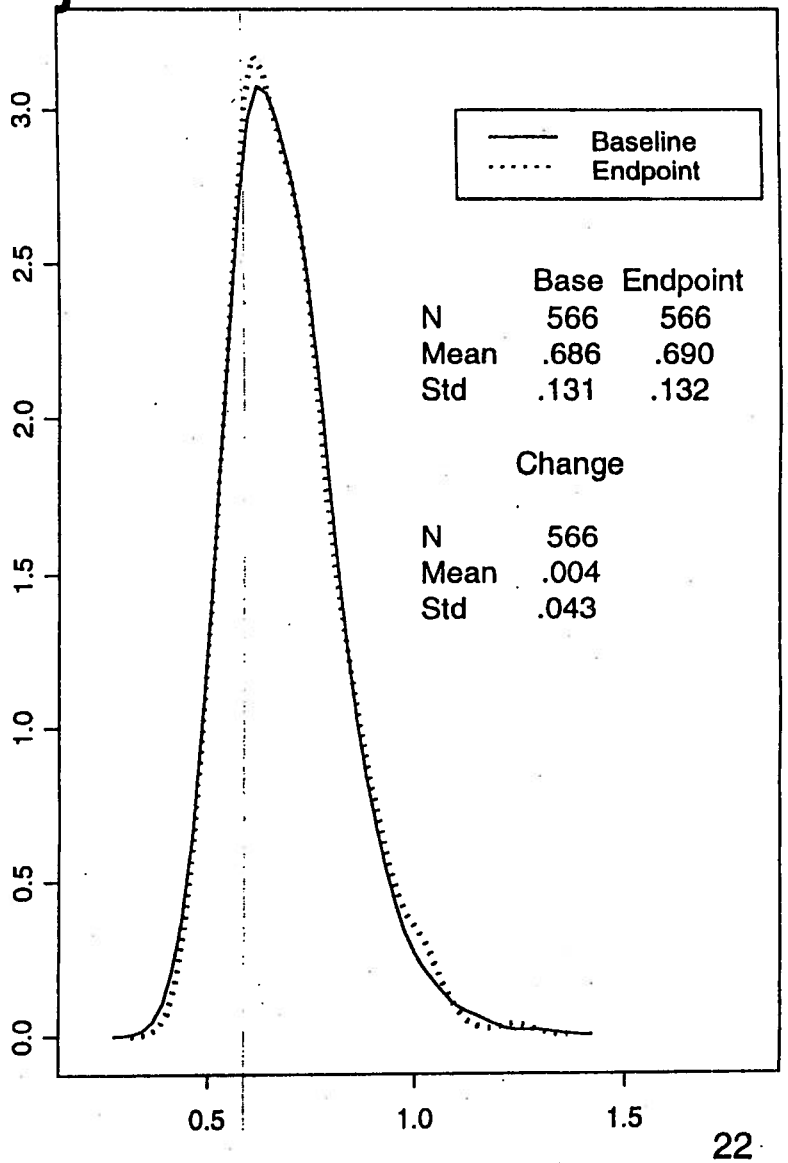
- 74 subjects have more than 0.1 mm change between baseline and endpoint

Subject	segment	Base.1	Base.2	M6	M12	M18	M24.1	M24.2	Change
000015	LCBA	1.2357	1.1786	1.5803	1.1542	**1.5239**	1.1354	1.4369	0.0790
	LCCA	1.0503	0.9370	0.7396	1.0331	1.0602	1.0867	0.9830	0.0412
	LCIA	1.1157	1.1539	0.8863	0.7759	0.9490	.	**1.8793**	**0.7445**
	RCBA	0.9827	1.1108	0.8545	0.9409	0.7247	0.6696	0.9333	-0.0702
	RCCA	0.7205	0.7052	0.6370	0.5749	0.8929	0.8815	0.7545	0.1051
	RCIA	0.7600	0.7123	.	0.9265	.	.	1.0880	0.3519
AVE IMT		0.9988	0.9236	0.9568	0.8649	1.0191	1.0092	1.1722	**0.2086**
000540	LCBA	**1.0781**	**1.2127**	.	**1.0425**	**0.7275**	**1.1034**	**1.2199**	0.0162
	LCCA	**0.8209**	**0.8898**	.	**0.7103**	**0.6431**	**0.9282**	**0.8743**	0.0459
	LCIA	0.5252	.	.	0.7149	0.5898	.	.	.
	RCBA	1.1993	1.1937	.	1.0391	1.0507	1.1145	1.0184	-0.1319
	RCCA	0.8364	0.9468	.	0.9771	1.0675	1.1730	1.0551	0.2225
	RCIA	0.5184	0.4340	.	.	0.7073	.	0.9890	0.5128
AVE IMT		0.8297	0.9361	1	0.8968	0.7977	1.0798	1.0313	**0.1331**

