PUBLIC SUBMISSION

As of: 11/30/11 8:25 AM
Tracking No. 80f563f2

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0002
Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0012
Jill Matzat RN, BSN, CCRA - Comment

Submitter Information

Address:
FL,
Organization: Medical Research Management

General Comment

Risk based monitoring should not be about central versus onsite. The majority of issues I identify via monitoring are due to lack of onsite visits, site selection, and monitor training. Risk based monitoring should mainly be about a focused approach oppose to 100 % SDV. Currently, Companies are using this guidance (one visit per year) to justify limited onsite monitoring. This is a major mistake on the part of the FDA. There is a direct correlation between adequate monitoring via onsite and quality data as well as HSP. I have been performing different models of risk based monitors since 1999. I am a firm believer in a visit after first subject is enrolled. If an issues it should occur until at least 2-3 subjects can be monitored without issues. I also only monitor critical elements while on site and use central monitoring for low risk items. All subjects have critical elements monitored not one visit per year. We only use monitors that have been extensively trained and competency tested, the training uses a systematic monitoring method, and we employ a system that has checks and balances such as periodic performance assessments to ensure monitoring adequacy.
The other issue is due to HIPAA most EMRs do not permit remote access making much of this suggestion null and void. Many EMRs do not even permit third party access and have to print all documents for monitoring.

The proposed guidance does not address appropraite delegation, PI oversight or eligibiity of subjects to enroll. Only onsite visits can determine this accurately.

Attachments

12340-05_Matzat- The Monitor Article

The attachment is restricted to show metadata only because it contains copyrighted data

wp-stepmethod

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Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring (Document ID FDA-2011-D-0597-0001)

Comments provided by Martin Landray, Jane Armitage, Carol Knott, Jonathan Emberson, Colin Baigent and Rory Collins on behalf of Oxford University Clinical Trial Service Unit (CTSU), Oxford, UK

28th November 2011

General Comment:
The draft FDA guidance on a risk-based approach to monitoring is a big step forward. Implementation of these guidelines should help to improve both the quality and cost-effectiveness of trials. There are a few aspects which would benefit from further clarification in order to avoid inappropriate interpretation by some in the future.

Lines 170-171 and 180-181
II.D. Steps FDA is Taking to Facilitate Wider Use of Alternative Monitoring Approaches
"The Agency also is initiating operational measures to ensure that its review, compliance, and other functions reflect this view of monitoring. Specifically, FDA:
...

- *Will ensure that all affected program areas within FDA are aware of the goals and purposes 180 of this guidance and its compatibility with current CPGMs"*

Comment: It will be essential that FDA inspections are conducted in accordance with the principles outlined in these guidelines. It would be helpful to state this explicitly, including consideration of any modifications that might be necessary to the FDA's standard operating procedures/guidances for inspection of Investigators and Sponsor sites.

Lines 240-251
IV.A.1 On-Site Monitoring
"On-site monitoring is an in-person evaluation carried out by sponsor personnel or representative(s) at the site(s) at which the clinical investigation is being conducted. On-site monitoring can identify data entry errors (e.g., discrepancies between source records and CRFs) and missing data in source records or CRFs; provide assurance that study documentation exists; assess the familiarity of the site's study staff with the protocol and required procedures; and assess compliance with the protocol and investigational product accountability. On-site monitoring can also provide a sense of the quality of the overall conduct of the trial at a site (e.g., attention to detail, thoroughness of study documentation, appropriate delegation of study tasks, and appropriate investigator supervision of site staff performing critical study functions). Therefore, on-site monitoring ordinarily should be devoted to assessing the critical study data and processes and evaluating significant risks and potential site non-compliance identified through other sponsor oversight activities."
Comment: One approach to on-site monitoring that can be particularly valuable is observation of participant visits (with the appropriate level of consent from participants). This can be very helpful in assessing whether the researcher (investigator or delegated staff) is effective in explaining study-related issues (important for consent, safety and encouraging compliance) and capturing important information (by contrast retrospective comparison of data recorded on the case report form with some routine medical record makes the assumptions that such documents exist, are accurate, and are available). Visit observations have been used by monitors in many trials for over 20 years and

have been found to be very effective in ensuring that participants are fully informed about the study both at the initial visit (when consent is taken) and throughout (as the participant's health or other issues change, and new information becomes available about the study treatments). Furthermore, observation of participant visits allows a direct assessment of the way in which study staff perform study procedures (e.g. clinical measurements) and prompt re-training where necessary.

Lines 251-254
IV.A.1 On-Site Monitoring
"On-site monitoring is particularly critical early in a study, especially if the protocol is complex, and includes novel procedures with which investigators may be unfamiliar. Findings at the site may lead to training efforts both at the site visited and elsewhere (see section VI.A)."

Comment: Delete "is particularly critical" and replace with "can be particularly helpful"

Line 267
IV.A.2 Centralized Monitoring

Comment: The explicit support for centralized statistical monitoring is very welcome. This approach is key to improving efficiency, by limiting the amount of on-site monitoring necessary, and increasing the effectiveness of visits that are done.

In addition to current reference 31 (Rory Collins presentation at CTTI work-stream 3 meeting), add: Buyse M, George SL, Evans S, et al. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. Stat Med. 1999; 18:3435-51.

Line 299-308
IV.B Identify Critical Data and Processes to be Monitored
"Sponsors should perform a risk assessment that generally considers the types of data to be collected in a clinical trial, the specific activities required to collect these data, and the range of potential safety and other human subject protection concerns that are inherent to the clinical investigation. Sponsors should consider the findings of the risk assessment when developing a monitoring plan. There is increasing recognition that some types of errors in a clinical trial are more important than others. For example, a low, but non-zero rate of errors in capturing certain baseline characteristics of enrolled subjects (e.g., age, concomitant treatment, or concomitant illness) will not, in general, have a significant effect on study results. In contrast, a small number of errors related to study endpoints (e.g., not following protocol-specified definitions) can profoundly affect study results, as could failure to report rare but important adverse events."

Comment: It is important to emphasise that randomized controlled trials can be remarkably robust to missing or incorrect data on clinical outcomes.

For errors that occur at *random* with respect to treatment allocation, data that are missing or measured with greater error (including diagnostic misclassification or inaccuracies in clinical or laboratory measurements) will add noise so that the chances of detecting a real effect are reduced but will not bias the results in favour of any particular treatment. Where the results are to be used to provide information on superiority of one intervention over another (including no treatment, usual care or some other comparator), such random errors are conservative. By contrast, for results

that seek to provide information that one intervention is not inferior to another (i.e. non-inferiority), such random errors are counter-conservative, increasing the probability of falsely concluding that two treatment strategies are similar.

Of much greater concern are errors that are *not random* with respect to treatment allocation since these may bias the study conclusions. Important examples include errors in random sequence generation or in allocation concealment (the ability to predict which treatment a participant is likely to get if they are included in the trial), and differences in the ascertainment of endpoints between the randomized treatment groups.

Furthermore, the extent to which missing data can be tolerated will depend on size of the study (or more specifically the number of relevant outcomes). For example in a trial with 1:1 randomization and 1800 primary events (800 vs. 1000 in the two randomized groups), the clinical and statistical conclusions would not be materially altered even if information about 20% events was missing (providing this was at random with respect to study treatment allocation).

Hence, the statement that "*a small number of errors related to study endpoints can...profoundly affect study results*" without the above clarification could be widely misinterpreted.

Line 310-311, 320-321
IV.B Identify Critical Data and Processes to be Monitored
"A study protocol should clearly identify those procedures and data that are critical to the reliability of the study findings. These generally should include:
• *Processes that underpin the integrity of these data, such as blinding or referring specified events for adjudication"*

Comment: The last bullet point (lines 320-321) should include randomization and allocation concealment (i.e. the ability to predict which treatment a participant is likely to receive if they are included in the trial) along with the other examples given (blinding or referring specified events for adjudication).

Line 326-330
IV.B Identify Critical Data and Processes to be Monitored
"The following types of data and processes should ordinarily be subject to more intensive (e.g., higher frequency and more comprehensive) monitoring:
- *Conduct and documentation of procedures and assessments related to*
  - *critical study endpoints,*

Comment: See comment in relation to Lines 299-308, above.

Line 326-327, 335-336
IV.B Identify Critical Data and Processes to be Monitored
"The following types of data and processes should ordinarily be subject to more intensive (e.g., higher frequency and more comprehensive) monitoring:
- *Adherence to protocol eligibility criteria intended to include only subjects from the targeted study population for whom the test article is most appropriate"*

Comment: The focus should largely be on those eligibility criteria that are designed to exclude individuals for whom the treatment may be less safe than the protocol intended.

Line 326-327, 337-338
IV.B Identify Critical Data and Processes to be Monitored
"The following types of data and processes should ordinarily be subject to more intensive (e.g., higher frequency and more comprehensive) monitoring:
- *Conduct and documentation of procedures for ensuring that the study blind is maintained, both at the site level and at the sponsor level, as appropriate"*

Comment: Not all trials are (or need to be) blinded. Similarly not all the parties involved (participants, investigators, monitors) are (or necessarily need to be) blinded but it is critical that the randomization process is concealed (and therefore unpredictable) and that where event adjudication is required it is conducted blind to treatment allocation.

Line 326-327, 339-340
IV.B Identify Critical Data and Processes to be Monitored
"The following types of data and processes should ordinarily be subject to more intensive (e.g., higher frequency and more comprehensive) monitoring:
- *Verification that initial informed consent was obtained appropriately, prior to any study-specific procedures"*

Comment: Verification is just one possible approach. Other approaches can be valuable:
- use of electronic systems, including electronic signature (as is done for some financial transactions) can ensure that consent is taken prior to study entry and can improve quality by ensuring that participants are made aware of each of the issues covered by the consent process and, where appropriate, specifically record their consent (or non-consent).
- observation of participant visits can help to ensure that participants are fully informed about the study both at the initial visit (when consent is taken) and throughout (as the participant's health or other issues change, and new information becomes available about the study treatments).

Line 326-327, 341-343
IV.B Identify Critical Data and Processes to be Monitored
"The following types of data and processes should ordinarily be subject to more intensive (e.g., higher frequency and more comprehensive) monitoring:
- *Procedures for documenting appropriate accountability and administration of the investigational product (e.g., ensuring the integrity of randomization at the site level, where appropriate)"*

Comment: See comment at beginning of this section. There are a number of errors that might introduce bias. "Randomization at the site level" is just one component and it would be helpful to introduce earlier the concept of errors that might introduce bias or which might introduce noise (and the implication of such noise on the interpretation of the results).

Lines 405-406

IV.D Monitoring Plan

"For each clinical trial, the sponsor should develop a monitoring plan that describes the monitoring methods, responsibilities, and requirements for the trial."

Comment: It would be helpful to explain that the Monitoring Plan should be part of a strategy for ensuring oversight of the quality of the trial. For example, by adding, "... and how these fit in with the overarching plan to maintain the quality of the clinical trial" to the end of the opening sentence in this paragraph.

Lines 501-508

V Documenting Monitoring Activities

"Documentation of monitoring activities should include the following:

- *The date of the activity and the individual(s) conducting it*
- *A summary of the data or activities reviewed*
- *A description of any noncompliance, potential noncompliance, data irregularities, or other deficiencies identified*
- *A description of any actions taken, to be taken, and/or recommended, including the person responsible for completing actions and the anticipated date of completion"*

Comment: Some of this activity could be onerous or unnecessary, particularly if activities are being undertaken very frequently or even continuously (e.g. central monitoring by automated IT checks). It would be better to require that monitoring activities should be documented in sufficient detail to allow retrospective audit that the Monitoring Plan was followed, perhaps listing the bullet points as "for example".

eClinical Forum

Date 10-Nov-2011

Address: Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852

RE: Docket No. FDA-2011-D-0597

Dear Sir or Madam:

We are writing on behalf of the eClinical Forum Electronic Records Working Group, which represents a cross-section of our member companies affected by this proposed guidance. The eClinical Forum was started in 2000, the idea of a group of people who were keen to meet and discuss all aspects of Electronic Data Capture and eClinical. In the ensuing time, the membership has grown, and there are now over 40 member companies from the Pharmaceutical and associated industries. Today we are a registered association in France.

Our mission is to provide a non-profit making environment to serve those members of the pharmaceutical and allied industries who are or will be involved in 'eClinical' (electronic data acquisition, processing and use) initiatives by focusing on those systems, processes and roles relevant to clinical data to support submission. We aim to establish open communication between members and stakeholders to provide the practical information, approach and learning experiences required to maximise the success of eClinical initiatives.

We have reviewed the subject document in detail and have developed a number of comments, both general and specific. Specific comments are contained in the attached table. In general, we are very pleased with the structure and content of this document and welcome it as a guidance.

We hope that our comments prove useful and contribute to the improvement of this draft guidance. Please contact either of us with any questions regarding eClinical Forum's comments.

With kind regards,

Richard Perkins
President
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Suzanne Bishop
Facilitator
suzannekbishop@gmail.com +1 908 752 4320

eClinical Forum

eClinical Forum comments re: Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

FDA Docket No. FDA-2011-D-0597

eCF#	FDA Line #	eClinical Forum Comment	eClinical Forum Recommendation
1	182 - 183	Will CBER also be contacted to voluntarily and prospectively submit and receive feedback on proposed monitoring plans?	Add CBER to text
2	297	In general, it would be nice to see the same diagram around risk assessment as in the EMA guideline (Line 248 Figure 1 and page 19-Risk Identification) to outline the risk based assessment and include examples.	
3	361	"...Examples may include studies with adaptive designs, stratified designs, complex dose titrations, or multiple device placement or unblinded studies."	Add complex or novel procedures to this list.
4	61-62	"FDA is considering the need for additional guidance describing overarching quality risk management approaches to clinical trial oversight." Will this guideline be similar to the EMA guideline?	
5	159- 162	Is this correct ..... "In addition, source data verification and other activities traditionally performed by on-site monitoring can now often be accomplished remotely, as both trial data and source data **typically** become part of the central submission."	Remove typically from this sentence
6	544	Define oversight. (Not how to do it, but what they expect) Lay out high level with words like'such as', and 'for example'. Can you approach this by using a risk-based approach to vendor management?	Add examples to the statement

AstraZeneca

Date: 22nd November 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number FDA–2011–D–0597
Response to FDA Call for Comments
Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear Sir or Madam:

Reference is made to the 29th August 2011 Federal Register notice announcing the request for comments on Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Mikael Werner, Change & Benefit Manager/ Lead Advisor, at +46 31 7064178.

Sincerely,

/RT

Mark Tuersley

Mark Tuersley
Study Standards Process and Tools Transition Director
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Enclosure

Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

AstraZeneca Response to FDA Call for Comments on Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring
Docket No. FDA–2011–D–0597

General Comments

- **Comment 1**

  The concepts described in the guidance align closely with thinking developed within AstraZeneca. Consequently implementation of this guidance will facilitate actualisation of a risk-based monitoring approach within AstraZeneca.

- **Comment 2**

  Overall, the guidance document is quite clear

- **Comment 3**

- Generally a very comprehensive guideline; however, there is quite a lot of repetition among sections and long explanations to why FDA is taking this step now. We think that it is possible to shorten the background section for the benefit of the reader to concentrate on the actual recommendations provided. Although this guidance is important and will provide important information on FDA's view, it will arrive at a point in time when centralized (remote monitoring) is already frequently used and as written it seems like it looks back more than forward.

- **Comment 4**

  The increased use of centralized monitoring, targeted monitoring and reduced monitoring may lead to a temporary or longer-term increase in the incidence of compliance issues at those sites that rely heavily on on-site monitors to perform their QC. To ensure that sites take full responsibility for the work performed at their facilities, a suggestion is made that guidance should be created to recommend that all sites participating in clinical studies have SOPs in place to govern the conduct of studies at those sites and that would further underscore the accountability of the Principal Investigator and Sub-Investigator(s) responsibilities.

- **Comment 5**

  Unfortunately, the proposed guidance does not give clear guidance HOW to implement and apply risk based quality management.

- **Comment 6**

- Impact of non-compliance by investigators in clinical trials should be confirmed in all countries by regulatory authorities and IRB/IECs – and not only by the sponsor of the trial

Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.		
Section	**Page or Line Number**	**Comment or proposed replacement text**
Section I-Introductio n	Line 19-20	Scope: Does this guidance also apply to studies conducted using marketed product eg non-interventional studies, RWE, HE/OR?
Section I &II	Line 30 to 34, 176	FDA indicates the guidance is not legally enforceable and should be viewed as a recommendation; yet plans are to update the CPGM monitoring compliance guidance manuals with these approaches. This would mean that FDA inspectors could hold Sponsors to a standard that is not required.
Section II D	Line 160, 194	There does not appear to be specific guidance around adherence to privacy legislation.
Section II D	Line 160, 194	Regarding use of centralised monitoring, the guidance makes a general assumption that either Sponsors have unrestricted access to subjects' electronic medical charts (the actual source) or they are condoning the use of study specific "source worksheets" that would be scanned and sent to the monitor. The use of "source worksheets" has confused the industry as these worksheets often contain information that is transcribed from the charts and cannot readily be considered source.
Section II D	Line 182-186	Steps FDA is Taking to Facilitate Wider Use of Alternative Monitoring Approaches According to the last bullet- "Voluntarily and prospectively receive feedback to monitoring plans." If this is implemented it is important to know the expectations from the agency on material provided (should SOPs etc be part of this review if referenced), time lines for review, expectations from the agency on suggestions on the plan.
Section II D	Line 197-198	This states that the complete absence of on-site monitoring will continue to be unusual. We would question whether we would ever have a complete absence of on-site monitoring to ensure the general quality of the clinical trial, some of which could not be performed remotely.

Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.		
Section	**Page or Line Number**	**Comment or proposed replacement text**
Section IV A	Line 256-295	Many of the central monitoring strategies proposed involve statistical analysis of data points, site characteristics; and performance metrics. This will place an increased financial burden on companies of all sizes to provide additional resources to perform complex statistical analyses to supplement traditional monitoring. Increased central monitoring means that a flexible workforce of CRAs would still be required to visit the sites to follow-up on identified issues.
Section IV A	Line 265	Centralized Monitoring Please add to bulleted list "Minimize impact of poor retention rate and risk of patients lost to follow-up on data quality". Also "Identify at an early stage requirements for further training needs on a study, country and site level".
Section IV A	Line 277 and 288	Although there is a disclaimer that implies that remote SDV is dependent on having accessibility to electronic records, in most countries, privacy and health information protection laws make this very difficult to achieve.
Section IV A	Line 277	The strategies and requirements around remote monitoring needs more development. For example, a description should be provided of typical source documents that can be reviewed remotely without breaching subject privacy; and any necessary security measures that need to be in place. For example, are they expecting the remote monitoring of source documents and CRFs to be done at the company location or can it be done at the CRAs home location where the computer may not have as many security controls?
Section IV B	Line 339	While the need for verification of consent prior to study-specific procedures is identified, there is no mention of verification of patient existence which is a key aspect of source data verification.

Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.		
Section	**Page or Line Number**	**Comment or proposed replacement text**
Section IV C	Line 348, 403	Recommend that FDA provide an example of an acceptable Monitoring Plan that incorporates the various monitoring strategies that are proposed in the guidance.
Section IV C	Line 348	Re the option to submit the Monitoring plan for review by FDA. AZ has developed a targeted Source Data Verification template and Local Monitoring plan that together capture the idea of Monitoring plan as described in the guidance. However, while the SDV template is developed centrally, the Local Monitoring Plans are developed on a country by country basis and may pose a challenge to this prior consultation approach.
Section IV C	Line 394-395	This talks of more monitoring at an early stage. It would be worth making it clear whether this is at the site-level or study-level
Section IV D	Line 431	Suggest add the following "....interpret the primary endpoint or data related to the general integrity of the trial, regardless of which monitoring method ....."
Section IV D	Line 473	We see co-monitoring described here as long existing best practice.
Section IV D	Line 487	The potential process for CDER Review of sponsor monitoring plan is seen as a positive way to obtain early feedback. Would the evaluation be of the initial plan and not amended versions?
Section V	Line 510	It is stated Monitoring documentation should be provided to appropriate management in a timely manner for review or, as necessary, follow-up. It would be helpful for guidance on whether all reports should be reviewed (MVRs, Contacts reports) or a sample of that documentation is acceptable.
Section VI A	Line 515	Suggest incorporating language as to what strategies a QA or QC function could employ to provide independent assessment and checks and balances of compliance to the Monitoring Plan.
Section VI A	Line 533-536	It is important to consider the use, appropriate to the study need, of other training methods than just training at site. However not sure why these are highlighted as "alternative training methods" since these methods should also be quite established by now and can be documented properly. Also investigators meetings are used.

PUBLIC SUBMISSION

As of: 11/30/11 8:22 AM
Tracking No. 80f1b059

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0002
Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0005
Anonymous - Comment

Submitter Information

Address:
IL,
Submitter's Representative: Self
Organization: Private

General Comment

It is with respect that I humbly must come forward and comment on the document: Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring (Document ID FDA 2011-D-0597-0002). I have to say, based on my 10 years of experience conducting and overseeing clinical trials and other forms of clinical and outcomes research, that I am in nearly complete disagreement with FDA regarding their position on centralized monitoring for select types and portions of clinical trials. I have seen many studies in need of on-site monitoring where it has either not occurred at all or not enough. I have monitored sites myself, in person, where fraud is taking place, and the only way I would have discovered it was by being at the site and seeing it with my own eyes, going through documents that have not been filtered, and seeing discrepancies between signatures, handwriting and errors/corrections. What the FDA does not seem to recognize is just how much human behavior plays into the conduct, and thus, data and results, of clinical trials. Centralized Monitoring, seems to be a way to cut corners in efforts to save time and money in the name of a more 'efficient' and 'appropriate' approach to clinical trials, which, in my mind, is really neither. I guarantee that centralized monitoring, if applied generally, would increase, not decrease, risks to both human subjects and that integrity of the data that is reported, and therefore, the safety of drugs approved for marketing. Further, the examples of ways it would be helpful, e.g. statistical analysis of current data, patterns among subjects and sites, etc., are not necessarily those that on-site monitoring seeks to achieve. Protecting human subjects cannot truly be done without in-person contact via on-site monitoring, and thorough review of all study and relevant clinical records. Ultimately, I would assert that the notion of centralized monitoring, with the exception of a few types of studie

Note - Comment is incomplete in regulations.gov

PUBLIC SUBMISSION

As of: 11/30/11 8:25 AM
Tracking No. 80f144e0
Comments Due: November 28, 2011

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0004
Anonymous - Comment

Submitter Information

Address:
UT,
Organization: University of Utah

General Comment

This is a well thought out document and is helpful in clarifying the regulation.

Submit a Comment

You are commenting on a Other:

Please note that you are provided 30 minutes to complete this form and submit your comment. If your session times out your

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Draft Guidance for Industry; Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (FDA-2011-D-0597-0002)

INFORMATION

First Name:	Kenneth
Middle Name:	Charles
Last Name:	Malley
Country:	United States
State or Province:	Pennsylvania
Organization Name:	ALmedtrac, Inc.
Submitter's Representative:	Kenneth C. Malley
Category:	Drug Industry - C0022

COMMENT

Reducing site inspections will increase the risk associated with patient safety, regulation compliance and data validation of trial results: 1) reduces, now effective 100% proof by physical inspections, 2) increases reliance on volumes of questionable/inscrutable data, 3) reduces the threat of possible inspection which in itself reduces the risk of fraud, waste, and abuse, 4) current monitoring techniques do not facilitate understanding and analysis of study issues, 5) centralization of current monitoring techniques will significantly decrease understanding and responsiveness to local issues and performance and abdicate FDA oversight responsibilities. There are major problems with the information needed and available to carryout monitoring oversight at the FDA: 1) the information is not consistent across clinical studies, 2) all the information is not in relatively standard electronic form, 3) the information does not have patient-level detail where compliance, patient safety and trial validation is taking place, 4) the information is not in real-time and places oversight in a catch-up, after-the-fact position, 5) the information is not time and date stamped to correlate with local site events designed into the protocol, 6) the same information does not support all levels of management involved in the trial: direct participants, review managers, oversight management. Overall the information is voluminous primarily consisting of pages words and numbers making it difficult to draw conclusions regarding site issues and performance, to justify follow up inspections, and does not facilitate correlation of source data and trial results. Effective site monitoring must rely on automated solutions and services to mitigate the risk of reducing physical inspections. An innovative solution was recently developed by Almedtrac, Inc. in collaboration with General Dynamics, U. of Pittsburgh and Carnegie Mellon U.. Contact: 1-877-888-9187, info@almedtrac.com, www.almedtrac.com

Attachments:

FDA-2011-D-0597

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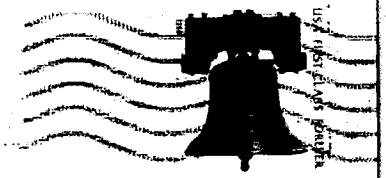

DOCKETS MANAGEMENT BRANCH (HFA-305)

FOOD & DRUG ADMINISTRATION

5630 FISHERS LANE, RM 1061

ROCKVILLE, MD. 20852

PUBLIC SUBMISSION

As of: 11/30/11 8:23 AM
Tracking No. 80f50d1e
Comments Due: November 28, 2011

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0008
Janet Athene Lane - Comment

Submitter Information

Address: United Kingdom,
Organization: University of Bristol

General Comment

We have conducted a systematic review of the published literature on on-site monitoring systems for clinical trials that would help inform this guidance. Presented at the SCT conference, abstract in Clinical Trials 2010 7:428, full paper under review at Clincial Trials. I can send this when accepted if you wish? we have just had referees comments and are revising the paper.

PUBLIC SUBMISSION

As of: 11/30/11 8:24 AM
Tracking No. 80f5cc85

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0002
Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0013
Colin Wilsher - Comment

Submitter Information

Address: United Kingdom,
Organization: BARQA

General Comment

The FDA Webinar stated that consent could be monitored remotely as well as on site. How can this be done remotely without violating data privacy and still giving assurances that the subjects have given genuine informed consent? More guidance on this would be welcome.

PUBLIC SUBMISSION

As of: 11/30/11 8:24 AM
Tracking No. 80f62936
Comments Due: November 28, 2011

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0014
Wayne Martin - Comment

Submitter Information

Address:
WA,
Organization: clinical research associate

General Comment

The content of this draft guidance is really nothing new; risk-based approaches to data monitoring have been implemented by many sponsors over the past 10 years. Unfortunately over the past 10 years the research landscape has also widely changed at the investigative site end with regard to the training/experience of site staff performing data capture. (In today's tight economy more and more sites are hiring people without medical training and/or research experience.) While remote/central data reviews are an invaluable adjunct to monitoring when an EDC system is utilized, it is unrealistic to expect that edit checks and reviews for data outliers, etc. will ultimately result in the same level of data accuracy resulting from on-site monitoring of data against the actual source documentation.

PUBLIC SUBMISSION

As of: 11/30/11 8:27 AM
Tracking No. 80f55070
Comments Due: November 28, 2011

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0011
Cheryl Elaine Kelly - Comment

Submitter Information

Address:
AZ,
Organization: St Joseph Hospital and Medical Center

General Comment

While lines 464 -469 seem to address monitor training it does not speak to qualifications or training necessary for a particular type of trial. Several references are made regarding investigator experience and knowledge level as appropriate for a particular study , but the same is never addressed for monitors who actually perform both onsite and remote monitoring. The level of expertise in relation to a particular trial of a monitor has direct bearing on the quality of data reported, esp. in the area of adverse events, which bears directly on human subject safety and effeciency of the study. I have had monitors come to verify data on intricate neurosugical clinical studies whose back ground and most recent job was in Human Resources. If monitors are coming to monitor clinical studies, they should at least have some sort of clinical background or training. The data management people should work with the data, but when it comes to deciding what gets reported to them for data inclusion and what does not and what emphaisis it has comes from the monitor. How accurate can that be if the monitor does not even know the terminology of the area to be monitored? How time consuming for the investigative site if for every explaination there needs to be an anatomy and physiology lesson preceeding it. I am not suggesting that each monitor be an expert in his/her field, but posess at least a general working knowledge of the subject matter, ie nurses, respiratory therapists, etc., for clinical trials. Someone who understands drug interactions, basic knowledge of how the body functions, etc. Sponsors should tailor monitor expertise and background to the nature of the study. Someone with a clinical background should be sent to monitor a clinical study as a safe guard to subjects both in the trials and those that will later use the products as the general public.

PUBLIC SUBMISSION

As of: 11/30/11 8:24 AM
Tracking No. 80f273d1

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0002
Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0006
Hans-Joachim Kremer - Comment

Submitter Information

Address: Germany,
Organization: Medical Writing Service

General Comment

I am overall appreciating the proposed guidance!
However, lines 339 to 340 currently read:
"Verification that initial informed consent was obtained appropriately, prior to any study specific procedures"
I am proposing to discard the words "prior to any study specific procedures" from this bullet point.
Rationale: The FDA Information Sheets "Screening Tests Prior to Study Enrollment" specifically and very thoroughly address problems with informed consents and screening tests prior to study enrollment. The words criticised above, however, appear to be too simple in this respect and would many people wonder, whether the rules outlined in the information sheets are still valid. In fact, few have recognised that information sheet, but many believe in the strict "prior to any...".
The attribute "appropriately" appears to be clear enough, given that there are so many rules around informed consents.

PUBLIC SUBMISSION

As of: 11/30/11 8:32 AM
Tracking No. 80f10277
Comments Due: November 28, 2011

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0003
Jules T Mitchel - Comment

Submitter Information

Address:
NY,
Organization: Target Health Inc.

General Comment

Congratulations on allowing the Industry to finally run clinical trials in a more sensible manner. This is an excellent guidance which will permit the Industry to replace labor-intensive, minimally productive procedures with currently available technologies and approaches to improve the monitoring of the quality of clinical trials and the safety of patients participating in clinical trials. Specifically, the following lines are critical:

Line 62: Quality is a systems property that must be built into an enterprise and cannot be achieved by oversight or monitoring alone.

Line 176: Will ensure that the bioresearch monitoring compliance program guidance manuals (CPGMs) 176 for sponsors, CROs, and monitors (CPGM 78.810) 24 and for clinical investigators and sponsor-investigators (CPGM 78.811)25 are compatible with the approaches described in this guidance

Line 204: Many other factors contribute to the quality and integrity of a clinical investigation. The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol. A poorly designed or ambiguous protocol or case report form (CRF) may introduce systemic errors that can render a clinical investigation unreliable despite rigorous monitoring. Study-specific training of investigators, other site staff, and monitors also **contributes significantly to study quality.**

PUBLIC SUBMISSION

As of: 11/30/11 8:33 AM
Tracking No. 80f520e5

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0002
Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0010
Anonymous - Comment

Submitter Information

Address:
AZ,
Organization: Anon

General Comment

Much is made in the guidance about the advancement of EDC systems and factors that influence study quality and integrity (lines 189-220). Given the increasing number of electronic systems used by sites (eg, eCRF, IWRS), what is curiously missing is any mention of data security as a component of on-site or centralized monitoring.
Data integrity is not possible without data security. And yet, in the monitoring plan parts of this guidance (lines 348-434), there is no reference to the monitoring of data security measures. This includes the most basic security measure of checking accounts to make sure only authorized users have access (ICH E6 5.5.3) CRO and sponsor monitoring plans are not completely different in this regard. Given that monitoring (either on-site or centralized) is the only way to determine who should have system access, it is unclear why data security is omitted.
Security problems typically begin with organizations (Baldwin. Heath Data Management Oct 1999). There is no published information to suggest that clinical trials function differently. So, clinical trials should take a proactive approach to data security. Aside from that, the same healthcare system that provides clinical research data is now afflicted with medical identify theft, the fastest form of identify theft in the US (MedPage Today Sept 23, 2011). This is not to suggest that sponsors should monitor any and all possible security problems that take place at their sites and within their organizations. Rather it is to suggest that data security/protection activities should be created that are risk-based, well-documented, monitored, and adjusted as circumstances emerge. To not explicitly recognize and formulate a plan to monitor data security is neither good risk management nor good quality assurance.

PUBLIC SUBMISSION

As of: 11/30/11 8:36 AM
Tracking No. 80f51351

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0002
Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0009
Anonymous - Comment

Submitter Information

Address:
NC,
Organization: Anon

General Comment

Definition of monitoring:
While it may be true that ICH E6 acknowledges the utility of central monitoring in assuring appropriate conduct of a trial (lines 189-196; ICH E6 5.18.3), it is important to note centralized monitoring in this guidance is not synonymous with central monitoring in ICH E6 5.18. Central monitoring in ICH E6 is performed by a monitor whereas centralized monitoring in this guidance is performed by a monitor, data manager, and/or biostatistician (lines 259, 265-285).
It is unclear why traditional and emerging data QC (conducted in the spirit of ICH E6 5.1.3) by data managers and biostatisticians should be re-identified here as monitoring. This guidance's idiosyncratic use of monitoring has the potential to cause ambiguity and confusion.
The Duke Ching, of Ch'i, asked Confucius about government. Confucius replied, "There is government, when the prince is prince, and the minister is minister; when the father is father, and the son is son."... "If names be not correct, language is not in accordance with the truth of things. **If language be not in accordance with the truth of things, affairs cannot be carried on to success."**

Ekopimo O. Ibia, MD, MPH
Director and U.S. Regulatory Policy Leader
Global Regulatory, Strategy, Policy, and Safety

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November 28, 2011

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA–2011-D-0597: Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck) is a global healthcare leader. Through a combination of the best science and state-of-the-art medicine, Merck has produced many important medicines and vaccines. Today the company is continuing to actively develop a broad portfolio of small molecules, vaccines and biologic products, including biosimilars to significantly improve worldwide patient access to important/life-saving therapies.

In the course of bringing Merck drug and biological product candidates through development, Merck scientific teams have acquired extensive experience that informs the comments below.

General Comments

We commend the Food and Drug Administration (FDA or the Agency) for issuing this guidance to assist sponsors in developing risk-based monitoring strategies and plans for investigational studies of medical products in order to enhance human subject protections and integrity of clinical trial data. Specifically, we applaud the guidance's focus on critical study parameters that relies on a combination of monitoring activities as well as the strong emphasis on greater use of centralized approach to monitoring; an approach that takes advantage of available technologies such as electronic data capture (EDC) but also acknowledges the role for on-site monitoring, when necessary. We urge the Agency to clearly define the balance between on-site and centralized monitoring. As written, the guidance may be interpreted as to overly lean toward centralized monitoring. A well-defined and balanced approach is crucial since available technology is unlikely to replace completely the benefits of the human element involved in on-site monitoring. In addition, the guidance recognizes that sponsors may already be leveraging centralized monitoring capabilities across functions (such as medical monitoring, SAE management, and data management).

The title and Lines 163-166 suggest the guidance aims to "clarify that risk-based monitoring, including the appropriate use of centralized monitoring and technological advances [...] can meet statutory and regulatory requirements under appropriate circumstances." However, as written, it is unclear if the focus of the guidance is on "risk-based monitoring" (i.e. only on higher risk areas) versus intense monitoring performed remotely.

Further, we note the additional emphasis on the creation of a dynamic monitoring plan with the expectation to document all monitoring aspects, including management of non-compliance. The approach attempts to define responsibilities for site, sponsor, and health authority. However, it is unclear if "documenting monitoring activities" is the expectation for centralized monitoring. The guidance should clarify if in-house personnel would be recommended to document their activities routinely, how the expectations would be accomplished for continual review across multiple sites, and how this documentation would work seamlessly with reports from on-site visits.

For additional clarity and in order for the guidance to sufficiently serve its purpose, we strongly recommend that CDER should:

- ensure internal consistency of the oversight processes across review divisions;
- describe the relationship of the guidance to the ongoing site selection model pilot within the CDER Office of Scientific Investigations (OSI);
- specify if the monitoring plan will be at the individual study level or is more appropriate for the entire program;
- make a distinction in the guidance between monitoring plan from the medical monitors' perspective vs. that of clinical research associates (CRAs) and other clinical trial staff; and
- recognize that if the monitoring plan is trial specific it may trump the sponsor's standard operating procedures (SOPs)

In addition, we believe this guidance should cross-reference the draft guidance on electronic source documentation.[1] As we noted in our comments regarding the latter draft guidance, it is critical that FDA and sponsors obtain a common understanding of EDC with respect to source data, data flow, and data release because the implications for implementing the draft guidance on electronic source documentation and the current draft guidance could be overly burdensome for clinical investigators and could impede sponsors' abilities to monitor safety and data quality in real time.

Moreover, while this draft guidance does not explicitly state how the monitoring plan may be submitted to the Agency for review, it seems to imply that much of what will be in the monitoring plan would be expected to be included in the protocol (Section IVB, pages 9-10). We are concerned that any expectation to include the monitoring plan in the protocol and thereby having it reviewed by CDER OSI could have the unintended consequence of delaying trial start up. Furthermore, Merck is committed to making protocols available to

[1] Draft Guidance for Industry: Electronic Source Documentation for Clinical Investigations http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM239052.pdf

peer reviewed journals at the time the covered study is submitted. To that end, we believe protocols should be focused on the essentials of study design and more peripheral issues would be best addressed in separate documents or appendices. Therefore, a preferred approach would be to submit the monitoring plan separately or as part of other non-protocol submission to the IND. If the guidance still expects submission of the monitoring plan in the protocol, the Agency should ensure it establishes clear turnaround times across appropriate review divisions and allow for it to be done as an appendix. Regardless of the Agency's preferred approach, the feedback should be timely and the guidance should clarify whether such feedback would be binding and if an ongoing study should be put on hold until the sponsor receives feedback on any monitoring plan or amended plan that may have been submitted for that study.