Distribution of 74 subjects vs. Others



Subjects with IMT change > 0.10mm



Subjects with IMT change < 0.10mm

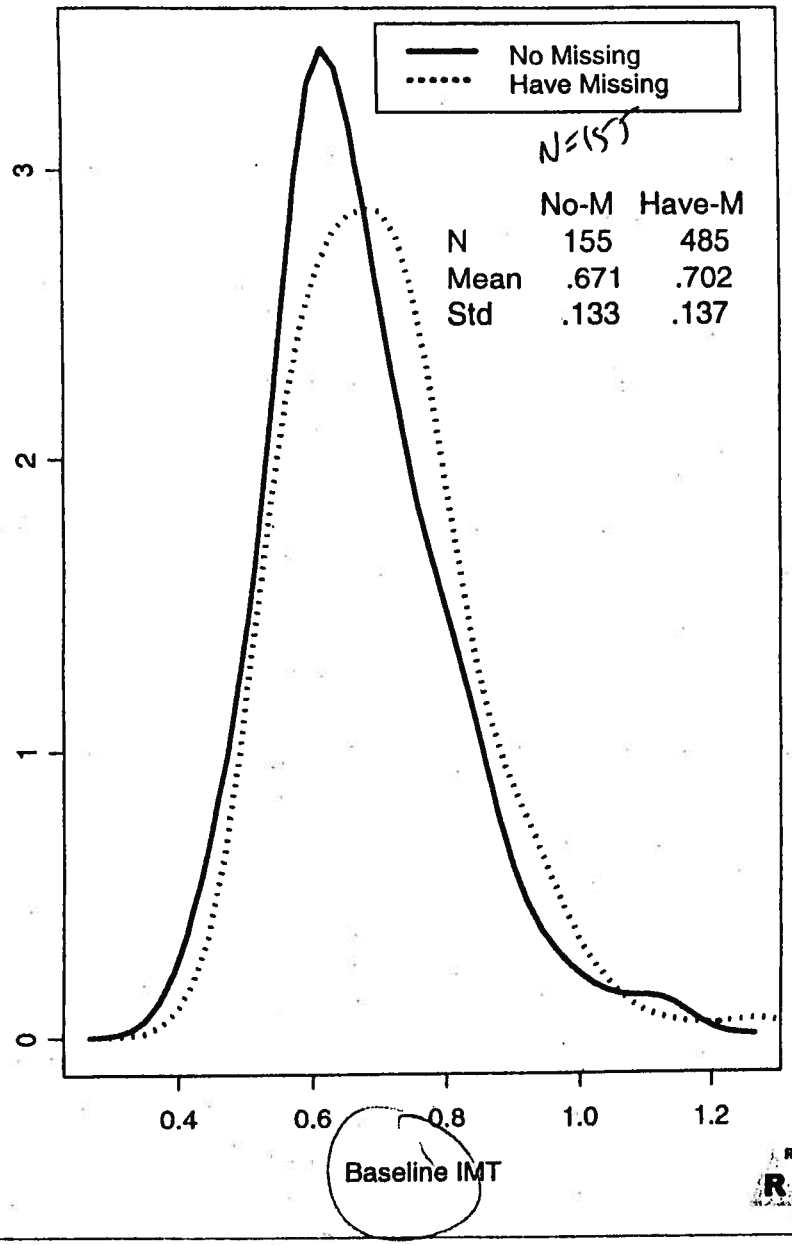
Restricted Confidential
Limited access

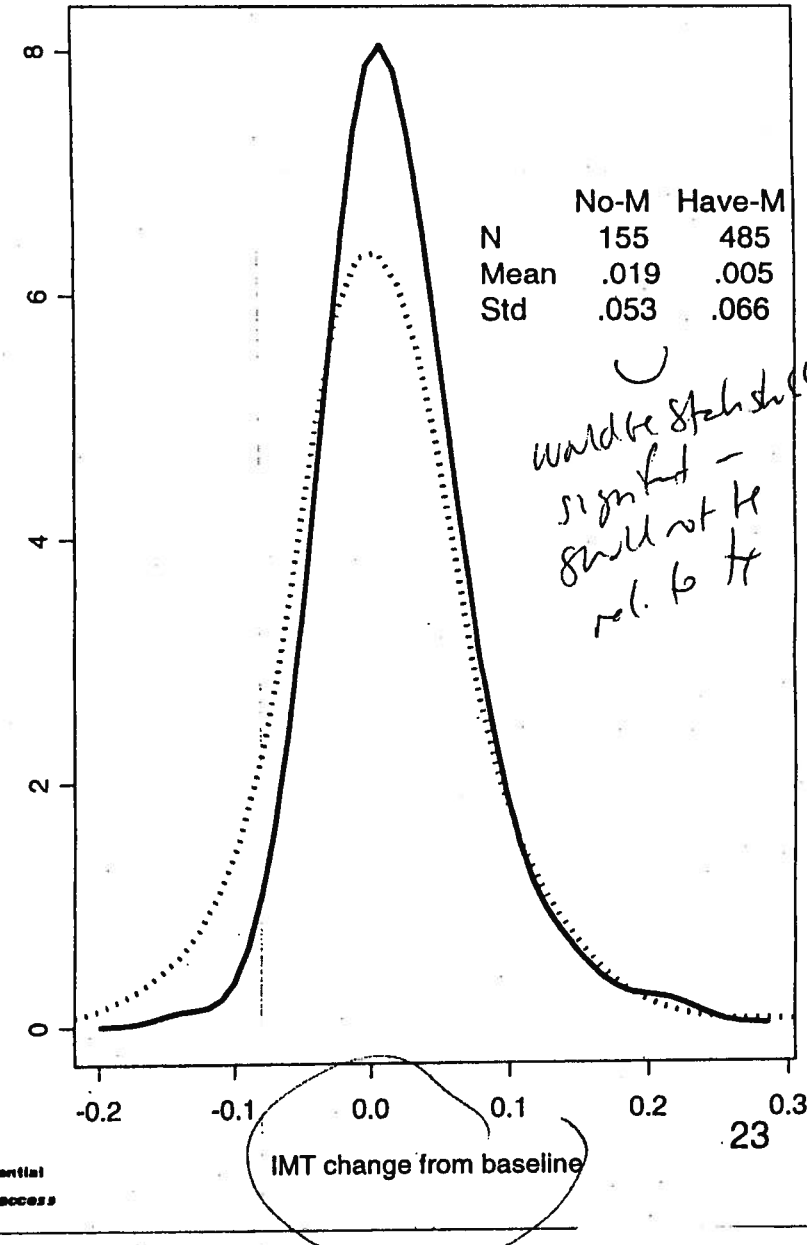
22

ATTACHMENT PAGE 46

MSPP 00210

Missingness





Missing IMT Value Recovery

- After matched pairs unmasked to CEL

Subject	segment	Base.1*	Base.2*	M6	M12	M18	M24.1**	M24.2**
000506	LCBA	1.1204	.	1.3888	1.2018	1.4378	.	1.2553
	Recovery	1.1204	**1.5445**	1.3888	1.2018	1.4378	**2.1356**	1.2553
000513	LCIA	.	.	.	.	.	.	.
	Recovery	**1.4864**	.	.	.	.	**1.5301**	**1.0790**
000734	LCCA	0.7144	0.6943	0.6099	0.5794	0.6672	0.7118	.
	Recovery	0.7144	0.6943	0.6099	0.5794	0.6672	0.7118	**0.432**

Statistical Issues

- There is an tremendous risk analyzing this data
- Recall that in sample size calculation
  - Effect size of 0.05 mm with s.d. of 0.20 mm
- Current standard deviation for primary endpoint is ~ 0.06 mm
  - Effect size of 0.01 mm can result in a p-value < 0.05
- Effect size of 0.01 mm
  - Positive direction: arguably clinically meaningful
  - Negative direction: harmful

Lessons learned

- Synchronized reading improves data quality
- Data become more consistent when pairs are unmasked
  - However, data still do not make sense when looked at longitudinally
- Should all visits be unmasked?
  - Visits are unmasked in contemporaneous trials with treatment assignment being blinded
  - There is no comparative data of masked vs. unmasked approach

Queries

- Examples of query resolution

Subject	segment	Base.1	Base.2	M6	M12	M18	M24.1	M24.2
000013	LCIA	0.6804	0.5920	0.7472	0.5482	0.7279	0.8354	0.5781
	FLAG						1	1
	Change	0.6804	0.5920	0.7472	0.5482	0.7279	**0.5942**	0.5781
000124	RCCA	0.9261	1.0713	0.6405	1.0524	0.9151	1.2880	0.9755
	FLAG	1	1				1	1
	Change	**1.0018**	1.0713	0.6405	1.0524	0.9151	1.2880	**1.2108**
000187	RCBA	0.8675	1.0587	0.7457	0.9520	0.9177	0.9703	0.9236
	FLAG	1	1					
	Change	0.8675	.	0.7457	0.9520	0.9177	0.9703	0.9236

From: Veltri, Enrico [Enrico.Veltri@spcorp.com]
Sent: Monday, September 17, 2007 8:48 PM
To: Mcnicholas, Sean; Strony, John
Subject: RE: ENHANCE - status

Soren is a prick. How's that for staying calm. Tell him to f' off. Rick.