Finally there is a reference to the practice that "government agencies and oncology cooperative groups visit sites only once every two or three years to qualify/certify clinical study sites". It would indeed be a very welcome innovation if a certification could be granted to study sites by an official body. This would ensure that adequate standards can be expected from the study site and on-site monitoring can be less intense.

Specific Comments
In addition to the general comments above, the table that follows provides specific comments on sections of the Draft Guidance.

We appreciate the opportunity to share our comments on the Agency's draft guidance titled Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring. For further information or questions, please contact me by phone at 301-770-8861, or email ekopimo_ibia@merck.com.

Sincerely,

Ekopimo Ibia, MD, MPH
Director and US Regulatory Policy Lead
Global Regulatory Strategy, Policy & Safety

159-161 & 277-278	While sponsors may have access to vendor-provided reports about source - lab assays, ePROs etc., the guidance seems to suggest that sponsors have centralized access to source documents, in addition to e-CRFs. Therefore, the Agency should clarify the guidance's frequent references to sponsor's ability to remotely monitor/verify source data. Generally, sponsors conducting trials, including trials conducted utilizing EDC, do not have access to source centrally or remotely.
262-265	The Agency's strong recommendation to use centralized monitoring will need a phased approach or pilot phase to understand and develop the appropriate centralized processes. If greater reliance is to be placed on centralized monitoring and the benefits of centralized monitoring are to be realized, existing processes will have to be re-engineered and development of additional technological capabilities will be necessary.
284-285	The draft guidance recommends that sponsors use centralized monitoring processes to complete administrative and regulatory tasks (e.g., collecting and archiving regulatory documents). It would be especially helpful if the Agency could provide additional information (with examples) on how such tasks could be completed by centralized monitoring.
292-295	The guidance may be interpreted to suggest that on-site monitoring is essential at the beginning of the trial and that that remote monitoring alone should be sufficient thereafter. Since guidances, generally, tend to become the standard, we urge that the Agency revise the section for clarity.
299-300 & 323-343	The recommendation to perform risk assessment for each trial will also need a phased approach or pilot phase to understand and develop the appropriate risk assessment methodologies appropriate to different trial phases. The extent to which errors will be more prospectively detected and remediated should increase as more knowledge is gained about the investigational drug and as more experience is gained using new risk-based assessments, tailored monitoring plans and centralized monitoring methods. Further, if the suggestion is to make risk assessment a crucial part of the monitoring process, the guidance is unclear regarding the expectation on the documentation as evidence that the assessment was done. In addition, the guidance is unclear if review of the assessment will be part of the inspection process.

406-407	The monitoring plan has traditionally been a document geared toward and used by clinical research associates (CRAs). The proposed monitoring plan in the draft guidance seems to be directed toward any role involved with monitoring. The increased depth and complexity of a monitoring plan would be more useful at a study (or program) level, but perhaps less user-friendly for the original CRA audience.
515-545	The guidance states that "[a] number of additional steps can be taken to ensure appropriate human subject protection and high data quality" but provides only two potential steps, one regarding training and the other delegation to a Clinical Research Organization (CRO). It would be beneficial if the Agency could furnish more examples in the guidance. Secondly, it is not quite intuitive to bring up delegation to CRO under this section. We suggest the Agency should clarify its rationale for doing so. Further, we suggest the Agency provide more detail regarding potential delegation to a CRO, especially in light of increasing industry move toward strategic outsourcing. For example, is it the Agency's thinking that there may be additional considerations with regard to selecting monitoring methods when a CRO is involved?

PUBLIC SUBMISSION

As of: December 07, 2011
Received: September 19, 2011
Status: DoNotPost
Category: Individual Consumer
Tracking No. 80f22919
Comments Due: November 28, 2011
Submission Type: Web

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-DRAFT-0005
Barbara Sanford - Comment

Submitter Information

Name: Barbara Sanford
Address: GA
Submitter's Representative: N/A
Organization: N/A

General Comment

Document:
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring (Document ID FDA 2011-D-0597-0001)

I have been a nurse for over 30 years and also a patient in a Clinical trial. I believe this draft document is vague, does not provide definitive guidance and the implications are irresponsible.

The most important aspect of a Clinical Trial should still be " patient safety ". This document suggests the most important aspect, moving forward, will be cost saving measures for the sponsors.

If a sponsor attempts to primarily monitor a trial electronically, how can they ensure investigators are truly performing their duties as dictated by Good Clinical Practice, Operating Procedures etc. (data errors, omissions, duplication, inaccurate data).

As we know, all investigators are not created equal. Most PI's want to do a good job. They may be a fantastic MD, but a very mediocre investigator.

Concern may already affect pt. safety

But other Investigators have been " black listed " for fraud and other serious errors of judgement that risked patient safety. If sponsors only periodically conduct on-site visits, if their is an unethical investigator identified, it may be too late. A patient would have possibly lost their life.

There should be "more" on-site oversight by sponsors, not less. Patient safety is not worth the risk, of saving a few dollars by cutting corners monitoring.

If this decision is already made, there should be a general announcement made by the FDA, to the public, that states they are relaxing sponsor oversight. This announcement should not be buried in another disclaimer in the Informed Consent.

This will give the public & potential trial participants knowledge of additional potential risks & lack of oversight , that will help them and their families decide if participating in a clinical trial is worth the risk of a trial that may or may not possess proper sponsor oversight.

This is a slippery slope !

PUBLIC SUBMISSION

As of: December 07, 2011
Received: September 22, 2011
Status: DoNotPost
Category: Individual Consumer
Tracking No. 80f27dbe
Comments Due: November 28, 2011
Submission Type: Web

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-DRAFT-0007
Linda M Vineski - Comment

Submitter Information

Name: Linda M Vineski
Address:
NY,
Organization: Personal comment - QA perspective

General Comment

Please consider:

Line 249-251 "on-site monitoring ordinarily should be devoted to assessing the critical study data and processes and evaluating significant risks and potential site non-compliance identified through other sponsor oversight activities." This implies on-site review is not one of the agency's suggested primary assessment tools. There is no mention of onsite and central monitoring combined early on to establish a sponsor/CRO/ site comfort level with protocol understanding and compliance then yielding to an optional sampling method for on-site review for ongoing oversite.

NJ covered in IV.C.

Line 277-278 - Verifying source data remotely... EMR central access by CROs/sponsors off-site in my opinion does not protect subjects and spelled out in a consent will significantly impact recruitment.

on agenda

Line 286-289: "Sponsors WHO PLAN TO RELY on central monitoring" once in a final document implies a sponsor can rely only on central monitoring. Is this what the agency wants in writing?

NO

"FDA encourages greater reliance on centralized monitoring practices & less emphasis on site

monitoring" contradicts the risk-based emphasis intended by the guidance. I agree with this emphasis - but feel there is much to be gained from quality on-site and central monitoring. The problem in the work I see is the quality not the approach. Assessing quality requires various modalities. This draft focuses more on approach not quality.

Line 467- 469 does not include the expectation of ethical human subject training.

Section V (in accordance with the regulations) does not (but in my opinion) should include written notification/communication with the site PI which on ocassion does not occur and should to ensure clear identification of the problem and corrective/preventative action plan for all improvement areas and all personnel responsible.

PUBLIC SUBMISSION

As of: December 07, 2011
Received: September 27, 2011
Status: DoNotPost
Category: Individual Consumer
Tracking No. 80f30f7f
Comments Due: November 28, 2011
Submission Type: Web

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-DRAFT-0008
Luba N Maxwell - Comment

Submitter Information

Name: Luba N Maxwell
Address:
GA,
Organization: American Military University

General Comment

To whom it may concern:

I completely agree with your efforts in order to make clinical trials safer for everyone. Modern science has come a long way since the inhumane and cruel trials that took place during World War II and we still have quite a bit to go before clinical trials are safe for humans & animals that undergo them.

I also believe that this regulations should be enforced in conjunction with the public database that **track's physicians records of malpractice records.**

NO

PUBLIC SUBMISSION

As of: December 07, 2011
Received: November 04, 2011
Status: DoNotPost
Category: International Public Citizen - I0007
Tracking No. 80f66234
Comments Due: November 28, 2011
Submission Type: Web

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-DRAFT-0017
David Montgomery - Comment

Submitter Information

Name: David Montgomery
Address: United Kingdom,
Organization: Individual comment

General Comment

On balance an excellent document encouraging new thinking (Lines: 188 – 189) as well as highlighting recurrent areas of weakness (Lines 207 – 209) - to remedy a bad protocol with copious doses of guidance and/or monitoring is an exercise in futility However, I do have concerns with: Lines 209 – 210 "Study-specific training of investigators, other site staff, and monitors also contributes significantly to study quality. "
464 – 469 "Training should include principles of clinical investigations, …… the study monitoring plan, …… techniques."
Lines 531 -532 "On-site visits should include sufficient time for mentoring, feedback, and additional training, if needed, ..."
The term training is already misused in clinical research, particularly when what is often intended is instruction or guidance. Furthermore, the use of the word mentoring is a bridge too far. In what way are sponsors' monitors qualified to fulfil these roles or are we going to waive the requirements of ICH GCP 2.8 for those undertaking a role which "contributes significantly to study quality."?
Providing instructions is rather different to providing training as Dr Robert Mager, said, "If telling was the same as training we'd all be so smart that we can hardly stand ourselves." Likewise an article in 2003 in the BMJ "There has always been an assumption that if a person simply knows a lot about their subject, they will be able to teach it."
To avoid misperceptions about the terms training and mentoring, what does the FDA expect

want to define what we mean by training. √

sponsors to provide: a review of study specific procedures and documents coupled with feedback during monitoring visits, as stated in ICH GCP or structured training complete with intended learning outcomes and evaluations?

The term training appears only twice in ICH GCP yet over the years it pops up increasingly in guidance documents and regulations e.g. 2009 FDA Guidance on Investigator Responsibilities defines adequate training – but what is meant by training?

BAUSCH + LOMB

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

November 21, 2011

Re: Docket No. FDA–2011–D–0597, Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring

7 Giralda Farms, Suite 1001
Madison, NJ 07940
T 877-442-6925

Dear Sir or Madam:

Reference is made to the August 29, 2011 Federal Register (Vol. 76, 53683-53685) whereby the Agency requested comments on Guidance for Industry entitled "Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring." The guidance is intended to assist sponsors in developing risk-based monitoring strategies and plans for clinical investigations of human drugs, biologics, medical devices, and combinations thereof. The overarching goal of the guidance is to enhance human subject protection and the quality of clinical trial data.

Bausch + Lomb is one of the best-known and most respected healthcare companies in the world. Our core businesses include contact lenses and lens care products, ophthalmic surgical devices and instruments, and ophthalmic pharmaceuticals. Founded in 1853, our company is headquartered in Rochester, N.Y., and employs more than 10,000 people worldwide. Our products are available in more than 100 countries.

We appreciate the opportunity to comment on this draft guidance and support the Agency in its efforts to provide industry with recommendations on a modern, risk-based approach to monitoring. We offer the following comments and recommendations to enhance the issuance of the final guidance.

A. Request for Clarification of "Source Data"

Section IV. A.2. *Centralized Monitoring* of the draft guidance (lines 277-278) states that centralized monitoring processes should be used to the extent appropriate and feasible to achieve various objectives including, "Verify source data remotely, provided that both source data and CRFs can be accessed remotely."

With regard to "source data", we believe the Agency is referring to masked electronic data from a third party such as lab test results, imaging data, etc. As presented in the draft guidance, "source data" may be misconstrued as original data containing confidential personal information.

BAUSCH+LOMB

To assure the safeguard of patient privacy we recommend the revision of lines 277-278 as follows:

Verify source data (e.g., lab test results, imaging) remotely, provided that both source data and CRFs can be accessed remotely.

B. Experience of the Clinical Investigator and Sponsor With the Investigator

Section IV. C. *Factors to Consider when Developing a Monitoring Plan* of the draft guidance (lines 379-381) appropriately notes that investigators who lack significant experience in conducting and overseeing investigations, using a novel or innovative medical device, etc. may benefit from more intensive monitoring and early mentoring.

We agree with the above statement and believe these recommendations can be enhanced by including "site personnel" as well; particularly in cases where the site personnel may be largely responsible for daily key activities. An assessment of experience may be based on both the clinical investigator's experience and those participating at the site in day to day study conduct.

To ensure the investigator and site are considered in totality when developing a monitoring plan, we recommend the following revision to lines 381-383: "In addition, the relative experience of a sponsor with the clinical investigator or other site personnel involved in conduct of trial may be a factor in determining an appropriate monitoring plan."

C. Reporting Suspected and/or Confirmed Data Falsification

Section IV. D.3. *Management of Noncompliance* of the draft guidance (lines 454-455) states "FDA recommends that sponsors develop and include specific processes for addressing, investigating, and reporting suspected and/or confirmed data falsification." Reference is also made in the draft guidance to FDA's February 2010 proposed rule on data falsification[1].

We remind the Agency that while this draft guidance references "suspected and/or confirmed data falsification" and references the proposed rule; finalization of the proposed rule, based on public comments submitted, may impact the definition of these terms interpretation and as such, the development of related processes.

We recommend that the Agency reference the final rule, once available in this guidance and consider any revisions and/or clarifications for the guidance. Specifically with respect to use of "suspected" and "data" and how these terms are defined.

[1] http://edocket.access.gpo.gov/2010/pdf/2010-3123.pdf

BAUSCH+LOMB

D. Clarification of "Important" Deviations

Section IV. D.3. *Management of Noncompliance* of the draft guidance (lines 456-458) states "Processes to ensure that root cause analyses are conducted where important deviations are discovered and that appropriate corrective and preventative actions…."

To ensure consistency in the interpretation and application of implementing corrective actions, we recommend that the term "important" be clarified[2]. Doing so can support a consistent management of noncompliance when addressing these deviations.

> *We recommend that "important" be clarified as a deviation that affects: patient safety, data integrity, and/or integrity of the trial as follows:*
>
> *Processes to ensure that root cause analyses are conducted where ~~important~~ deviations which may impact the patients' safety, trial data, and/or trial integrity are discovered and that appropriate corrective and preventive actions…."*

E. Monitoring Plan Amendments

Section IV. D. 5 *Monitoring Plan Amendments* (lines 493-496) states, "Sponsors should consider what events may require review and revision of the monitoring plan and establish processes to permit timely updates where necessary. For example, a protocol amendment, change in the definition of significant protocol deviations, or identification of new risks to study integrity, could result in a change to the monitoring plan.

We agree with the above but believe the examples provided can be further enhanced by adding "frequent outliers by a study site" since variances in reporting adverse events, experience of study site personnel, or outliers in ensuring quality in the course of a clinical investigation, will not become apparent until study is in process.

> *To enhance the examples provided, we recommend revision of lines 493-496 as follows, "Sponsors should consider what events may require review and revision of the monitoring plan and establish processes to permit timely updates where necessary. For example, a protocol amendment, change in the definition of significant protocol deviations, frequent outliers by a study site, or identification of new risks to study integrity, could result in a change to the monitoring plan."*

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[2] Reference is made to the EMA Reflection Paper on risk based quality management in clinical trials (published 5 August 2011) which provides specific context regarding 'important deviations' http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf

BAUSCH+LOMB

We appreciate the opportunity to provide feedback on the draft guidance and trust these comments will enhance the final guidance, when issued.

Sincerely,

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November 22, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
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Subject: Docket No. FDA-2011-D-0597- Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear Ms. Kux:

Quintiles, a fully integrated biopharmaceutical services company offering clinical, commercial, consulting and capital solutions worldwide, appreciates the opportunity to comment on the FDA Draft Guidance for Industry – Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (hereinafter Draft Guidance), published in the August 29, 2011 Federal Register (Vol. 76, No.167). The Draft Guidance has been reviewed and discussed by representatives of Quintiles Quality Assurance, Clinical Operations, Data Management, Regulatory Affairs, and Legal departments.

Quintiles has long supported the concept that risk-based also known as "triggered" monitoring, if appropriately supported by robust operating procedures and best practices, meets the regulatory and ICH GCP requirement of "adequate monitoring", and, accordingly, Quintiles has been developing just such procedures and best practices.

Quintiles applauds the Agency in the issuance of the Draft Guidance, as it clearly attempts to provide the clinical research community with strategies for monitoring activities that reflect a progressive, and effective approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study efficiently. Further, Quintiles is encouraged by the issuance of the Draft Guidance and that the FDA has taken steps to help define and provide guidance around alternative monitoring models, and in particular, that centralized monitoring may be leveraged as a more efficient and effective resource as part of the overall monitoring plan.

Below, Quintiles makes several comments and recommendations to help realize the goals stated by FDA in developing this Draft Guidance which are to assist sponsors in developing risk-based monitoring strategies and plans for clinical investigations of human drugs, biologics, medical devices, and combinations thereof and to encourage sponsors to use a variety of approaches to meet their monitoring responsibilities when

conducting investigational new drug (IND) or investigational device exemption (IDE) studies. Quintiles recognizes that the overarching goal of this guidance is to ensure human subject protection, enhance the quality of clinical trial data, and increase efficiency in the conduct of clinical trials.

***

Firstly, Quintiles recognizes that the European Medicines Agency (EMA) published a draft Reflection Paper, August, 2011, on risk-based quality management in clinical trials. In the UK, a revision to the previously published paper, 'Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products', was released in October, 2011, with the inclusion of Appendix 2, 'Guidance on risk-proportionate approaches to the management and monitoring of clinical trials'. This paper was the result of a joint project by the Medicines and Healthcare products Regulatory Agency (MHRA), Medicines Research Council and the Department of Health in the UK. Both of these documents include elements of concepts around risk- based monitoring that are included in the FDA Draft Guidance.

Quintiles strongly encourages FDA to consider how it may work with these agencies to standardize the concepts of risk-based monitoring approaches put forth by each in order to ensure harmonization of approaches used in running global clinical trials.

Section II Background

Lines 62-63 state that quality is a systems property that must be built into an enterprise and cannot be achieved by oversight or monitoring alone. Quintiles agrees that quality must be part of the inherent design of all processes applied to the conduct of clinical trials; however, we recommend that FDA clarify what is meant by a "systems" property to ensure that readers do not interpret this to be applicable only to technology.