-----Original Message-----
From: Mcnicholas, Sean
Sent: Friday, September 14, 2007 4:51 PM
To: Strony, John; Veltri, Enrico
Subject: FW: ENHANCE - status

Comments ..... And please stay calm and reply back only to me Sean

Sent by GoodLink (www.good.com)

-----Original Message-----
From: Christiansen, Soren Bo (WS)
[mailto:soren_christiansen@merck.com]
Sent: Friday, September 14, 2007 04:48 PM Eastern Standard Time
To: Allibone, Kathleen M; Hill, Barbara; Bastos, Jose A.; Strigini, Bruno; Christiansen, Soren Bo (WS); Granata, Francesco; Helfer, Gerda; Petitti, Joanne; Mendoza, Miriam; Jones, Monica; Oschmann, Stefan; Mcnicholas, Sean; Silva, Ariane D.; Warner, Grey F
Subject: ENHANCE - status

To the Board : I have to express my concern over how SPRI is interacting with one of the most important customers in EMEA. During the meeting at Dr. Kasteleins Hospital it was agreed to conduct a meeting with outside Consultants by mid September. According to email below there has been no communication to Dr. Kastelein with respect to when the meeting will take place. This raises a question, in my mind : is this high enough on the SPRI priority list ? Thanks Soren

---

From: J.J.P. Kastelein [mailto:j.j.kastelein@amc.uva.nl]
Sent: Friday, September 14, 2007 3:05 AM
To: Christiansen, Soren Bo (WS)
Cc: O'Malley, Justine; Nouss, Edgar M.
Subject: RE: ENHANCE Stand by - revised

Dear Soren,

Thanks for the changed statement. I have no further questions.

I have heard nothing about the Consultant Meeting. I will write Strony and Veltri right now.

Regards, John

****
John J.P. Kastelein, MD, PhD
Professor of Medicine
Chairman, Dept. of Vascular Medicine
Academic Medical Center
Meibergdreef 9, Room F4-159.2

Schering Plough ENHANCE consultancy report

Michiel L. Bots, MD, PhD
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Contents

Summary

The CIMT measurements seem to be done according to the procedures outlined in the protocol. The CIMT measurements in ENHANCE have been done in a consistent manner, leading to reproducibility findings that compare well with that of published studies from other multi-centre randomized trials. The number of missing data points is most likely somewhat higher that what has been reported earlier. Yet, the evidence shown to me is sufficient to indicate that the CIMT data in ENHANCE are fine: i.e., no better, no worse than what has been reported in the literature.

However, the SP/MSD team would like to their utmost to potentially further reduce the measurement variability in the data, given the restriction of the availability of the imaging information. Based on the information there might be three ways to address that. Firstly, reduction of missing CIMT values by evaluating whether CIMT can be validly measured from other image selections of the same visit. Secondly, a longitudinal outlier analyses, i.e. identification of the outlier, re-evaluation, and potentially change the CIMT value in the dataset. Thirdly, optimise the statistical analyses of the data, i.e., use the state of the art model statistical models to assess difference in change in CIMT across treatment arms in randomised controlled trials.

Important to realise is that the above mentioned activities might reduce measurement variability to some extent. The expected effects on variability are however likely to be modest. Again, randomisation in ENHANCE protects against bias in the estimate of the difference in CIMT change between treatment arms.

1. Introduction

During a recent telephone conversation between members of the Schering Plough team of the ENHANCE study, among which Toni Bransford and John Strony, the SP/MSD team would like to have dr. Bots as an independent consultant for advice regarding CIMT issues in the ENHANCE trial.

ENHANCE is a randomised controlled trial evaluating the combination of Ezetimibe + simvastatin versus simvastatin alone on progression of carotid intima-media thickness as assessed with ultrasound.

From the conversation, the following was understood

- The study is still in its blinded phase. The timeline to de-blinding of the study has been extended until several issues are resolved.
- The design of the ultrasound component of ENHANCE had 7 visits in which CIMT was assessed (femoral IMT and distal common carotid M-mode was measured as well, but since CIMT is the primary endpoint, in this document CIMT will be discussed only).
- Visits included a duplicate baseline assessment, a duplicate assessment at 12 months (sample), a single assessment at 18 months and a duplicate assessment at the end of the study.
- The ultrasound images provided to the core laboratory were a single still frame of the far wall of the right common carotid segment, a still frame of the far wall of the right bifurcation, a still frame of the far wall of the internal carotid segment, and three similar images obtained from the left carotid. In total a maximum of 6 images were provided to the core lab for CIMT measurement at each visit. There is no additional image information available (for example clip or a videotape).
- The reading protocol indicated that the images of e.g. the right common carotid of all the 7 visits were displayed on one PC screen so that all images should be read simultaneously. This approach should enhance comparability in the readings. Furthermore, the approach should identify images where measurements should be performed on that were clearly different in anatomy from the other images. In ENHANCE angles information was not available.
- For each visit the CIMT values of all six segments are averaged to provide an aggregated CIMT value for each visit. Next, the aggregate CIMT values from

the duplicate visits (baseline and end of study) are averaged. Duplicate visits are Visits 3, 4 and 13, 14 (baseline and endpoint). In a randomly selected subset of subjects, an additional IMT ultrasound image will be performed one week after visit nine as part of a quality control program to ensure standardization of image acquisition and analysis.

- The primary outcome variable in ENHANCE is change in CIMT between baseline (visit 3-4) and end of study (visit 13-14). CIMT is the average of all at least four mean CIMT values measured from the image.

Questions that arose from the SP/MSD team dealt with whether or not the reading protocol was actually closely followed during the reading process. Secondly, the data that were available to SP showed sometimes large CIMT differences between visits, (sometimes large differences between visits 1 week apart). These differences were beyond what was to be expected from normal progression. The main question was what should be done with these differences. So this leads to the main two objectives.

2. Objectives

1. Has the reading of the ultrasound images been done according to the procedure outlined in the protocol?
2. How can the 'outliers' be addressed in an adequate manner before de-blinding of the study occurs?

3. Methods

- Three meetings were set up in Amsterdam at the core lab to address these issues. One on Tuesday, 16 January 2007 from 13.00-15.00 and one one Thursday, January 18, 2007 from 12.00 -13.00 hours, and one on Thursday, January 18, 2007 from 13.00-15.00 hours.
- During these meetings information should become available to fully address and discuss the objectives.
- Bots will develop the questions and will provide a written report.

4. General aspects regarding the objectives

Has the reading of the ultrasound images been done according to the procedure outlined in the reading protocol?

During the planned meetings, the core laboratory needs to provide the information on how the images have actually been read. A presentation would suffice.

In addition, information should be given about the process of the procedures installed when a selected image does not match the anatomical segment of what has been requested. For example, when a far wall right common carotid artery image is requested, and the image provided is actually the far wall of the right bifurcation. In general, three ways are present to deal with such images; (1) when possible, request re-scanning of the participant; (2) measure the image anyway, and use the measurement in the estimate of the primary endpoint; (3) leave out the image in the measurement procedure (missing). These approaches should be outlined in the imaging/reading protocols of the study.

The best solution would be the request of rescan of the participant. The second best is to have a judgement call by the reader to indicate how the selected image actually deviates from the other images based on the anatomical image information and to what extent the deviation is expected to affect the measured CIMT. When deviations are small (i.e., the CIMT is likely a good reflection of what the CIMT in the segment is expected to be), measurement should provide a good estimate of the CIMT value; when the deviation is considered large (a totally different segment with a priori expectation of thicker/ thinner CIMT value), a 'no measurement' is appropriate. The third solution, i.e., a priori perform no measurement, may lead to having more missing values for that measurement than needed.

The effect of missingness of CIMT information on the progression rates and on the ability of finding a treatment difference is here of importance. Since the study was blinded for the treatment, and the sonographer can not identify which participants are 'progressors' and which participants are 'regressers', the effect of missing imaging information is likely to be a random phenomenon. This is unlikely to affect the mean progression rate in the group, but may reduce the precision of the progression estimate a little. The latter may reduce to some extent the ability to detect differences between groups, although the magnitude of the difference between the groups is expected to be correct.

How can the 'outliers' be addressed in an adequate manner before de-blinding of the study occurs?

An 'outlier' is a CIMT value that is clearly different from other CIMT values for a similar segment (or for the primary outcome) that have been measured in a time sequence. For example, in one participant a common CIMT value of 0.70 mm measured at first baseline visit, a common CIMT value of 1.50 mm measured two weeks later, and a common CIMT value of 0.71 mm measured after 12 months, and a common CIMT of 0.75 mm measured at 13 months. The same may apply to the aggregate CIMT value; an aggregate value of 1.25 mm, 1.70 mm, 1.20 mm and 1.18 mm, respectively. Note that outliers can also go into the other direction: 1.25 mm, 0.80 mm, 1.20 mm and 1.18 mm.

The contribution of an 'outlier' on the study findings depends on what the primary outcome CIMT is. For example, when the primary outcome in a trial is difference in progression of the aggregate CIMT, and when the primary outcome is based on the average of 6 CIMT values, the first example outlier will lead to a contribution of an outlier to the observed CIMT aggregate of (1.50 mm- 0.70 mm)/6 = 0.133 mm. The aggregate CIMT of that visit will be overestimated with 0.133 mm. An outlier of 0.30 mm, contributes 0.05 mm to the aggregate, which is within the reproducibility range. This reasoning shows that only considerable outliers potentially affect the final CIMT estimate of a certain visit.

An outlier may be due to (1) a real biological process, e.g. a haemorrhage in the arterial wall at the location of the measurement (found in 2-4% of the participants); (2) a CIMT measurement from an image that shows a different anatomical location (imaging problem) and (3) a mistake in the reading of the image (reader problem).

There are different ways to identify an outlier. It can be done on segment specific measurements of all the visits or on the aggregate CIMT value for each visit. Since the aggregate is the main variable of interest, which also shows less variability from visit to visit as compared to segment specific values, it might be more appropriate to use the aggregate for assessment of outliers. To the best of my knowledge there have been no published reports that provide a recommendation for assessment of outliers. One of the approaches that has been taken in one of the trials (three years, 9 CIMT measurements) I have been involved in was to calculated the mean of all the aggregate CIMT estimates of all visits (study mean). Next, calculate for each visit the difference between the visit CIMT and the mean of all the aggregate values during

study (study mean) and take one 20% upward and downward from that mean as being an outlier. In this study, 20% difference reflected around 0.20 mm difference in aggregates between visit specific values and the overall study mean. Of the identified outliers examine all the CIMT values of the segments to identify the potential CIMT value that is actually responsible for the outlier.