Lines 79-80 indicate that findings from monitoring should be used to correct investigator and site practices that could result in inadequate human subject protection and/or poor data quality. Quintiles recommends that the wording be expanded to include all non-compliance, for example. The findings should be used to correct investigator and site practices that could result in inadequate investigator oversight and instances of non-compliance, that jeopardize human subject protection and data integrity.

Lines 93-106 illustrate the successful use of risk-based monitoring strategies using less extensive on-site monitoring by academic coordinating centers, cooperative groups, and government organizations. The examples are provided to demonstrate that use of alternative monitoring approaches should be considered by all sponsors when developing risk-based monitoring strategies and plans. However, the section is vague regarding how risk-based monitoring should be approached, the types of studies referred to in the examples as well as the elements of the strategies and the circumstances under which they were used successfully. For example, based on Quintiles' experience, risk-based monitoring strategies, including on-site and various methods of remote monitoring can be applied successfully on all studies of various clinical trial phases and indications. A successful risk-based model will employ monitoring from a variety of perspectives, not just

direct investigator monitoring on site and from in-house by assigned monitoring staff. Rather, the model must include the monitoring of data coming in from sites as well as on-going and retrospective information about site processes and performance, such that there is a continuing evaluation of, and reaction to, risk as the study progresses. Monitoring on this scale requires commitment of resources of expertise and technology. In order to bring a level of maturity to the model, there remains a need to incorporate technology into the process such that the ongoing review and analysis of incoming data by medical staff, data management and biostatistics, for example, can automatically trigger an increase, decrease or other change in scope necessary to ensure subject safety and data integrity. Maturity in this area requires the support of Information Technology (IT), to build systems, capable of collecting and organizing data, into the infrastructure of a sponsor's / CRO's processes. For example, Quintiles has introduced Infosario™, a comprehensive system that leverages data, processes, systems and expertise. This system provides current, quality information that gives an immediate picture of study status and subtle underlying trends, allowing on-going monitoring of the data to trigger monitoring activity automatically and to address issues proactively, quickly and efficiently.

Similarly, Lines 138-139 make reference to FDA's 1998 guidance on Providing Clinical Evidence of Effectiveness for Drug and Biological Products, which cites successes in studies which had very little on-site monitoring, but addressed quality control in other ways. The referenced guidance also stresses consideration of trial design and size, specifically mentioning factors such as simplicity of procedures and non-critical entry criteria. These characteristics seem to emphasize studies with relatively small sample size and simple design; however, the statements are unclear regarding applicability to larger more complex trials. As stated above, Quintiles believes risk-based monitoring strategies, including on-site and various methods of remote monitoring can be applied successfully on all studies of various clinical trial phases and indications when risks are identified appropriately upfront and during on-going data reviews, supported by appropriate resources, that trigger monitoring activity. The criteria for applicability of risk-based, alternative monitoring methodologies to various clinical trial phases, i.e., Phase I-IV should be clearly stated in the Draft Guidance.

Lines 152-153 introduce the concept of focusing on critical data. To ensure this concept is clearly understood within the context of the Draft Guideline, Quintiles recommends that a definition of the term is included. Additionally, Quintiles recommends strengthening this section in the following ways.

- Re-position this section earlier in the Draft Guidance in order to underline the importance of identifying critical data as a key component of risk-based monitoring.
- Make reference to the more in-depth discussion of critical data in section III B of the Draft Guidance. Such as:
    - Endpoints (Primary Analysis Data)
    - Safety Assessments
    - Randomization/Blinding
    - Informed Consent
    - Protocol Eligibility
- Provide key elements of an appropriate approach to identification of critical data.
    - The clinical trial protocol is the guiding document that should be consulted when defining critical data.

- Critical data should be tied to aspects of the protocol that include, but are not limited to, primary efficacy and/or safety endpoints, serious adverse events, subject eligibility, Investigational Product accountability, and protection of subject rights.

Lines 159-161 indicates source data typically become part of the central submission. However, the Draft Guidance is not clear in its intent regarding inclusion of source data in submissions. While we recognize that some data, such as from a clinical or analytical lab, may be imported directly into the trial database and become part of a submission, it is unusual for common site source data, i.e., subject medical records, to be included in submissions. Rather, subject data should be housed at the investigational site and available upon request.

In addition, Quintiles questions the statement that data verification can "now be accomplished remotely". We do not believe that 'verification' is the correct description in this instance, because an actual verification of documentation that resides at the site cannot be done remotely. Many research institutions have been reluctant to provide remote access to medical records and even when subject's charts are accessed electronically, access is given locally, often using the site's computers.

We note that the EMA's Guidance addresses privacy protections with respect to remote monitoring. With respect to global clinical trials, patient privacy issues should be harmonized among the regulatory agencies and data protection authorites with a balancing of the importance of protecting data integrity and patient safety with patient privacy.

Lines 164-166 indicate that FDA is encouraging the use of technological advances (e.g., e-mail, webcasts, and online training modules) within risk-based monitoring, and that such use can meet statutory and regulatory requirements under appropriate circumstances. Quintiles recommends that this section of the Draft Guidance should include an expanded discussion of different technologies that could be used for central monitoring, for example, clinical trial management systems (CTMS), electronic data capture (eDC), electronic medical records (eMR), project planning tools, social media, videotaping, etc. In addition, we recommend inclusion of a discussion regarding how such varied systems would be validated.

Quintiles applauds FDA for its commitment stated in Lines 176-179 to ensure that the bioresearch monitoring compliance program guidance manuals are compatible with the approaches described in this guidance. We would look forward to issuance of updated compliance program guidance documents and any joint FDA-industry sessions the Agency may consider implementing to ensure consistent interpretation.

Line 198 indicates the expectation that the complete absence of on-site monitoring will likely continue to be unusual, per ICH E6. Quintiles strongly agrees that there will continue to be value in some level of "triggered" on-site monitoring. However, the degree to which triggered monitoring is employed will depend on the clinical

trial design. While some trials, such as observational / non-interventional studies, may require little on-site monitoring, other clinical trials may more typically require on site review of data collection and entry, investigator supervision, site compliance, critical data review, investigational product management and suitability of the research facility .

Quintiles believes that the use of appropriately planned triggers for on-site visits are a key element in the reduction of risk. Elements such as predictive algorithms and historical data can be used to pre-determine a schedule of site visits and predict expected work volume and resourcing needs. As data is obtained and centrally monitored for sites on an on-going basis, the schedule of events is adjusted and a visit may be triggered to occur sooner or later than the pre-determined schedule.

Line 194 notes the advancement in eDC systems enabling centralized access to both trial and source data. Quintiles agrees that such advancements leverage risk- based monitoring with central monitoring; however, we suggest that FDA expand this section beyond the use of eDC, to include all data sources and systems used.

Section III. Factors That Influence Study Quality and Integrity

The Draft Guidance, in Line 221, Footnote (28), encourages sponsors to seek consultation with the appropriate review division regarding quality aspects of clinical trial design. More guidance is needed to clarify the process for consulting with the FDA's medical product center, for example, the timelines for receipt and review within the Agency, any standard format that would be required, and guidance on the type and content of any documents submitted for review should be included.

Section IV. General Monitoring Recommendations

Quintiles agrees with the guidance provided in Lines 248-254, regarding the propriety of on-site assessment of site-critical study data and processes and evaluating significant risks and potential site non-compliance at an early stage of the study. Typically, the site selection and/or initiation visits address these issues. We also believe that a complete risk-based management plan will encompass some level of data mining. Quintiles encourages FDA to provide additional guidance regarding what the agency deems critical activities for the site selection and site initiation visits. In addition, we request that some guidance around FDA's expectations of how the leveraging of previous data and information related to study design, site experience, etc. would be utilized to formulate a risk-based monitoring plan.

Line 277 should be clarified to instruct how the FDA relates source-data verification to electronic medical records and what constitutes source data in this context. If FDA is advocating direct transfer of electronic medical records directly into clinical trial databases, we strongly urge a discussion around what constitutes an appropriate process. If direct transfer of the electronic medical record is available, does the Agency believe this negates the need to conduct additional on-site source data verification, which could be necessary to ensure there is no conflicting non-electronic data available? Also, where trials are conducted under US

requirements in emerging countries, there may be resistance on privacy grounds to allowing direct access to electronic medical records. In this case, the Draft Guidance should include directions to sponsors and monitors regarding how these records should be monitored.

Line 299 states that Sponsors should perform a risk assessment. We recommend that a clear definition of risk assessment also be included.

Lines 394-398 refer to "tapered monitoring".. Quintiles questions whether the concept would be better described as "flexible" monitoring, as this would encompass the need either to increase or decrease frequency, as circumstances dictate.

Line 417 requires that the description of monitoring approaches include criteria for determining the timing, frequency, and intensity of planned monitoring activities. It would be helpful if the Draft Guidance would also include examples of information required in the descriptions of these activities, and that examples are consistent with clinical trials of commonly conducted phase II-III trials, e.g., cardiovascular, diabetes, oncology, clinical nervous system (CNS).

At Line 455, FDA recommends that sponsors include in the monitoring plan specific processes related to detection of misconduct. Sponsors typically have standard procedures in place that are employed across projects, specifically to investigate and report suspected misconduct. Also, Quintiles questions the necessity to include this information in each monitoring plan as well, but rather make reference to standard procedures already in place.

Lines 487-489 state FDA's intention to evaluate a process through which sponsors may voluntarily submit monitoring plans for review. However, in a recent FDA webcast related to the Draft Guidance, there seemed to be a conflicting message indicating the submission of monitoring plans may become a requirement. In addition, this section of the Draft Guidance includes a footnote (35) referencing the requirement, under 21CFR 812.25(e), to submit monitoring plans for significant risk device studies. The Draft Guidance should clearly state the Agency's intent regarding voluntary or required submission.

Section V. Documenting Monitoring Activities

Quintiles recommends that the information in Lines 501-510 provide more guidance reporting of both on-site and centralized monitoring. The requirements for documentation of activities of either on-site or remote monitoring should be included in the clinical monitoring plan.

Section VI. Additional Strategies to Ensure Study Quality

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Lines 531-532 advise that on-site visits should include sufficient time for mentoring, feedback, and additional training, if needed, during the conduct of the study. Quintiles agrees that these elements are crucial to ensure study quality and data protection, but should be extended to centralized activities as well.

* * *

Quintiles appreciates the opportunity to provide comments to this Draft Guidance. In summary, Quintiles supports the Agency's efforts, through this Draft Guidance, to provide the clinical research community with strategies for monitoring activities that reflect a modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively. We believe that this guidance will help define and provide encouragement around alternative monitoring models that leverage centralized monitoring as a more efficient and effective resource as part of the overall monitoring plan. Our recommendations would further enhance the goals of the Agency to assist sponsors in developing risk-based monitoring strategies and plans for clinical investigations and to make clear that sponsors can use a variety of approaches to meet their monitoring responsibilities when conducting investigational new drug (IND) or investigational device exemption (IDE) studies.

Further, Quintiles endorses the comments submitted by the Association of Clinical Research Organizations (ACRO).

Sincerely,

Florence Reavis

Florence Reavis, RAC
Director, Quality Assurance
Quintiles

KUROS

Submission of comments on „Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring“ Docket No. FDA-2011-D-0597

Commenter: Kuros Biosurgery AG
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Date: November 23, 2011

Page	Chapter No.	Line number	Item/Question	Comment and rationale
NA	NA	NA	General comment	EMA recently has released a draft reflection paper on risk-based quality management in clinical trials for consultation. Since ICH intends to harmonize quality standards across industry, Kuros believes that FDA and EMA should not release guidance documents in isolation but instead harmonize their draft guidance and reflection paper, which in principle cover the same aspects. This would facilitate companies to be compliant with all guidelines.
NA	NA	NA	General comment	There are many detailed guidance documents existing which address GCP requirements and how to comply with them. Ensuring GCP is dependent on different factors, e.g. the number of parties involved, etc. It is therefore difficult to create one guidance which is applicable to different organizational structures. It would be more useful to get feedback on the outcome of FDA's and EMA's inspections; i.e. to get information on the key findings discovered during inspections and their consequences. This would be a more constructive learning exercise for industry.
5-6	II. D	182-186	"FDA [...] will consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans. Sponsors of IDE studies wishing to solicit feedback on their monitoring procedures prior to the submission of the IDE application may either submit a pre-IDE, or contact CDRH's Division of Bioresearch Monitoring."	• Will similar processes be established for all of FDA's divisions? • How binding will the feedback be? • How will compliance by industry be ensured? Instead of submitting monitoring plans for review or providing guidance on how efficient monitoring should be accomplished, sponsors should be encouraged to identify their main risks and risk mitigation strategies.

novo nordisk®

General Correspondence
Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

November 17, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2011-D-0597

Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear Sir or Madam:

Novo Nordisk Inc. appreciates the opportunity to provide comments to the above-referenced docket on the Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.

Novo Nordisk is a pioneer in biotechnology and a world leader in diabetes care and has a leading position within areas such as hemostasis management, growth hormone therapy, and hormone therapy for women. Novo Nordisk manufactures and markets pharmaceutical products and services that make a significant difference to our patients, the medical profession, and society.

After reviewing the draft guidance, we identified one area that warrants comment as detailed below.

Development of monitoring plans

In Part IV, Section C. "Factors to Consider when Developing a Monitoring Plan," the draft guidance states that a monitoring plan should normally focus on "critical data and processes identified by the risk assessment." The guidance also overviews a number of factors for consideration during the risk assessment (lines 350 to 401). We recommend that FDA elaborate

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on how the risk assessment could be performed when developing the monitoring plan (e.g., how should sponsors evaluate the factors described in this section of the draft guidance?).

Secondly, this section also discusses how more intensive monitoring approaches may be needed for more complex study designs, and gives unblinded studies as one example of a complex study design (lines 361-362). As the complexity of study designs is an important aspect to consider when developing a monitoring plan, we recommend that the Agency provide additional information on the complex study design examples in this section. For example, it would be helpful to know what aspect of unblinding FDA sees as introducing more complexity into the study design.

Novo Nordisk fully supports FDA's efforts to assist clinical investigation sponsors in developing risk-based monitoring strategies. We appreciate your consideration of our comments on this draft guidance.

Sincerely,

Jois Kottoskie for Eddie Li

Eddie Li, Ph.D.
Vice President, Regulatory Affairs
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Because health matters

23 November 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA–2011–D–0597

Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear Sir/Madam:

Reference is made to the Federal Register notice of 29 August 2011 (76 FR 53683), announcing a request for comments on the **Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.**

Sanofi-aventis U.S. Inc, a member of the Sanofi Group, appreciates the opportunity to provide feedback on this draft guidance, and offers the following comments:

GENERAL COMMENTS

The Agency has stated several times within the guidance that centralized and on-site monitoring are not competitive but rather complementary, but there is no further guidance on how to determine an adequate balance between the two. Does FDA have examples or proposals for typical and appropriate ways to achieve a balance between the two approaches, for example, for pivotal phase III trials as opposed to phase IV/post-marketing trials?

Another concern is related to clinical trials conducted outside the United States. Consider the paradigm of the foreign investigator that did not have the same "obligations" and "consequences" as investigators conducting their studies within the U.S.

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SPECIFIC COMMENTS:

1. Page 5 line 159-160

Reference Text

In addition, source data verification and other activities traditionally performed by on-site monitoring can now often be accomplished remotely, as both trial data and source data typically become part of the central submission.

Comment:

The reference to "as both trial data and source data typically become part of the central submission." is unclear.

Due to data privacy concerns, routine access to electronic medical records is not routine. It would be beneficial if the agency could facilitate remote sponsor access to EMR. A more explicit agency position in this guidance on the benefit of remote EMR access and acknowledgement that sponsor access is feasible with appropriate subject consent would be beneficial to overcome constraints imposed by institutions based on their interpretation of data privacy rules.

2. Lines 159 - 163, 277-278, and 287 - 289

Reference Text

In addition, source data verification and other activities traditionally performed by on-site monitoring can now often be accomplished remotely, as both trial data and source data typically become part of the central submission. These electronic data capture (EDC) systems are making it possible to implement centralized monitoring methods that can enable decreased reliance on on-site monitoring

Verify source data remotely, provided that both source data and CRFs can be accessed remotely

The extent to which centralized monitoring practices can be employed will depend to some extent on accessibility of electronic records and EDC systems.

Comment:

The line items referenced above support the Agency's endorsement of the use of electronic source data and direct remote access to these.

Sanofi would like to inquire about the Agency's position regarding the use of electronic health records (EHR), which are certified according to the criteria required by the HITECH Act and defined by HHS in 45 CFR 170. Although the HHS criteria include the requirement for an audit log, it appears that this audit trail is not compliant with the requirements in 21 CFR 11. In

particular, 45 CFR 170.210(b) requires that the audit log records the date and time, the patient identification, the user id, and the general activity performed by the user including the creation, modification, access, and deletion of EHR. However, the HHS audit log does not preserve the original data in case of a record modification or deletion, as would be required for a part 11 audit trail (21 CFR11.10 (e)).

Upon inquiry with the certification authority (CCHIT) we learned further that the lack of this feature in the audit log is intentional, because the audit log is primarily for the use by IT security staff, which has no need to receive information about a patient's medical condition. Per the CCHIT website, there are currently a total of 394 EHR systems in use, which have an audit trail that is certified according to HHS criteria. Therefore, and because of the incentives available for the purchase of HHS certified EHR systems, the likelihood of encountering such EHR systems in hospitals and physician offices that participate in clinical trials is high.

Will FDA exercise enforcement discretion when HHS certified EHR systems that are not compliant with part 11 are utilized as source data for clinical trials, or will hospitals and physicians who participate in clinical trials be required to implement additional measures to enhance the audit logs of their EHR systems to become compliant with part 11?

3. Lines 159-168 and lines 277-278

Reference Text:

In addition, source data verification and other activities traditionally performed by on-site monitoring can now often be accomplished remotely, as both trial data and source data typically become part of the central submission. These electronic data capture (EDC) systems are making it possible to implement centralized monitoring methods that can enable decreased reliance on on-site monitoring. This guidance is therefore intended to clarify that risk-based monitoring, including the appropriate use of centralized monitoring and technological advances (e.g., e-mail, webcasts, and online training modules); can meet statutory and regulatory requirements under appropriate circumstances.

Comment:

Within the EU framework, which has strict data protection and privacy rules, it appears difficult to give the sponsor remote electronic access to source data or have sponsors keep a copy of them on one of their servers. In the EMA reflection paper, "Expectations for Electronic Source Data and Data Transcribed to Electronic Data Collection tools in Clinical Trials," there is a requirement that source data at site level needs to remain under the exclusive control of the investigator.