Another possibility that may be used in ENHANCE may be to use the duplicate baseline and end of study data to identify on segment level those measurements that for example differ more than 50% among each other. A potential down side is that you miss the longitudinal aspect of outliers since you do not relate the baseline value with 12 month, 18 month and end of study measurements.

Finally, one may also use the reproducibility data of the mean absolute difference in the aggregate CIMT (0.03-0.05 mm) and define an outlier based that value plus and minus 2 or 3 times the standard deviation of the arithmetic mean difference of the aggregate CIMT value. Given that the standard deviation of the arithmetic mean difference of an aggregate is around 0.06-0.010, this approach would lead to identification visits that difference 0.03-0.05 mm +/-0.12 – 0.30 mm from the overall study mean.

What approach is taken to define an outlier, there are no standards, and the choice remains arbitrary. It is usually a balance between workload, time and costs and estimates of potential benefit for the data. The latter is difficult to judge, and one has to rely on reproducibility data as collected in the study. ENHANCE is unique here in having duplicate measurements at two time points and great potential to evaluate the effect of the outlier procedures.

When an outlier has been defined, the evaluation may indicate that is it is a real morphological change (accelerated progression of atherosclerosis, haemorrhage) or 'measurement error'. The latter comprises ultrasound protocol deviations (scanning wrong vessel or wrong segment) or image reading errors (measuring ultrasound imaging artefacts, difficult atherosclerotic plaques, or inaccurate boundary tracing). Morphological changes do not need any action. The measured CIMT is correct, and remains in the database. Reading errors need to be corrected. So the image is re-read and the CIMT value of the re-read image is being used in the final dataset. Ultrasound protocol deviations constitute a different problem. When possible, another image may be selected from clips or videotapes and read. However, in ENHANCE

this is not available. Thus the solution chosen may be is to have a judgement call by the reader to indicate how the selected image actually deviates from the other images based on the anatomical image information and to what extent the deviation is expected to affect the measured CIMT. When deviations are small (i.e., the CIMT is likely a good reflection of what the CIMT in the segment is expected to be), measurement should provide a good estimate of the CIMT value; when the deviation is considered large (a totally different segment with a priori expectation of thicker/ thinner CIMT value), a 'no measurement' is appropriate.

The effect of having missing imaging data (due to lack of compliance of the imaging protocol) depends on whether missing images/readings affect the CIMT progression rate and whether it affect the ability to detect differences between treatment arms.

Missingness of CIMT data only affects progression rates when missingness is related to factors that determine the CIMT progression rate. This can be easily examined in the existing blinded dataset given the basic assumption in a blinded dataset that the risk factor relations are stronger that any treatment effect. Using the group with complete data, one can study the relation between baseline risk factors and CIMT progression. From these analyses, factors that are related to an increased or decreased progression can be identified. Next, one may evaluate whether these factors are different among subjects with missing values due to imaging aspects.

Since the study was blinded, and the sonographer can not identify which participants are 'progressors' and which participants are 'regressers', the effect of missing imaging information is likely to be a random phenomenon.

5. Results based on discussions and material provided

Has the reading of the ultrasound images been done according to the procedure outlined in the protocol?

During the meeting of Tuesday, the core lab showed how measurements were done. These were indeed done in a manner that was described in the protocol. The core lab indicated that when of the 7 images there were one or two that were clearly distinct from the others, in terms of anatomy, no measurements were done, and no CIMT data came in the data base.

Of note is that when a 'no-measurement' was seen for a given segment there was not a systematic attempt to check where an CIMT could be read from another image

of the same visit. For example, when a far wall bifurcation of a participant during visit 13 could not be measured due to anatomical differences and/or wrong imaging, there was no attempt to check whether a bifurcation far wall CIMT might be measurable from the CCA or ICA selections at that visit.

How can the 'outliers' be addressed in an adequate manner before de-blinding of the study occurs?

Before the discussion on outliers starts, first the reproducibility of the data needs to be evaluated. This included reproducibility data from visits 3-4 and from visits 13-14 and indicated that the reproducibility of CIMT (the entire process including variability due to imaging and reading) is excellent in this study. The Intraclass correlation coefficients were high, the mean CIMT differences between visits and their corresponding standard deviations were small. The same applied for the mean absolute CIMT difference and the standard deviations. These data are well in line with studies that have been published in the literature. Based on these findings there seems to be little concern regarding the validity and precision of the data.

Yet, the SP statistician sees in the segment specific data large differences that are considered beyond 'biological variation'. Based on these findings, I have checked in one of our datasets obtained from a randomised controlled trial the variation we found in the maximum CIMT measurements of the far wall bifurcation. Our data strongly resemble the ENHANCE data in terms of the magnitude in differences in CIMT values between visits.

The core lab has re-evaluated all the images of the visits 3-4 that had a CIMT value that was 50% of more different. The re-evaluation dealt with new evaluation, re-reading, and possible setting to 'no- measurement'. A similar exercise was done for the visits 13-14. Next, the statistician evaluated how the reproducibility based on the original data changed when the 'corrected' outlier data were used. This improved in particular the standard deviation of the mean differences. Yet, the improvement was very modest.

Of note is that this outlier exercise did not evaluate longitudinal outliers based on differences between visits 3-4 and visits 13-14, but only 'cross-sectional' outliers.

The SP statistician indicated that there was concern with missing data. Of the common carotid segment CIMT was missing for 4% of the participants, for the

bifurcation segment 12% and for the internal segment 12%. This is higher than in the studies of the consultant but in line with observational studies. However, the ultrasound protocol used by the consultant are much more extensive in terms of collecting imaging information, and therefore allows for obtaining CIMT information from other sources when the selected images are too poor.

In the discussion two aspects came up: First can we reduce the missing data?, and second does this affect the CIMT estimate of the visit?. The only approach of a reduction of missing data is to check whether information on CIMT can be validly collected from other selections of that same visit. This has not been explored by the core lab, and a pilot on feasibility might be useful.

Missingness may affect the CIMT value. Yet, the current statistical models that are used in the analysis of CIMT trial data do appear to take care of that in an adequate manner. The current approach to analyse CIMT progression trial data is a multi-level, repeated measures linear mixed effects model. Levels used for the data are usually subject, and carotid artery site within subject, and the repeated measure was time. The model may be specified in terms of fixed effects for carotid artery site, age, sex, reader, ultrasound machine, randomized treatment group, time, and the interaction of randomized treatment group and time. Time is a continuous variable, and is the interval in years from date of randomization to date of CIMT measurement. Random effects within the model are intercepts and slopes, for subjects, and sites-within – subjects. The dependent variable is measured CIMT. Differences in annualized change between the 2 randomized treatment groups are tested by evaluating the statistical significance of the time-by-treatment interaction term. A feature of the model is that it fits regression lines to profiles of CIMT values, consisting of pre-randomization values, values from visits during the treatment period, and values from end-of-study visits. If a subject withdrew with an incomplete profile after the first post-randomization ultrasound visit lines can still be fitted to the data available. Unfortunately, in the ENHANCE statistical protocol a different approach has been taken, which is based on averaging of the values. Since that approach is suggested to be less powerful and more susceptible for bias (due to missing data), the present statistical approach might need some re-consideration.

Of note is to realise that this is a randomised controlled trial, the features mentioned above affect both treatment arms. In general, missingness and outliers affect the precision of the CIMT progression estimate, and may affect the ability to

detect a difference in CIMT progression between the treatment groups. How large that effect is can not be determined validly.

Finally, the SP statistician indicated that the lentgh of the CIMT measurement introduces variability. Apparently, there are some subjects in which the length of the tracings differs between visits, which may have a profound effect on the mean CIMT value from that image. The only solution I can suggest is to use the maximum CIMT rather than the mean value CIMT of an image. One has to realise, however, that the reproducibility of a single segment specific maximum CIMT measurement is generally lower than that of a segment specific mean CIMT measurement. The reproducibility of an aggregate based on maximum CIMT measurements may not be very different from that of an aggregate based on mean CIMT measurements. The advice would to evaluate this further in the current blinded dataset, not by using individual segment data but by using the mean maximum aggregated CIMT values.

6. Conclusion / recommendation

The CIMT measurements seem to be done according to the procedures outlined in the protocol. The results from the reproducibility study showed that the CIMT measurements have been done in a consistent manner, leading to reproducibility findings that compare well with that of published studies from other multicenter randomised trials. The number of missing data points is most likely somewhat higher that what has been reported earlier. This can be attributed to having only one image for CIMT analysis. Yet, the evidence to me is sufficient to indicate that the data are fine.

However, the SP/MSD team would like to their utmost to potentially further reduce the measurement variability in the data given the availability of the imaging information. Based on the information present, there might be three ways to address that. Firstly, reduction of missing CIMT values by evaluating whether CIMT can be validly measured from other image selection at the same visit. Secondly, a longitudinal outlier analyses, i.e. identification of the outlier, re-evaluation, and change in the dataset. Thirdly, optimise the statistical analyses of the data as indicated above.

The definition of an outlier is based on the findings of the reproducibility study. The parameters to use are the mean absolute difference between visits 3-4

measurements (e.g. 0.03 mm), and the standard deviation of the arithmetic mean difference between CIMT values of visits 3-4 (e.g. 0.06). An outlier may then be defined as present when a difference in CIMT values between the visit 3, visit 4, visit 13 and visit 14 values is above or below 0.03 +/- 3*0.06 = a value above or below 0.21 mm.

Important is to realise that the above mentioned activities might reduce measurement variability to some extent. Since this is expected to involve only a small number of the measurements, the expected effects on variability are likely to be modest. Again, randomisation protects against bias the estimate of the difference between treatment arms.