We also foresee similar problems in the US under HIPAA. While sufficient de-identification of datasets would likely be manageable in a one-time transfer of data from EHR, many clinical trials continue over longer periods of time, so that real time monitoring of electronic source data would require ongoing or repeated access to and transfer from the EHR. Ensuring that such transfers always capture data from the correct patients and avoiding any mix-ups may require

retaining more patient identifiers in the sponsor's database than permissible under HIPAA or acceptable to IRBs and patients.

We suggest that FDA add to this draft guidance a statement of precaution where it discusses remote comparison of electronic source and CRF data.

4. Pages 5-6, Lines 170-186:

Reference Text

The Agency is also initiating operational measures to ensure that its review, compliance, and other functions reflect this view of monitoring. Specifically, FDA:

- *Has withdrawn the 1988 guidance on monitoring of clinical investigations.*
- *Is issuing this draft guidance encouraging risk-based monitoring approaches, including adoption of alternative monitoring methods.*
- *Will ensure that the bioresearch monitoring compliance program guidance manuals (CPGMs) for sponsors, CROs, and monitors (CPGM 7348.810) and for clinical investigators and sponsor-investigators (CPGM 7348.811) are compatible with the approaches described in this guidance.*
- *Will ensure that all affected program areas within FDA are aware of the goals and purposes of this guidance and its compatibility with current CPGMs.*
- *Will consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans (see section IV.D.4). Sponsors of IDE studies wishing to solicit feedback on their monitoring procedures prior to the submission of the IDE application may either submit a pre-IDE, or contact CDRH's Division of Bioresearch Monitoring.*

Comment:

Sanofi welcomes the proposals for operational measures on how to ensure upfront review and compliance of chosen approaches. However, if most sponsors submit study-specific monitoring plans for review prior to application this would require dedicated Agency resources allowing for rapid feedback and avoidance of bottlenecks during the initiation of a clinical trial. If sponsors choose to avoid prior review (which appears to be voluntary) in order to gain time (e.g., if review times are too long due to lack of resources), they carry the risk of a negative future outcome, perhaps too late to remediate any shortcomings perceived by the agency or by inspectors.

Although the FDA plans to update the compliance manuals for inspectors and raise inspectors' awareness of the risk-based approach, there is a concern on how to ensure this in practice. Issues that could arise include how to prevent inspectors from citing sponsors for taking too much risk, for insufficient site coverage, or for allowing isolated errors (which is a potential consequence of a risk-based approach).

5. Page 5 line 182-184

Reference Text

Will consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans (see section IV.D.4).

Comment

The process to submit monitoring plans for review would be useful if it resulted in consensus agreement on critical data elements that would be applicable through any later BIMO evaluation.

6. Pages 9-10, Lines 310-343

Reference Text

A study protocol should clearly identify those procedures and data that are critical to the reliability of the study findings. These generally should include:

- *Data that are critical to the reliability of the study findings, specifically those data that support primary and secondary endpoints*
- *Other data that are critical to subject safety, such as serious adverse events and events leading to discontinuation of treatment*
- *Processes that underpin subject safety and ethical treatment, such as seeking appropriate medical consultation or scheduling extra visits in the event of specified clinical or laboratory findings*
- *Processes that underpin the integrity of these data, such as blinding or referring specified events for adjudication .....*

Comment:

The list of critical parameters and procedures (i.e., patient existence and eligibility, endpoints, safety related data, blinding/randomization, informed consent and IP mgt) covers quite a bit of information (even routine lab determinations if considered to fall into safety data). If all of these areas need attention, then it is difficult to distinguish where the savings of risk-based prioritization lie. This was a frequent feedback from monitors when they applied a random/focused SDV procedure, which was previously tested by Sanofi in several large trials; several monitors felt it was even easier and faster to do 100% than to apply the selection rules.

7. Page 13, lines 487-489

Reference Text

CDER intends to evaluate potential processes through which sponsors could voluntarily submit their monitoring plans to the appropriate review division and request feedback from the clinical trial oversight component for the Center.

Comment:

- The draft guidance indicates it is not a requirement to submit the Monitoring Plan to the Agency for review - what could be the implication, if any, if the Monitoring Plan were not submitted?
- If the Monitoring plan is submitted with an initial risk minimization plan, is it a requirement to submit subsequent amendments each time the risk assessment changes?
- Will FDA describe the review process (particularly timelines) of the monitoring plan?
- To what extent does the FDA requires risk minimization for sponsor's monitor training records?

8. Page 14, line 509-511

Reference Text

Monitoring documentation should be provided to appropriate management in a timely manner for review or, as necessary, follow-up.

Comment:

The statement to provide monitoring documentation to "appropriate management" in a timely manner seems to address internal communication within the sponsor. The guidance should also more specifically address requirements/expectations for communication of monitoring outcomes/findings to the investigator/study site.

Sanofi appreciates the opportunity to provide feedback and hopes the comments provided are useful in the finalization of this draft guidance.

Sincerely,

Brian E. Harvey

Brian E. Harvey, M.D., Ph.D.
Vice President
U.S. Regulatory Policy

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SQA is a professional membership organization dedicated to promoting and advancing the principles and knowledge of quality assurance essential to human, animal and environmental health.

23 November 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
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Re: Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (Docket 2011-D-0597-0001)

On behalf of the Society of Quality Assurance (SQA) Clinical Specialty Group, we appreciate the opportunity to submit comments to the Food and Drug Administration (FDA) on their recently released *Draft Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring*.

SQA is a professional membership organization dedicated to promoting and advancing the principles and knowledge of quality assurance essential to human, animal, and environmental health. Current membership of the Society approaches 2,500 Active and Affiliate members in more than 30 countries working in industry, government, academia, and consulting. The Society includes general membership, special interest and administrative Committees, Regional Chapters, and Specialty Sections. More information about SQA can be found at www.sqa.org.

SQA supports FDA's position that the time has come to re-address how monitoring should be conducted during investigational studies in support for FDA applications. Much time, money, and effort has been devoted to monitoring with little changes in overall negative Inspection findings over the years. We support FDA's stance that developing risk-based monitoring strategies and plans for conducting clinical investigations to be a viable approach to obtain adequate Sponsor oversight, protection of the rights, welfare, and safety of human subjects, and the quality and integrity of the resulting data submitted to FDA.

As FDA reviews the comments they receive on this draft guidance, we respectfully request that you consider our following comments in regards to this guidance.

- Page 2, I. Introduction, lines 73-80: "For purposes of this guidance, monitoring generally refers to the methods used by sponsors of investigational studies, or CROs delegated responsibilities for the conduct of such studies, to oversee the conduct of and reporting of data from clinical investigations, including appropriate investigator supervision of

study site staff and third party contractors. The primary focus should be on the processes that are critical to protecting human subjects, maintaining the integrity of study data, and compliance with applicable regulations. The findings should be used to correct investigator and site practices that could result in inadequate human subject protection and/or poor data quality."

Comment: The first sentence in the paragraph appears too broad and may ultimately be misinterpreted with respect to what the guidance is intended to cover. Although the sentence that follows states the *primary* focus, it does not mean it is the only focus. The first sentence essentially states that for this guidance, monitoring refers to:

1. The methods used to oversee the conduct of clinical investigations AND
2. The methods used to oversee the reporting of data from clinical investigations.

Those two elements can extend to every aspect of study oversight, e.g., clinical investigator management, clinical vendor management, data management, investigational product management, from the sponsor's own internal systems to the clinical vendors and clinical investigators. There does not appear to be any distinction from the paragraph that precedes the one in question, which intends to be more general.

A possible solution is to revise the first sentence of the paragraph to read, ""For purposes of this guidance, monitoring generally refers to the methods used by sponsors of investigational studies, or CROs delegated responsibilities for the conduct of such studies, to oversee the conduct of and reporting of data from clinical investigators..." as this seems to be more consistent with the focus of this particular guidance.

- Page 5, II. Background, Section C. Rationale for Facilitating Risk-Based Monitoring, lines 159-162: "In addition, source data verification and other activities traditionally performed by on-site monitoring can now often be accomplished remotely, as both trial data and source data typically become part of the central submission. These electronic data capture (EDC) systems are making it possible to implement centralized monitoring methods that can enable decreased reliance on on-site monitoring."

  Comment: We would recommend that further clarification be provided in regards to the difference between trial data and source data. One interpretation could be that trial data is data recorded on the CRF while source data is found within the subject's medical records, or it could be interpreted that they are one and the same. For example if one was to interpret trial and source data to be the same then the traditional process of source verification which requires a check of source or raw data against the Case Report Form would not be necessary. Further clarification of these two terms upfront would head off considerable confusion. Definitions of "trial" versus "source" data would be helpful in ensuring misinterpretation by Industry and Clinical Investigators of what FDA means by these two terms does not occur.

- Page 7, IV. General Monitoring Recommendations, Section A. Types of Monitoring 2. Centralized Monitoring, the last bullet point (lines 284-285): "Complete administrative and regulatory tasks (e.g., collecting and archiving regulatory documents)."

  Comment: Further clarification would be beneficial. Is this referring to the collection of documents electronically from the sties, in lieu of a monitor visiting the site to collect the forms? Are there other tasks this relates to?

- Page 9, IV. General Monitoring Recommendations, Section B. Identify Critical Data and Processes to be Monitored, lines 339-340: "Verification that initial informed consent was obtained appropriately, prior to any study-specific procedures."

  Comment: We suggest expanding this point beyond the initial informed consent. As in certain cases there are significant changes/modifications to the consent form after the study has initiated. We believe it is just as relevant to check that informed consent was obtained in a timely fashion anytime significant changes to the informed consent form have occurred.

- Page 10, IV. General Monitoring Recommendations, Section C. Factors to Consider when Developing a Monitoring Plan, lines 360-362: "Examples may include studies with adaptive designs, stratified designs, complex dose titrations, or multiple device placement or unblinded studies."

  Comment: Clarification of inclusion of unblinded studies in this list would be helpful as it is unclear as written why the FDA feels that the inclusion of this type of study is important within the context of this section.

- Page 10, IV. General Monitoring Recommendations, Section C. Factors to Consider when Developing a Monitoring Plan, lines 366-367: "More objective endpoints (e.g., death, hospitalization, or clinical laboratory values and standard measurements) may be more amenable to remote verification."

  Comment: What source data (other than data obtained from Sponsor vendors such as in the case of electronic centralized lab data) does the FDA anticipate would be available to the monitor for remote verification on a routine basis? Even though we understand that FDA does not oversee the HIPAA regulations, because of HIPAA restraints Sponsor monitors are currently finding it more difficult and at times impossible to obtain direct access to source data while at the Investigative site. If FDA foresees monitors accessing raw data from medical records, further direction on how this can be achieved, e.g., which processes/procedures need to be in place to achieve this goal while meeting HIPAA and maintaining subject confidentiality would be beneficial.

- Page 10, IV. General Monitoring Recommendations, Section C. Factors to Consider when Developing a Monitoring Plan, lines 379-381: "Investigators who lack significant experience in conducting and overseeing investigations, using a novel or innovative

medical device, or with the surgical procedure associated with medical device use may benefit from more intensive monitoring and early mentoring."

Comment: It would be helpful for the FDA to clarify if their use of "intensive monitoring" is on-site monitoring. Line 387 specifically indicates this, but it is not consistently addressed throughout the guidance and could potentially lead to confusion.

- Page 13, IV. General Monitoring Recommendations, Section D. Monitoring Plan, 4. Training and Study-specific Information, lines 464-480:

    - "Description of any specific training required for personnel carrying out monitoring activities, including personnel conducting internal data monitoring, statistical monitoring, or other centralized review activities

      Training should include principles of clinical investigations, critical protocol-specific requirements, the study monitoring plan, applicable standard operating procedures, and appropriate monitoring techniques.

    - Planned quality monitoring to ensure that sponsor and CRO staff conduct monitoring activities in accordance with the monitoring plan, applicable regulations, guidance, and sponsor policies, procedures, templates, and other study plans.

      For example, many companies have successfully implemented on-site co-monitoring visits (i.e., monitoring visits performed by both a study monitor and the monitor's supervisor or another evaluator designated by the sponsor or CRO) to evaluate whether monitors are effectively carrying out visit activities, in compliance with the study monitoring plan. These visits may be conducted either for randomly selected monitors or may be targeted to specific monitors, based upon questions arising from review of monitoring visit documentation.

    - A brief description of the study, its objectives, and the critical data and study procedures, 479 with particular attention to data and procedures that are unusual and require on-site training"

Comment: The three bullets presently in this section should be separated by different headers to avoid confusion. For example,

4. Training
5. Quality Assessments of Monitoring
6. Study Essentials

The first bullet is appropriately identified as training; however, the second bullet is a quality control/quality assurance activity that is neither training nor informational. The third bullet if kept under the present header could erroneously give the impression that only *brief* training is necessary. Monitors need comprehensive training rather than a brief

description. Monitors who are not provided detailed training on the study often do not have a complete understanding of the study and its requirements and, therefore, do not often recognize deficiencies, seriousness of missed or out-of-window visits/tests, and other issues. The brief study description should be included in a monitoring plan under a Study Essentials section along with the objectives and identification of critical data fields and critical study procedures. The last part of the third bullet, "particular attention to data and procedures that are unusual and require on-site training" should be moved up under Training.

- Page 13, IV. General Monitoring Recommendations, Section D. Monitoring Plan, 4. Training and Study-specific Information, lines 482-485: "A monitoring plan may reference existing policies and procedures (e.g., a standard operating procedure describing issue investigation and resolution). In this case, the sponsor should take appropriate steps to ensure that monitors, whether sponsor or CRO employees, are aware of and are trained on these policies and procedures as well as on the monitoring plan."

  Comment: Based on experience in reviewing monitoring plans that lack sufficient reference information and training on revisions, it is recommended to revise this paragraph to read, "A monitoring plan may reference existing policies and procedures (e.g., a standard operating procedure describing issue investigation and resolution). The monitoring plan should identify for each referenced document, its number, version, title, and owner (i.e., sponsor or CRO). The sponsor should take appropriate steps to ensure that monitors, whether sponsor or CRO employees, are aware of and are trained on all relevant documents, including any revisions that occur during the study."

- Page 15. VI. Additional Strategies to Ensure Data Quality, Section B. Delegation of Monitoring Responsibilities to a CRO, lines 543-545: "Although sponsors can transfer responsibilities for monitoring to a CRO(s), they retain responsibility for oversight of the work completed by the CRO(s) who assume this responsibility."

  Comment: It would be beneficial if the FDA would provide further guidance as to what is meant by oversight of the work completed by the CRO. That is, what is expected in terms of documentation to support that appropriate oversight was administered by the sponsor? For example beyond the contract between the Sponsor and CRO and associated documents including SOPs, could this include meeting minutes that reflect the participation of CRO and sponsor personnel in managing the conduct of the study, and the use of joint monitoring of sites by the CRO and Sponsor? A discussion of Sponsor oversight of CRO activities would be beneficial in ensuring proper vendor management is occurring. One can derive some hints based on the Good Manufacturing Practice/Quality System guidances put forth by the FDA but we feel it would be beneficial to hear from the FDA how this applies to the clinical vendor oversight perspective.

- The following terms are used interchangeably throughout the guidance including the guidance document title: investigation, study, and trial. In an effort to prevent any confusion, we recommend choosing and consistently using one term.

Thank you for consideration of these comments.

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November 28, 2011

The Honorable Margaret A. Hamburg, MD
Commissioner
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

RE: Draft Guidance for Industry; Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring; Availability [FDA-2011-D-0597]

Dear Commissioner Hamburg:

The American College of Cardiology (ACC) is pleased to submit comments to the Food and Drug Administration (FDA) on Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring." The College, a 39,000-member nonprofit medical society, is dedicated to enhancing the lives of cardiovascular patients through continuous quality improvement, patient-centered care, payment innovation and professionalism. Comprised of physicians, nurses, nurse practitioners, physician assistants, pharmacists and practice managers, the College bestows credentials upon cardiovascular specialists who meet its stringent qualifications. Above all, the ACC's commitment to its members and their patients has driven the College to be a leader in the formulation of health policy, standards and guidelines a staunch supporter of cardiovascular research. The College provides professional education and operates national registries for the measurement and improvement of quality care.

Overall, the ACC is supportive of efforts to streamline the process of monitoring clinical investigations. Streamlined processes will reduce administrative costs for the federal government, monitoring entities, and organizations conducting clinical trials. This will hopefully translate towards a reduction in costs for the end user and the healthcare system.

However, the ACC does have concerns regarding the sections of the draft guidance pertaining to remote monitoring. Through the National Cardiovascular Data Registry® (NCDR®), the College has extensive experience collecting data from a variety of sources. The information technology systems used by hospitals and physician practices vary greatly, and these systems are still not interoperable. Additionally, there are a myriad of regulations governing the use of those data and the systems. Most institutions do not allow external entities, such as NCDR, direct access to their systems. They are concerned that they may violate the Health Insurance Portability and Accountability Act (HIPAA) or other laws.

The ACC strongly recommends that the FDA work with the HHS Office of Civil Rights to guide institutions in understanding how remote monitoring can occur in compliance with the HIPAA Security Rule.

Recognizing this guidance would de-emphasize lengthy source document verification, the ACC does still believe that the verification of essential data points, such as safety and efficacy endpoints, is paramount to the ethical conduct of clinical trials. Current HIPAA interpretations and institutional regulations make it difficult to conduct any source document verification remotely. Furthermore, many catheterization laboratories are still operating on a paper-based hemodynamic record system. Often their records are not available electronically. As an interim step, the ACC would recommend that the FDA work with the Office of the National Coordinator for Health Information Technology to encourage the widespread adoption of standardized electronic health record systems that can be used to transmit data using HL7 specifications and structure data for seamless interchange with CDISC-compliant clinical trials. Once this has been implemented, the discussion of remote monitoring of clinical trial data can be revisited as the standard method of monitoring for clinical trial data.

The ACC appreciates the opportunity to review this draft guidance. The College would welcome the opportunity to work with the FDA on this issue and many others. Please direct any questions or concerns to Lisa P. Goldstein at (202) 375-6527 or lgoldstein@acc.org.

Sincerely,

David R. Holmes, Jr., M.D., F.A.C.C.
President

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TO: U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)
CENTER FOR DEVICES AND RADIOLOGIC HEALTH (CDRH)

FROM: NOVELLA CLINICAL
(DURHAM, NORTH CAROLINA)

SUBJECT: COMMENTS TO DRAFT GUIDANCE IN REGARDS TO A RISK-BASED APPROACH TO MONITORING (AUG 2011)

DATE: NOVEMBER 28, 2011

CC:

GENERAL COMMENTS

Thank you for the opportunity to review the draft guidance in regards to a risk based approach to monitoring. This is an important guidance that has the opportunity to have a profound impact on enhancing human subject protection and the quality of clinical trial data for the development of medical products. Below, please find a summary of comments, questions and suggestions on the document:

- Lines 182-183 – This section states that there may be the possibility of establishing procedures within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans. Will this also apply to CBER and CDRH? Additionally, will there be a time limit established for review by the Agency as with protocols?

- Lines 190-220 – In regards to the access of remote data, many institutions do not allow remote access to Electronic Medical Records (EMR). In addition, data security does not seem to be mentioned in the document and seems to be relevant to the topic of remote accessing EMRs. Consider expanding on this area or providing additional guidance.

- Lines 256-285 – In regards to the utilization of centralized monitoring in lieu of on site monitoring (where possible), does the Agency have an expectation on how to track feedback/performance regarding the site? For example, when utilizing on-site monitoring visits, feedback regarding the visit would typically be captured in the form of a monitoring report and/or follow-up letter.

- Hybrid Monitoring Plan- As not all institutions utilize electronic medical records and even fewer allow remote access, would it be acceptable to have a monitoring plan that tailors to the systems availability of participating sites? E.g., 3 of 10 sites in a study can

have data reviewed remotely but remaining 7 must all have 100% on site review of data due to lack of EMR?

- PI responsibility – Although this document discusses an alternate approach to the common practice of 100% Source Data Verification (SDV), suggest the inclusion of information regarding the PI's having the primary responsibility to ensure the safety of the patient and conduct of the trial. This of course is not withstanding the initial and ongoing training provided the Sponsor or CRO who have been delegated this responsibility.

- Training and Experience - If a remote or centralized process is utilized on a clinical trial, will it be necessary for Sponsors and or CROs to demonstrate their CRAs or clinical staff have completed any specialized training program and experience specific to this type of risk-based monitoring as required in 21 CFR 312.53 (d)?

PUBLIC SUBMISSION

As of: December 07, 2011
Received: November 28, 2011
Status: Posted
Posted: December 05, 2011
Category: Academia - E0007
Tracking No. 80f756d8
Comments Due: November 28, 2011
Submission Type: Web

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0032
Johanna Stamates, University of Miami - Comment

Submitter Information

Name: Johanna Stamates
Address:
FL,
Submitter's Representative: Johanna Stamates
Organization: The University of Miami

General Comment

In an effort to gain further knowledge and guidance on the monitoring requirements from an academic standpoint, we would like to request further clarification to some parts of the guidance: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, as would apply to Sponsor-Investigators holding INDs at academic institutions.

In reference to Part IV, page 7, lines 224 – 229 (General Monitoring Recommendations), a risk based plan for monitoring is defined as a "mix of centralized and on-site monitoring practices". Further clarification would be ideal for Sponsor-Investigator IND trials that are multi-center, involving separate institutions in regards to monitoring requirements and whether or not a hybrid model, including different methods of monitoring (on site for some, 100% centralized for others) would be acceptable for sites participating in the same trial.

In reference to Part VI, page 14, lines 523 – 536 (Clinical Investigator Training and Communication), further clarification would be ideal for Sponsor-Investigator responsibilities for protocol training, not only for the monitor(s) (who happen to be part of the same academic institution) but also the training of the site staff.

As of: December 07, 2011
Received: November 28, 2011
Status: Posted
Posted: December 05, 2011
Category: Private Industry - C0003
Tracking No. 80f748ee
Comments Due: November 28, 2011
Submission Type: Web

PUBLIC SUBMISSION

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0001
Draft Guidance for Industry; Availability: Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-0031
Regeneron Pharmaceuticals, Inc. - Comment

Submitter Information

Address:
NY,
Organization: Regeneron Pharmaceuticals, Inc.

General Comment

Regeneron Pharmaceuticals appreciates the opportunity to comment on the Agency's draft guidance and respectfully submits the following comments:

Line 75 - There is a challenging boundary between what the investigator's responsibility is and where undue influence by a sponsor may be considered to occur. Can the agency elaborate on the role of the sponsor in investigator supervision?

Line 271 - To adequately conduct centralized monitoring, sponsors will need to adopt a sampling approach to review data. We propose that industry be provided an opportunity to establish jointly a minimal sampling standard for acceptance by the Agency.

Line 277 – As the acceptance of electronic source documentation continues, we would propose that, where possible, the electronic verification of source documentation be accepted within the bounds of this guidance.

Line 487 - When a sponsor voluntarily submits a monitoring plan for review, what is the timeline for the Agency's review?

Document Management

Document ID: FDA-2011-D-0597-0029 **Docket ID:** FDA-2011-D-0597

Details | Submitter Info | Attachments

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Viewable on Regulations.gov

Title : SAIC Frederick - Comment

Comment on Document ID: FDA-2011-D-0597-0001

Received Date : 11/28/2011

Submitter Info

Tracking Number : 80f74809

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Organization

Organization Name: SAIC Frederick

Submitter Representative

Submitter's Representative: Amy Adams

Category

Category: Federal Government - G0007

Submission

Comment: 1. In section IV. General Monitoring Recommendations, A, #2, bullet 5 discusses remote source documentation verification. Would HIPAA laws interfere with this type of monitoring? This does not appear to be an industry standard as it is very difficult to gain electronic access to source documentation (i.e. electronic Medical Records), hence is this the direction the FDA would like for industry to move in and can you offer any advice for this type or monitoring? 2. In section II. Background, D bullet 5, has a timeline for this review been considered for this review process? If it becomes a lengthy process, the study may have already begun enrolling subjects and monitoring should begin shortly afterward, hence the monitoring plan may hold up monitoring. Also, how strictly will you hold industry to your recommendations for the monitoring plan? 3. General comment – What is the FDA's expectation in regards to the completion of

protocol procedures that have not been monitored? For example, if the monitoring focus is reduced to a limited number of subjects or visits, how would it be received if the FDA were to audit subjects that were not monitored and note errors/omissions?

Original Comment:

Views:

Attachments

Title	Restrictions	Views

This document does not have any attachments.

Society for Clinical Data Management
DATA DRIVEN

2011 DEC -8 A 10:01

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November 30, 2011

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

In reference to docket number: FDA-2011-D-0597

The Society for Clinical Data Management (SCDM) has formed a task force to provide the Food and Drug Administration (FDA) a review and response on the Draft Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.

We appreciate the opportunity to provide the FDA with our comments on this issue as it has a significant impact on our respective members. The attached document provides detailed comments/suggestions/recommendations on specific sections of the draft guidance.

As way of background, SCDM represents 2,800 data management professionals supporting the clinical research process and, as a society, is the leading provider of data management professional education and certification.
We applaud the FDA's efforts on this important issue and hope that our feedback helps improve the final version of the document. Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

Jonathan Andrus, M.S., CQA, CCDM
VP, Data and Study Operations, BioClinica, Inc.
Past Chair and Current Board Member, SCDM
jonathan.andrus@bioclinica.com or 484.928.6034

on behalf of the team.

Leigh Smith, CCDM
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2			It would be good to make references to ICH early on in the guidance as to give readers the understanding that this is applicable to global clinical trials and not just ones covered under 21 CFR 312.
7	243		".....and missing data in source or CRFs". Remove "or CRF". With EDC and with paper studies (some at least), monitoring occurs after data are in house which means that missing CRF data are already detected and potentially resolved so it is not part of what "On-site" monitoring is or should be.
7, 9, 10	224-229, 302-303, 350	General Monitoring Recommendations	I would suggest changing the language around a monitoring plan to be more inclusive of data management tools and activities. Consider referring to it as a Clinical Data Monitoring Plan, especially in light of your recommendations around centralized monitoring.
8	277-278		It is unclear if central monitoring would always mean that there should be verification of source data remotely. Is this just one of the ways? Is this implying the data can be reviewed remotely?
11	400-401	Quantity of Data	Unclear as to what this sentence means and its implication within this draft guidance.
14	515-516	Additional Strategies to Ensure Study Quality	What are the additional steps that can be taken to ensure appropriate human subject protection and high data quality?

Comments of the Network of Coordinating Centres for Clinical Trials (KKS-Netzwerk)

Guidance for Industry
Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring

Draft Guidance distributed for comment purposes.
8/24/2011
Docket No. FDA-2011-D-0597

General comments:

We highly appreciate the draft EMA reflection paper on quality management in clinical trials as well as the draft FDA guidance on risk-based-monitoring. Both papers could be used complementary.

We agree with the statement in the FDA guidance that quality is a systems property that must be built into an enterprise and cannot be achieved by oversight or monitoring alone. We also share the view that risk-based approaches to monitoring, such as focusing on the most critical data elements, are more likely to ensure subject protection and overall study quality, and will permit sponsors to monitor the conduct of clinical investigations more effectively than routine visits to all clinical sites and 100 % data verification.

We therefore very much welcome the clarification within the guidance document that sponsors can use a variety of approaches to fulfil their responsibilities related to monitoring investigator conduct and the progress of investigational new drug studies and that a combination of monitoring activities including on site and centralized monitoring methods can be used, which can be identified by focussing on critical study parameters.

All agree - I do

One very important point to achieve quality nevertheless is that the findings should be used to correct investigator and site practices that could result in inadequate subject protection and / or poor data quality. We therefore appreciate the recommendation that the documentation of monitoring activities should include the responsibilities for completing actions and the anticipated date of completion.

The idea to establish processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans is also very much appreciated. We would recommend that this stays a voluntary measurement.

We think that the recommendations provided are as valid for investigator initiated clinical trials as for clinical trials conducted by industry.

Specific comments:

II: Background

D Steps FDA is Taking to Facilitate Wider Use of Alternative Monitoring Approaches

190 -193: FDA sees the guidance with the greater emphasis on centralized monitoring to be consistent with ICH E6, as the flexibility in ICH E6 was intended to permit innovative new approaches to improve the effectiveness of monitoring. in general we agree with this statement, but we find it necessary that at least one on-site visit per site should be conducted to review patient safety and reliability of the data.

EUCROF

Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

DRAFT GUIDANCE

Docket No. FDA-2011-D-0597

Name of Organization	Country
EUCROF European CRO Federation **Secretariat** Marian Ritchie Viale dei Parioli12 00197 - Roma - Italia Tel: +39-06 807.60.72 Email : info@eucrof.eu Representative on this matter : **Dr. Dagmar Chase** Tel: +49 - 89-92 92 87-0 Email: dagmar.chase@clinrex.com	**CRO Associations located in EEA:** **Belgium** **Czech Republic** **France** **Germany** **Italy** **Norway** **Spain** **The Netherlands** **UK** **plus Associated Members from** **Greece** **Portugal** **Poland** **Ireland**

EUCROF

1. EUCROF Comments on Proposed Text

Chapter	Paragraph/ Section/ Line	Page no.	Comment	Proposed change
II	78 – 80	3	"The findings should be used to correct investigator and site practices ...." EUCROF misses acknowledgement to the fact that through on-site monitoring deficiencies of the clinical trial protocol might be detected, e.g., it might be impossible to translate a protocol into medical practice. Focus here is only on deficiencies of investigators and site practices. We think, however, that on-site monitoring can support more than just on-site performance.	Add: In addition, the findings might surface that the clinical trial protocol is defective and cannot be translated into medical practice.
II, B	84 – 110	3	The information presented in this section does not provide sound scientific evidence for any type of monitoring approach. It is simply a listing of what was reported in the CTTI survey by sponsors of different nature. To draw the conclusion from that survey that sponsors should consider different monitoring approaches is lacking scientific evidence. While, for very good reasons, sound scientific evidence is required to get an authorization for a medical treatment, it appears that monitoring methods used in the past out of necessity and lack of resources form sufficient reasoning for recommendations for the future. However, this document allows replacement of one non-evidence-based method of monitoring by other non-evidence-based methods, which is fair enough.	Add: "Only very limited scientific evidence for any monitoring approach is available at the moment. Corporate and public institutions are encouraged to conduct more research on different types of quality control measures in order to better substantiate proposed monitoring strategies.

Chapter	Paragraph/ Section/ Line	Page no.	Comment	Proposed change
II, C	154 – 156	5	As long as evidence is missing the statement should be formulated more carefully.	"For example, incorporation of centralized monitoring practices, where appropriate, MIGHT improve a sponsor's ability to ensure the quality and integrity of clinical trial data."
II, C	156 - 158	5	The papers cited to prove this statement present mostly concepts, not evidence.	Add: "Evidence has to be obtained to support this concept."
II, C	159 - 161	5	EUCROF doubts that source data and trial data become "typically" part of a submission in such a way that source data verification can be done remotely. We acknowledge the fact that more and more source data are available electronically, and SDV might not be necessary for these data, however, we cannot see that SDV can be done remotely.	Please clarify
II, D	196 - 198	6	For the issues listed in lines 329 – 343 (adherence to inclusion criteria, maintenance of the study blind, drug accountability, informed consent) it is hard to see how they should be controlled without on-site monitoring.	It should be emphasized that some critical issues cannot be controlled by central monitoring unless a sponsor has full access to medical records (which is still the exception).
IV	227	7	"The monitoring plan should identify various methods intended to be used …" Although this comment is on terminology only, EUCROF thinks that it should be mentioned that usually the term "Monitoring Plan" describes the methods for on-site monitoring (and forms a tool which is taken on-site by the on-site monitors), whereas centralized monitoring methods are usually described in a plan, which is called "Data Management Plan" or "Data Validation Plan" reflecting the	Include a statement on terminology in order to avoid confusion.

Chapter	Paragraph/ Section/ Line	Page no.	Comment	Proposed change
			fact by which discipline (department) the activities are carried out.	
IV, A, 1	241 - 248	7	As mentioned for lines 78 – 79, on-site monitoring might also detect weaknesses of the clinical trial protocol. It is not a given that a clinical trial protocol is always perfect for implementation. This aspect is missing.	Widen the goals of on-site monitoring .
IV, A, 2	277 - 278	8	If source data are accessed by sponsors, appropriate measures have to be implemented to protect patient confidentiality.	Add: "If source data are accessed remotely, data protection measures should be established which prevent sponsors to access un-coded patient data.
IV, A, 2	279 - 280	8	These lines refer to very similar issues as the lines 265 – 267.	Combine lines 265 – 267 with lines 279 - 280.
IV, A, 2	281 - 283	8	Part of these lines refer to very similar issues as the lines 268 – 270.	Combine lines 268 – 270 with lines 268 – 270.
IV, A, 2	292 - 295	8	It is hard to see how a sponsor could check whether consent was obtained correctly and whether drug accountability is done properly if study sites are visited only once, early in the conduct of the study. EUCROF thinks, that at least two monitoring visits would represent the minimum, the early one to check on availability of source data, train procedures etc. and a late one to check ICFs, drug accountability, etc. See also lines 339 and 340. This is a contradiction.	
IV, B	305 - 306	9	Baseline characteristics like "age, concomitant treatment, or concomitant illness" often have an impact on the decision whether a patient is eligible for the trial. Furthermore, not checking this information might put the subject at severe	Find another example for "not so important data"

Chapter	Paragraph/ Section/ Line	Page no.	Comment	Proposed change
			risk. In this case a 100% control of the correctness of this information is crucial.	
IV, B	317 - 319	9	It is not clear why "seeking appropriate medical consultation or scheduling extra visits in the event of specified clinical or laboratory findings" is "critical to the reliability of the study findings". These actions are critical for subjects' safety.	Please explain or delete.
IV,B	327	9	Comprehensive monitoring is explained in line 352 as 100% SDV. In this line 327 "intensive monitoring" is defined as high frequency and comprehensive. Does this mean that for the types of data and processes defined in line 329-343 100% SDV of 100% pts would be the norm?	Please clarify
IV,B	329-343	9-10	We understand that the items listed in the bullet points ordinarily require on-site monitoring. Is this a correct interpretation? Or can "higher frequency and more comprehensive monitoring" also be understood as centralized monitoring?	Please clarify
IV, B	336	9	"test article" is a term which is used nowhere else in the text. We understand that "test article" does not include any comparator product in controlled trials.	Please clarify. Maybe the use of the term "investigational product/device" would be better.
IV, D, 4	480	13	"unusual"	Add "in relation to clinical routine "after "unusual".

November 15, 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room1061
Rockville, Maryland 20852

Re: Request for Comments on the Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring [Docket No. FDA-2011-D-0597]

Dear Sir/Madam:

The attached comments on the above mentioned draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated $49.4 billion in 2010 in discovering and developing new medicines. Industry-wide research and investment reached a record $67.4 billion in 2010.

A PhRMA team of experts from our member companies has carefully reviewed the draft guidance and would like to take this opportunity to provide comments. The General Comments are provided in the body of this letter while the Section and Line-Specific Comments are attached below. We applaud the Agency for producing the guidance and welcome continued dialogue on this important topic.

Overall PhRMA welcomes this draft guidance as a positive step forward that we hope will promote more effective and efficient oversight of clinical trials. With the ever increasing size and complexity of clinical trials, a risk-based approach facilitates use of an appropriate mix of on-site and centralized monitoring activities which we expect will enhance human subject protection and the quality of clinical trial data.

We encourage the Agency to continue to collaborate with other major regulatory agencies, such as EMA (Reflection paper on Risk-Based Quality Management in Clinical Trials) and MHRA (Risk-Adapted Approaches to Clinical Trials) on providing a harmonized framework for risk management of clinical trials.

Pharmaceutical Research and Manufacturers of America

950 F Street, NW, Suite 300, Washington, DC 20004 • Tel: 202-835-3544 FAX: 202-715-7089 • E-Mail: mgarvin@phrma.org

PhRMA supports the concept of a risk-based approach to clinical trial monitoring; however, the document seems to lack specific guidance on the development and utilization of a risk assessment plan, appropriate mitigation plans and the execution of those mitigation plans through the monitoring plan. The inclusion of guidance on the use of risk management tools, along with potential applications for using risk-based monitoring strategies would help facilitate the implementation of such risk-based approaches.

PhRMA requests that FDA clarify the references to remote monitoring of source data. Sponsors do not routinely have access to source data remotely. Remote access to electronic medical records presents additional legal and data privacy challenges in addition to technological challenges (e.g., HIPAA compliance). PhRMA proposes alignment with this draft guidance to the FDA Guidance for Industry-- Electronic Source Document for Clinical Investigations, which further clarifies acceptable methods for sponsors to access source data remotely.

PhRMA welcomes the opportunity to voluntarily obtain feedback from the Agency on proposed monitoring plans. We propose that the Agency's feedback be an element of voluntary engagement between the sponsor and Agency. We look forward to further information following Agency evaluation around how this process might work including considerations for timing, reviewers and expectations of the process.