Hankin, Joan E

From: Askine, Mark W
Sent: Wednesday, January 16, 2008 7:18 PM
To: Hankin, Joan E; Dean, Robert; Brony, Michael
Cc: Davis, Kristin; Abrams, Thomas W
Subject: Vytorin promotional materials

The action item from our meeting with Drs Temple, Parks, and Colman this evening is that we will inform the sponsor of Vytorin that they need to revise their promotional materials to clearly convey the information about the lack of additional CV benefits with Vytorin compared to Zocor, consistent with the following statement from approved PI for Vytorin: "No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been demonstrated."

We can discuss in greater detail tomorrow. Thanks.

Mark

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Sandra Kerr
Senior Director, Office of Medical/Legal
Merck & Co., Inc.
U.S. Human Health
P.O. Box 1000, UG3BC-10
North Wales, PA 19454-1099

RE: NDA 21-687
Vytorin® (ezetimibe/simvastatin) Tablets
MACMIS ID#: 12594

Dear Ms. Kerr:

This letter concerns proposed direct-to-consumer (DTC) promotional materials for Vytorin® (ezetimibe/simvastatin) Tablets (MACMIS ID# 12594) submitted on July 22, 2004, by Merck & Co., Inc. (Merck) on behalf of Merck/Schering Plough Pharmaceuticals (MSP), to the Division of Drug Marketing, Advertising, and Communications (DDMAC). The submission contained the following promotional materials:

- 60-Second television advertisement (TV ad) storyboard and rough-cut videotape (*Cholesterol Portraits*)
- Print ad
- 1-877-VYTORIN script
- Fulfillment Letter Package
  - Letter
  - Envelope
  - Patient Brochure
- Brochure Holder

On February 11, 2005, DDMAC provided written comments on various issues in the proposed materials, including comments related to disclosing that Vytorin contains two medicines (Zetia/ezetimibe and simvastatin/Zocor).

However, our letter did not comment that the Vytorin product claim materials failed to disclose a limitation to the efficacy of Vytorin that is identified in the **CLINICAL STUDIES/*Primary Hypercholesterolemia/Simvastatin*** Section of the Vytorin approved product labeling (PI):

> In two large, placebo controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction and stroke; and the need for coronary and non-coronary revascularization procedures.
>
> No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established. (emphasis added)

In addition, the **CLINICAL STUDIES/*Primary Hypercholesterolemia*/*Ezetimibe*** Section of the Vytorin PI states:

> In two multi-center, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ezetimibe significantly lowered total-C (-13%), LDL-D (-19%), Apo B (-14%), and TG (-8%), and increased HDL0C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

In sum, one of the drug components in Vytorin, simvastatin, reduces the risk of heart attack, heart-related death, stroke, or heart procedures. The other drug component in Vytorin, ezetimibe, has not been shown to prevent any of these cardiovascular outcomes. Furthermore, using the combination simvastatin and ezetimibe product, Vytorin, has not shown any additional cardiovascular benefit compared to using simvastatin alone.

Therefore, upon further review in consultation with the Division of Metabolic and Endocrine Drug Products, and pursuant to the provisions of 21 CFR 202.1(j)(4), we are informing Merck that the Vytorin product claim promotional materials would be misleading because the pieces do not include contextual information disclosing a limitation to the efficacy of Vytorin regarding clinical outcome benefits.

Consequently, we recommend revising any DTC Vytorin product claim promotional material, by adding context, in consumer-friendly language, communicating not only that Vytorin contains two medicines (Zocor and Zetia), but also by conveying that taking the combination drug Vytorin has not been shown to provide any additional cardiovascular outcome benefits compared to using Zocor alone.

Note that this change of opinion applies to the following Vytorin promotional materials (advertising or promotional labeling):

- All Vytorin DTC product claim materials, provided in consumer-friendly language
- All Vytorin product claim materials directed to healthcare providers (HCP), provided in language consistent with the Vytorin PI efficacy limitation
- All Vytorin product claim materials (DTC or HCP), whether they contain comparative efficacy claims/presentations or non-comparative efficacy claims/presentations

Because these comments about disclosing the Vytorin clinical outcomes limitation constitutes a change of opinion, you will be provided a reasonable period of time to revise any Vytorin (DTC or HCP) ad or any other promotional material currently in use that contains these or similar claims or representations. Accordingly, all revisions should be completed within 90 days of receipt of this letter or at the next production, whichever comes first. Please notify DDMAC in writing by February 6, 2008, regarding your intent to comply with our request and the specific date the revisions will be implemented.

If you have any questions or comments, please direct your response to the undersigned by facsimile at (301) 796-9878, or at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications 5901-B Ammendale Road, Beltsville, Maryland 20705-1266.

In all future correspondence on this matter, please refer to MACMIS ID# 12594 as well as the NDA number. DDMAC reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joan Hankin, JD
Consumer Promotion Analyst
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joan Hankin
1/23/2008 03:39:39 PM