PhRMA believes that the monitoring plan, not the protocol, is the appropriate place to differentiate important data points from non-important data points. The protocol should be value-neutral so that clinical investigators pay equal attention to obtaining all data as well as data inclusive of the primary/secondary endpoints. The draft guidance also implies that the monitoring plan may consist of one document, when in many cases it may consist of a compilation of sponsor SOPs and other existing documents. We recommend that the guidance reflect the fact that one document is not necessary to describe the monitoring plans, so that sponsors have flexibility with using existing documents that outline monitoring procedures across functions.

It would be helpful to understand the Agency's definition and expectations for "real time" review and acceptable means to document such reviews. The draft guidance emphasizes real-time (lines 274 and 386) concerning the centralized data review.

It would be helpful, especially to sponsors who decide to implement an alternative approach to monitoring, to have more detailed plans regarding specific anticipated changes to the BIMO Compliance Program Guidance Manuals (7348.810 and 7348.811), including plans to update and implement these manuals.

Your consideration of these comments and line specific proposals is appreciated.

Please contact me if you have any questions.

Sincerely,

Michael Garvin

Michael Garvin, Pharm.D.

1. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
20-21	Comment: The second sentence "The overarching goal of this guidance is to enhance human subject protection and the quality of clinical trial data", does not seem to encompass the overall intent of the guidance. Proposed change: The overarching goal of this guidance is to maintain human subject protection and the quality of clinical trial data in an efficient and effective manner through the appropriate use of the varied monitoring tools and methods currently available.
89	Comment: Clarification of wording – sponsor vs. company Proposed change:".... To all clinical investigator sites by **sponsor personnel...."**
159-161	Comment: In line 159, the guidance states "...source data verification...can now be accomplished remotely..." In line 161 it further states "These electronic data capture (EDC) systems are making it possible to implement centralized monitoring methods..." Is the reference to EDC referring to electronic case report form information or electronic source data, which could include medical records? If EDC in this case relates to electronic medical records, it can be difficult for sponsors to access this information remotely. We appreciate that the Agency's intention for these statements may be to incorporate future electronic capabilities and we welcome working with the Agency to further understand how remote data verification will be accomplished. Comment: Currently the source data is not part of the central submission, but PhRMA agrees that at some point in the future this may be

Line number(s) of the relevant text	Comment and rationale; proposed changes
[illegible]	[illegible]

the case.

Proposed change: We recommend removing the wording "*source data typically* ....become part of the central submission". (lines 160-161)

182-184 Comment: The draft guidance states that FDA will consider establishing processes for sponsors to submit and obtain the review of proposed alternative monitoring plans based on a risk based approach. It is recommended a plan/process be defined by FDA to establish a mechanism and/or guidance that allows for the sponsor to submit, discuss and obtain feedback on detailed, protocol-specific risk based monitoring plans to promote clear understanding in the application of the risk based approach.. This plan should also be applicable for significant revisions to an existing risk-based monitoring plan.

204 Comment: The draft guidance mentions the FDA expectation that a multi-factor approach is needed to ensure quality and integrity of the clinical trials. Per footnote 27, the Agency is considering the need for an additional guidance to describe quality risk management approaches.

Proposed change: We support the creation of an additional guidance for quality risk management approaches in clinical trials.

207-209 Comment: We suggest the FDA encourage the use of protocol assessment/evaluation tools for guidance on quality design parameters for protocols and eCRFs. We encourage the FDA to build communication between the FDA Review Division and the Inspection Division on protocol design responses.

out of scope

310-320 Comment: Draft guidance states "A study protocol should

Line number(s) of the relevant text (e.g. Lines 20-23)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes').
	clearly identify those procedures and data that are critical to the reliability of the study findings." The Protocol should be value-neutral so that sites pay equal attention to obtaining all data as well as data inclusive of the primary/secondary endpoints. Proposed change (if any): A **study monitoring plan** should clearly identify those procedures and data...
339-340	Comment: The Agency only mentions verification of initial informed consent was obtained appropriately; this could imply that there would be an expectation that reconsent would not need to be checked. Proposed change: Verification that ~~**initial**~~ informed consent was obtained appropriately,...
345 - 346	Comment: Investigator staff qualifications, delegation of duties and Principal Investigator oversight are not mentioned as items that need more intensive level of monitoring, yet non verification of these items could have a significant impact on the data collected and the protection of patient safety. Additionally, these reasons have been included in recent Warning Letters to Clinical Investigators. It would be advantageous to add items to the guidance as considerations for more frequent monitoring activities. Proposed change: Include additional bullet to section that begins on line 322 • Verification of investigator staff qualifications, delegation of duties and Principal Investigator oversight
360-362	Comment: Question inclusion of "unblinded" studies in section "Complexity of the study design". Proposed change: Delete unblinded and replace with "blinded".

Line number(s) of the relevant text	Comment and rationale; proposed changes
	(If changes to the wording are suggested, they should be highlighted using 'track changes')
405	Comment: "For each clinical trial, the sponsor should develop a monitoring plan..." This implies that the monitoring plan is one document, when in many cases it will be a compilation of sponsor SOPs, forms and other existing documents related to monitoring activities. Proposed change: "...the sponsor should develop a monitoring plan, **which may be a compilation of multiple documents and references to sponsor SOPs** that describes the monitoring methods.
436	Comment: The guidance document notes the communication of the results of the monitoring to the sponsor and CRO; however, there is no indication how/when the investigator will be informed of these results/outcomes.
482-485	Comment: This text under D.4 should be for the whole section D and not just under section 4. Proposed change: Move to line 410 before the last sentence and change sentence in lines 482-485 to "Sponsors should take appropriate steps to ensure that monitors whether sponsor or CRO employees, are aware of and trained on policies and procedures that comprise or are referenced by the monitoring plan.
531	Comment: Clarification of wording – coaching vs. mentoring Proposed change (if any): "...sufficient time for **coaching, feedback"**

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AdvaMed
Advanced Medical Technology Association

November 28, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA–2011–D–0597: Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring; Availability

Dear Sir/Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, we are pleased to submit these comments in response to the notice of availability of *Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring; Availability*.

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. Our members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent of such technology purchased annually around the world. These members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have less than $30 million in sales annually.

AdvaMed has both general comments and specific comments below.

General Comments

AdvaMed commends FDA for proposing risk-based monitoring. Current informatics and statistical techniques allow for new ways to assure high clinical data quality during clinical trials and we believe the appropriate, synergistic use of on-site and centralized monitoring methods could lead to both more effective and more efficient monitoring of human subject and of study data. We also commend FDA for clearly communicating that FDA understands that 100% on-site data verification is unnecessary for all trials and that risk-based monitoring approaches, including centralized monitoring, can and should be incorporated where appropriate.

The FDA's description in section II. D. of the guidance of their efforts to facilitate the wider use of alternative monitoring methods is also noteworthy and demonstrates FDA's understanding of the network of change that will be needed to successfully move industry (and all parts of the Agency) to adopt and accept newer monitoring methods.

FDA has indicated a willingness to allow sponsors to voluntarily submit their monitoring plans for review (Section II. D. last bullet and Section IV. D. 4.). If submission of monitoring plans is to add value and improve quality, the review will need to occur at the earliest stages of the clinical trial planning before the investigational device exemption (IDE) submission. Review of the plan must be timely; any delay in clinical trial startup is expensive and it can be challenging to sponsors to reinvigorate site interest after delays in the trial. FDA should commit to review the entire plan and clearly specify which elements of the plan may not be acceptable along with reasons and suggestions. The sponsor should also have an opportunity to discuss and revise portions of the plan in order to reach a common "acceptance" of the entire plan. Finally, in order to minimize the potential for CMS Medicare contractors to deny coverage for device clinical trials, it will be important for FDA to avoid issuing conditional approvals for monitoring plans whenever possible.

AdvaMed would also like to strongly encourage FDA to explicitly articulate in the monitoring guidance that device sponsors may transfer responsibility for monitoring to contract research organizations (CRO), as is currently allowed under 21 CFR 312.52 and as is detailed in Section VI. B. of the draft guidance for IND trials. We are not aware of any requirement in 21 CFR 812 that prohibits the transfer of any or all responsibility for device trial conduct to a CRO and we believe explicit support by FDA for such transfer of responsibility for device trials can only enhance human subject protection and the quality of clinical trial data by giving CROs a shared responsibility for the conduct of device trials and thus a strong rationale to comply with all relevant FDA regulations and guidance.

Specific Comments

Please find our specific comments in the enclosed table. The line numbers reference the enclosed line-numbered version of the draft guidance.

In closing, thank you for the opportunity to provide our comments and recommendations on the draft guidance on a risk-based approach to the monitoring of clinical trials. Please don't hesitate to contact me if you have any questions.

Sincerely,

Tara Federici

Tara Federici
Vice President
Technology and Regulatory Affairs

AdvaMed Specific Comments on *Draft Guidance for Industry, Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring*

Comment #	Line #	Change	Reason
1	20 - 21	Add the following: The overarching goal of this guidance is to enhance human subject protection and the quality of clinical trial data in an efficient and effective manner through the appropriate use of the varied monitoring tools and methods available.	To provide more clarity as to the objective of the guidance.
2	41	Add: The increase in the use of electronic medical records, advances in data transfer, informatics and in statistical techniques have also enabled a risk-based approach to monitoring that allows use of centralized or remote monitoring.	Not all trials have increased in complexity. New technologies and new techniques have also facilitated the use of a risk-based monitoring approach that includes remote monitoring.
3	78 - 80	Insert the following: The findings should be used to correct the investigator and site practices that could result in inadequate human subject protection and/or poor data quality as well as provide visibility to the sponsor as a means for appropriate escalation and action.	Although the sentence explains that findings should be used to correct, it fails to mention that findings should also be used to escalate the issue to the sponsor for appropriate action.
4	164 - 165	Add "fax" to examples	Provide additional information/examples in the guidance of how sponsor may remotely monitor original source data that are not generated electronically.

AdvaMed Specific Comments on *Draft Guidance for Industry, Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring*

Edit #	Line	Change	Reason
5	184 - 185	Strike and insert underlined text: Sponsors of ~~IDE~~ device studies wishing to solicit feedback on their monitoring procedures ~~prior to submission of the IDE application~~ may either submit a pre-IDE	Not all clinical studies are required to be conducted under IDE, certain IVD studies for example. However, these studies may also benefit from feedback.
6	200+ Section III	It would be a valuable addition to the guidance for FDA to add elements of GCP that are the responsibility of the site personnel (e.g., proper documentation, timely data submittal, proper consenting procedures, etc.).	This section currently only lists factors that influence study quality and integrity from the Sponsor or CRO perspective and site personnel play an important role in study quality as well.
7	268	Add the following: Target on-site monitoring by identifying higher risk clinical sites (e.g., sites with data anomalies, high enrollment sites, sites new to clinical research, sites with a recent change in critical personnel, or a higher frequency of errors, protocol violations, or dropouts relative to other sites)	Provides additional examples
8	274	Add the following: Monitor data quality through programmed edit checks or routine review of submitted data in real-time to identify missing data, ...	Acknowledges that Electronic Data Capture (EDC) systems can be programmed to detect errors by rejecting values that are inconsistent with the study entry criteria or logic so they can be immediately corrected by the site data entry personnel. This can be a powerful way to save resources.

auth scope

		Change	Reason
9	277 - 278	Insert the following: Verify source data remotely, provided that both source data and CRFs can be accessed or are available remotely. FDA should also include references to data protection guidance in this guidance.	Not all companies may have access to electronic data capture but they may have access to scanned forms, etc. FDA should also include references to data protection guidance as a reminder and to emphasize the need to protect patient data.
10	283	Add new bullet: • Escalate study compliance risks to the sponsor	This is a key concept that should be added to the guidance.
11	284	Strike and add the following: Complete administrative and regulatory tasks (e.g., collecting and archiving regulatory documents monitoring reports, investigative reports, etc.)	Additional clarity
12	289	Insert underlined sentence: The extent to which centralized monitoring practices can be employed will depend to some extent on accessibility of electronic records and EDC systems. However, the original source data submitted to the sponsor via e-mail or fax may also facilitate centralized monitoring in situations where remote access to electronic source documents is not feasible.	Remote monitoring should not be precluded in situations where remote access to electronic records or EDC systems is not possible, such as when internal e-hospital record systems (electronic source documents) do not allow for access outside of the institution.

AdvaMed Specific Comments on *Draft Guidance for Industry, Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring*

Edit #	Line #	Change	Reason
13	292	Insert underlined sentence: Sponsors who plan to rely on centralized monitoring processes should ensure that the processes and expectations for site record keeping, data entry, and reporting are well-defined and ensure timely access to clinical trial data and supporting documentation. <u>Documentation of centralized monitoring processes can be accomplished by mechanisms such as monitoring reports, follow-up letters, etc.</u>	The guidance document, as written, does not identify that FDA expects centralized monitoring visits to be documented.
14	322	Add the following: A sponsor's <u>centralized or on-site</u> monitoring activities should focus on these critical measurements	Additional clarity.
15	348	Add number and location of study sites as a factor to consider.	Additional factor.
16	369	Add the following: . . . more intensive monitoring <u>(on-site and/or centralized, as appropriate)</u> to determine whether follow-up	Additional clarity.

Item	Line	Change	Reason
17	462	Add: • A discussion of training of all parties on test product accountability and blinding procedures, when appropriate. • A discussion of the criticality of documenting training and of plans for training new personnel who come on board during the study.	These are important aspects to emphasize in the guidance.
18	501	Insert the following: Documentation of monitoring activities <u>onsite or remotely</u> should include the following:	Clarification
19	536	Insert underlined text: It may be necessary to implement alternative training and communication methods (teleconferences, webcasts, or online training modules) for providing and documenting ongoing, timely training and feedback, as well as to provide notification of significant changes to study conduct or other important information. <u>Documentation of alternative training can be accomplished by documenting the date of training, topics covered, and individuals in attendance.</u>	Provide examples on how FDA expects the sponsor to document alternative training and communication.

Guidance for Industry
Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Ann Meeker O'Connell at 301-796-3150, (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800, or (CDRH) Chrissy Cochran at 301-796-5490.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
August 2011
Procedural

November 28, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA Draft Guidance for Industry on "Oversight of Clinical Investigations: A Risk-based Approach to Monitoring" [Docket No. FDA–2011–D–0597]

Dear Sir/Madam:

Pfizer Inc is providing comments on the FDA (Agency) draft guidance for industry on *Oversight of Clinical Investigations: A Risk-based Approach to Monitoring* that was published in the *Federal Register* of August 29, 2011 (76 Fed. Reg. 53683-53685).

We appreciate the opportunity to comment on this draft guidance and trust that the Agency will take these comments into consideration. Accordingly, please refer to the attached table of comments/recommendations.

Please do not hesitate to contact the undersigned if there are any questions or if clarification is needed.

Sincerely,

Lorraine Waring
Senior Director, Site Monitoring Process Owner
Pfizer Inc
860 441 3072

Attachment

November 28, 2011

SUBMISSION OF COMMENTS ON FDA DRAFT GUIDANCE ON "OVERSIGHT OF CLINICAL INVESTIGATIONS: A RISK-BASED APPROACH TO MONITORING" [DOCKET NO. FDA–2011–D–0597]

COMMENTS FROM: PFIZER INC

1. GENERAL COMMENTS

Pfizer appreciates the issuance of this draft guidance. We agree with the concept of a risk-based approach to monitoring and have utilized centralized monitoring methods where appropriate. However, we believe the final guidance should include specific guidance on the development and utilization of a risk assessment plan, which is the cornerstone of utilizing a risk-based approach, and include appropriate examples of risk mitigation. The inclusion of risk management tools and examples, along with potential applications for using risk-based monitoring strategies would help facilitate the implementation of such risk-based approaches and further ensure that expectations are consistent amongst all stakeholders. In addition, although we support the use of centralized monitoring methods, Pfizer believes that the final guidance should give equal emphasis to the fact that other monitoring methods may also be appropriate, and should also not create any new expectations for monitoring beyond what is required under current regulations.

Pfizer also agrees with FDA's position "encourag[ing] sponsors to tailor monitoring plans to the needs of the trial"[1] and believes that the final guidance should continue to emphasize that monitoring plans be tailored to the needs of the trial, taking into account the study phase and experience of the sponsor with the study drug. Consistent with the principles of quality risk management,[2] sponsors should be encouraged to use monitoring approaches commensurate with the perceived level of risk. The final guidance should also recognize that other factors should also be considered with regards to using on-site monitoring or centralized monitoring or a combination thereof for a particular clinical trial, including the availability and accessibility of appropriate technologies to both sponsors and investigators, and the applicability of any local laws (including privacy laws) and regulatory requirements.

[1] FDA, Draft, Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, Aug. 2011, at ln. 188-89, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.

[2] FDA, Guidance for Industry: Q9 Quality Risk Management, June 2006, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf.

2. SPECIFIC COMMENTS ON TEXT

Line Number(s)	Comment and Rationale	Proposed change (if applicable)
66-71	The draft guidance states: "We are aware that the term *monitoring* is used in different ways in the clinical trial context. It can refer to the assessment of clinical investigator conduct, oversight, and reporting of findings of a clinical trial; the ongoing evaluation of safety data and the emerging risk-benefit profile of an investigational product by a medical monitor; and the monitoring of internal sponsor and CRO processes and systems integral to proposing, designing, performing, recording, supervising, reviewing, or reporting clinical investigations." For completeness, we would recommend the inclusion of data-management and statistics, since these groups may also be involved in the monitoring of clinical data, e.g., with regards to data capture and interim data analyses, depending on the monitoring plan.	"…It can refer to the assessment of clinical investigator conduct, oversight, and reporting of findings of a clinical trial; ***the review of clinical trial data by data management personnel or a statistician in connection with data capture activities or an interim data analysis***; the ongoing evaluation of safety data and the emerging risk-benefit profile of an investigational product by a medical monitor…"
156-159	It would be useful to add examples of the use of centralized monitoring versus on-site monitoring and their potential outcome (e.g., the use of centralized monitoring to perform statistical analyses to identify data trends) in addition to footnoting the three publications suggesting that data anomalies may be more readily detected by centralized monitoring than by on-site monitoring.	
159-163	With regards to centralized monitoring and electronic data capture (EDC), please provide examples or references on how "both trial data and source data" [e.g., informed consent, medical histories] "typically become part of the central submission."	
176-179 and 182-184	This section describes steps that the Agency is taking to facilitate the wider use of alternative monitoring approaches. Please clarify the timing for the following steps:	In the meantime, we encourage the Agency to work proactively with sponsors and other stakeholders on the development and implementation of risk-based monitoring plans, when appropriate.

Line Number(s)	Comment and Rationale	Proposed change (if applicable)
	• "[FDA] [w]ill ensure that the bioresearch monitoring compliance program guidance manuals (CPGMs) for sponsors, CROs, and monitors (CPGM 7348.810) and for clinical investigators and sponsor-investigators (CPGM 7348.811) are compatible with the approaches described in this guidance." • "[FDA] [w]ill consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans…Sponsors of IDE studies wishing to solicit feedback on their monitoring procedures prior to the submission of the IDE application may either submit a pre-IDE, or contact CDRH's Division of Bioresearch Monitoring."	
192-196	The draft guidance states: "FDA believes it is reasonable to conclude that the flexibility described in ICH E6 was intended to permit innovative new approaches to improve the effectiveness of monitoring: notably, the advancement in EDC systems enabling centralized access to both trial and source data and the growing appreciation of the ability of statistical assessments to identify clinical sites that require additional training and/or monitoring." Please clarify the expectations regarding the capturing of source data by EDC as mentioned above. Specifically, the final guidance should recognize that the remote capture and monitoring of source data is only possible when the original record (or a certified copy thereof) is initially captured electronically and in accordance with local privacy laws and requirements.	"…notably, the advancement in EDC systems enabling centralized access to ***the original records or certified copies*** of both trial and source data, ***where appropriate and in accordance with local laws and requirements***…"
205-209	The draft guidance states: "The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol." However, the next sentence introduces a second tool, *the case report form (CRF)*, along with the *protocol* as documents that "may introduce systemic errors" if they are "poorly designed or ambiguous." For consistency with the second sentence, we suggest that the first sentence be	"~~The most~~ ***Two*** important tools for ensuring human subject protection and high-quality data ~~is~~ ***are*** a well-designed and articulated protocol ***and case report form (CRF). When these documents are*** poorly designed or ambiguous, ***they*** may introduce systemic errors…"

Line Number(s)	Comment and Rationale	Proposed change (if applicable)
	modified to reference the CRF too.	
251-253	It may be helpful to clarify the term *early* or provide examples, with regards to the sentence, "On-site monitoring is particularly critical early in a study, especially if the protocol is complex, and includes novel procedures with which investigators may be unfamiliar."	"…early ***(as determined by the risk assessment and study complexity)***…"
258-260	The draft guidance states: "Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) at which the clinical investigation is being conducted." For clarity, we suggest the use of the qualifying term *assigned* since the personnel may vary depending on the monitoring plan, and placing *clinical monitors* before *data management personnel, statisticians* since that may represent a more logical progression.	Centralized monitoring is a remote evaluation carried out by ***assigned*** sponsor personnel or representatives (e.g., ***clinical monitors,*** data management personnel, ***and/or*** statisticians, ***etc.,*** ~~***or clinical monitors***~~) at a location other than the site(s) at which the clinical investigation is being conducted."
277-278	Among other points the draft guidance states: "Centralized monitoring processes should be used to the extent appropriate and feasible to achieve the following:" • "Verify source data remotely, provided that both source data and CRFs can be accessed remotely" We suggest emphasizing that this scenario would generally be an exception, since it is presently uncommon for source data such as signed informed consents and/or medical records to be accessible remotely for clinical trials. Also, for global studies, remote access of source data may not be permitted due to local privacy laws and requirements.	• "Verify source data remotely, ***provided that both*** source data and CRFs can be accessed remotely, ***and in accordance with local privacy laws and requirements***."
297	This section introduces the term *risk assessment* with regards to clinical monitoring. We recommend that the FDA issue additional draft guidance for comment regarding the Agency's expectations and recommendations for	We propose that the final guidance should include a detailed appendix, providing guidance on risk factors and risk adaptive approaches, and recommend that the draft appendix

Line Number(s)	Comment and Rationale	Proposed change (if applicable)
	developing and implementing such risk assessments. We suggest the introduction of risk assessment much earlier in this guidance which would then frame the discussion of appropriate monitoring approaches that could be used to mitigate the identified risks. We would also suggest adding an appendix providing further detailed guidance on items to consider in the development of a risk assessment; similar to the October 2011 Medicines and Healthcare products Regulatory Agency (MHRA) paper on risk-based approaches.[3] In the spirit of global harmonization with respect to clinical trial monitoring processes, we would also encourage coordinating approaches with the guidance provided by the MHRA, where possible.	should be released for public comment and stakeholder input.
302-306	The draft guidance states: "Sponsors should consider the findings of the risk assessment when developing a monitoring plan. There is increasing recognition that some types of errors in a clinical trial are more important than others. .., a low, but non-zero rate of errors in capturing certain baseline characteristics of enrolled subjects (e.g., age, concomitant treatment, or concomitant illness) will not, in general, have a significant effect on study results." These examples may be better understood in context of a late phase non-interventional study. For additional clarity, can the Agency provide some examples and/or cited references concerning the "increasing recognition that some types of errors in a clinical trial are more important than others"?	
348	An additional factor to consider when developing a monitoring plan is *prior clinical experience with the investigational product and the phase of clinical development*. For example, the use of a centralized monitoring approach for phase IV trials.	Propose expansion of this section to add prior clinical experience with the investigational product as a factor.

[3] MHRA, MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, Oct. 10, 2011, at 6-18, available at http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf.

Line Number(s)	Comment and Rationale	Proposed change (if applicable)
357	With regards to the *complexity of the study design* as a factor to consider when developing a monitoring plan, examples are provided of studies that may require more intensive monitoring approaches (e.g., *increased frequency of review and/or multiple monitoring approaches*). For further clarity with regards to utilizing a risk-based approach towards monitoring, examples of studies where less intensive monitoring approaches may be appropriate would also be useful. Possible examples include non-complex studies utilizing a conventional study design (while taking into account the other factors to be considered) and phase IV non-interventional studies.	
407-410	The draft guidance states: "All sponsor and CRO personnel who may be involved with monitoring, including those who review and/or determine appropriate action regarding potential issues identified through monitoring, should review the monitoring plan." Rather than *All* Sponsor and CRO personnel, we believe the scope should be limited to protocol specific personnel only i.e., "**are** involved" rather than "**may be** involved". In addition, clarity is requested regarding the phrase "should review the monitoring plan." Is the Agency referring to familiarity with one's assigned responsibilities under a monitoring plan versus a review of the entire monitoring plan by all involved Sponsor and CRO personnel, regardless of their assigned roles?	
487-489	The draft guidance states: "CDER intends to evaluate potential processes through which sponsors could voluntarily submit their monitoring plans to the appropriate review division and request feedback from the clinical trial oversight component for the Center."	As mentioned earlier, we encourage the Agency to work proactively with sponsors and other stakeholders on the development and implementation of risk-based monitoring plans, when appropriate.

Johnson & Johnson

ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, N.J. 08933

November 28, 2011

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: ***Docket No. FDA-2011-D-0597: Comments on Updated Draft Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring***

Dear Sir/Madam:

Johnson & Johnson's Medical Devices & Diagnostics' family of companies (Johnson & Johnson MD&D) is the world's largest and most diverse medical devices and diagnostics company, with its entities having supplied doctors and patients with hundreds of life-changing medical devices, including HIV drug resistance kits, orthopedic implants, endoscopic surgical tools, vascular stents and blood glucose monitors, to name a few.

We commend and support the FDA on updating the proposed draft guidance entitled *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.* We believe that this updated guidance will be helpful in aligning the device industry with the current informatics and statistical techniques that are available. These alternative monitoring approaches allow for new ways to assure high quality data during clinical trials beyond on-site source data verification. The guidance is comprehensive, lists critical to quality items, allows a high degree of flexibility and is still precise in defining requirements (e.g., monitoring plan). The language is easy to follow, transparent, and designed to change behavior which will refocus industry to be more comfortable in reducing on-site monitoring techniques and increasing its use of centralized monitoring. The FDA's description, in section D of this guidance, of their efforts to facilitate the wider use of alternative monitoring methods is commendable and shows that the agency understands the network of change that will be needed to successfully move industry (and all parts of the agency) to adopt and accept newer monitoring methods. The appropriate and synergistic use of on-site and centralized monitoring methods could result in more effective and more efficient monitoring that should lead to higher quality clinical studies while enhancing subject protection.

In this submission, we focus our comments on two main areas of concern: 1) awareness that future technological advances may further increase use of centralized monitoring in lieu of on-site monitoring, and 2) establishing a process for obtaining pre-approval on proposed monitoring.

Future technological advances

Using current methodologies, some amount of on-site monitoring is expected, but future advancement in technology may increase the use of centralized monitoring such that the complete absence of on-site monitoring could become possible. The draft guidance document does mention that new and innovative

approaches may enable the increased utilization of centralized monitoring for both trial and source data. We support the agency's forward thinking approach in updating the guidance to include the acceptance of centralized monitoring and its recognition that alternative risk-based monitoring methods are more likely to ensure subject protection and lead to more effective and efficient clinical investigations when compared to traditional on-site monitoring. The guidance would be further strengthened by acknowledging in which cases clinical investigations may be conducted in the absence of on-site monitoring (e.g., with incorporation of proper escalation protocol, accessibility of electronic records and EDC systems, etc).

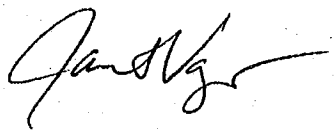
Pre-Approval Processes

We commend the agency's consideration of potential processes through which sponsors can voluntarily submit monitoring plans for feedback. The establishment of such a process will provide a measure of certainty that the sponsor's plans are in alignment with the agency's expectations in the event that the sponsor, CRO or study site should be audited. It is important that any process pertaining to the review of monitoring plans not delay the commencement of the clinical study. Furthermore, we support FDA's initiative in facilitating the wider use of alternative monitoring approaches through the education of all parties involved with clinical oversight (e.g., reviewers, inspectors, other agency departments).

Additional specific comments are included in the attachment to this letter.

Johnson & Johnson MD&D appreciates this opportunity to comment on the proposed draft guidance entitled *Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.*

Sincerely,



Minnie Baylor-Henry, JD
WW Vice President, Regulatory Affairs

Janet Vargo, PhD
Executive Director, Clinical Trial Design

Johnson & Johnson

Attachment: Additional Specific Comments

Below, please find a list of specific comments organized by Line Number.

Item No.	Line No.	Recommended Change
1	20-21	Reword sentence to make it more inclusive: "The overarching goal of this guidance is to maintain human subject protection and the quality of clinical trial data in an efficient and effective manner through the appropriate use of the varied monitoring tools and methods currently available."
2	27	Suggestion to define "centralized monitoring" the first time it is mentioned and distinguish risk-based monitoring activities in this guidance from those activities usually performed by data safety monitoring committees
3	41	Addition to the sentence: Suggest adding the increase in use of electronic medical records, and advances in data transfer, informatics and statistical techniques that can be applied to more efficiently and effectively monitor clinical quality "off site".
4	48	Revise sentence for clarity "The regulation requires sponsors of clinical investigations in humans involving drugs, biological products…"
5	78-80	Reword sentence to include the ability to escalate/surface and increase transparency/visibility to the sponsor and FDA. "The findings should be used to correct investigator and site practices that could result in inadequate human subject protection and/or poor data quality as well as provide visibility to the sponsor as a means for appropriate escalation and action."
6	163-166	Reword sentence to allow hybrid approach to monitoring "This guidance is therefore intended to clarify that risk-based monitoring, including the appropriate use of centralized monitoring with or without on-site monitoring and various technological advances ..."
9	196-198	Suggest addition "… continue to be unusual, *at least in the near future.*"
10	200 Section III	Recommend revision of section to add elements of GCP that are the responsibility of the site personnel as well (e.g., proper documentation, timely submittal of data, proper consenting procedures, etc.)
11	226-227	Add the following sentence: "Alternatively, a monitoring procedure may be developed for those studies whose monitoring tasks are repetitive in nature".
12	251-252	Suggest changing to "on-site monitoring *may be* particularly critical especially if the protocol is complex…"
13	254	Recommend adding "although it is recognized that advancing technologies may mitigate the need for mandatory on-site monitoring" after "elsewhere".
14	265	Clarify sentence: "Replace, *augment or reduce* on-site monitoring for monitoring activities that can be done as well or better"
15	268	Revise sentence to make it more inclusive: Add sites that are new to clinical research or recent change in critical staff
16	274	Add the following sentence: "When collecting data through EDC, where possible, program checks into the entry

		system such that data entered that is inconsistent with study entry criteria or logic be rejected immediately so that the site data entry personnel can correct the entry immediately."
17	277-288	Suggest addition: "...when data protection can be assured and country regulations can be followed."
18	284-285	Expand the bullet to include examples of what types of administrative and regulatory tasks might be completed through centralized monitoring.
19	348	Suggest addition "Number and location of study sites" as a factor to be considered
20	369	Suggest addition: "...more intensive monitoring *(on-site and/or centralized, as appropriate)*..."
21	375	Clarification needed for this section: It is not clear why more intensive monitoring would be beneficial when there are differences in standards of medical practice or in subject demographics. For example, translations of consents or assents, infrastructure differences such as a lack of internet access, removing ability to review data in real time..
22	379	Clarification: "Investigators *and site staff* who lack significant experience in conducting and overseeing investigations..."
23	417	Suggest inclusion of some examples of monitoring activities such as remote, onsite monitoring, telephone and web conferences, email exchange could all be considered monitoring activities.
24	423-424	Suggest addition "...the site should be considered for *increased* targeted on-site visits and training."
25	426	Add as section to assure that the sponsor, and when appropriate, sponsor upper management is informed to cover upward notification: On the importance of determining in advance of the study escalation procedures to inform sponsor management when critical non-compliance or other study quality or human protection issues are identified by the sponsor or the CRO.
26	427-428	Suggest addition "Identification of possible deviations or failures that would be critical to study integrity and how these are to be recorded, reported *and resolved with corrective and preventative actions*"
27	441	Suggest addition "of routine monitoring results to management, *investigators, monitors* and other stakeholders..."
29	462	1. Add discussion of training of all parties on test product accountability and blinding procedures, when appropriate. 2. Add discussion of the criticality of documenting training and of plans for training new personnel who come on board during the study.
30	481	Suggest adding - Description of plans for refresher or re-training for compliance issues, longer or slow enrolling studies.
31	487-489	We commend the agency for this suggestion as it will provide a measure of certainty that the sponsor's plans are in line with the agency's expectations should the sponsor,

study addressed

no

no

		CRO, or study site be audited by the agency. IT would be helpful if the process were defined with associated timelines.
32	503	Suggest addition "The date of the activity and the individual(s) conducting *and participating* in activity"
33	518	Suggest addition: "A fundamental component of ensuring quality monitoring is a sponsor's compliance with *the protocol,* written monitoring plans and any accompanying procedures."
34	524	It is suggested that this section should be more flexible, as we believe training of experienced investigators and their staff can effectively be handled by WebEx/video conferencing technologies .

PUBLIC SUBMISSION

As of: December 07, 2011
Received: December 05, 2011
Status: Draft
Category: Drug Industry - C0022
Tracking No. 80f7b981
Submission Type: Web

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0002
Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-DRAFT-0050
- EComment

Submitter Information

Name: Francoise Rossi
Address:
Paris, France,
Submitter's Representative: Regulatory Intelligence
Organization: LFB

General Comment

"General comment"

We understand that the monitoring practices must change to adapt to a more globalization of clinical trials in order to speed up the collection of data from the investigators sites and reduce the costs. For these reasons, systems like EDC are very good tools.
However, we do not think that these systems should be used without a good percentage of on-site-monitoring. The proposal made in this guide to make one on-site-monitoring in few sites at the beginning of the trial is in our opinion not sufficient to guaranty the absence of fraud along the conduct of the whole trial.

The risk of validating this guide is to create two kinds of sponsors:
- those who will continue to use a good percentage of on-site-monitoring to assure the quality and the integrity of their data
and
- those who will act on this guide to do faster and cheaper

The result of this is, in our opinion, that some new drugs may be marketed too quickly with the possible risk of post-marketing adverse events/serious adverse events, not appropriately identified during the "monitoring phase" of the trial(s).
This approach does not seem to take much care of the safety of future patients.

PUBLIC SUBMISSION

As of: December 07, 2011
Received: December 06, 2011
Status: Draft
Category: Drug Industry - C0022
Tracking No. 80f7c95a
Submission Type: Web

Docket: FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring; Availability

Comment On: FDA-2011-D-0597-0002
Draft Guidance for Industry; Oversight of Clinical Investigations; A Risk-Based Approach to Monitoring

Document: FDA-2011-D-0597-DRAFT-0052
- EComment

Submitter Information

Name: Gina M. Newton
Address:
MA,
Organization: Millennium: The Takeda Oncology Company

General Comment

While I feel the guidance includes some valuable information, I feel as though it's still unclear the parameters in which a sponsor must conduct on site versus central monitoring. I think you will have sponsors that will always continue to monitor in a more conversative manner (myself included) in an effort to ensure data quality, an for the agency to view my sponsor conduct as adequate for fear of being too flexible and having this result in quality issues. The guidance seems to encourage a more lax approach in monitoring but then concludes with giving many instances where this approach would not work. I feel in the end, we may filter down to very limited trials using this more lax approach. I for one am not confident that central monitoring can take the place of on site monitoring. I've have many experiences where things are not as they seem until you are actually on site - I cannot imagine going to a site as little as yearly. I hope you find this feedback helpful! Again, there was definitely value in this guidance, I just still feel that sponsors (at least myself) will still be more conservative to ensure data quality and appropriate oversight as viewed by the agency.

Comments and Suggestions on Draft Guidance entitled:
Guidance for Industry: Oversight of Clinical Investigations –
A Risk-based Approach to Monitoring

(Document ID FDA-2011-D-0597-0001)
Issued: 24 August 2011

Timothy King
tdnk68@frontier.com
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23 November 2011

Thank you for allowing me to comment. My comments are general but mostly pertain to section IV.B – Identify Critical Data and Processes to be Monitored and also IV.D.1 – Description of Monitoring Approaches.

When "targeted" data monitoring has been used in clinical trials, as opposed to 100% Source Document Verification (SDV), the process has tended to be transparent. A common approach is to announce to the study team and investigator site staff that the first three patients will be monitored and then every third patient thereafter. Therefore, investigators know, a priori, which subjects are likely to be reviewed.

I suggest that any targeted monitoring approach employ randomization. While 100% of certain key variables may be reviewed (primary endpoints, key safety data, inclusion and exclusion criteria, for example), the remaining data to be source verified should be chosen randomly.

To make this operationally feasible, the randomization schema should be programmed into the electronic data capture (EDC) system, whenever EDC is used. A randomized approach may not be feasible for traditional paper-based case report form (CRF) studies.

On a related note, the current paper-based data systems and "major" EDC systems (i.e. Oracle InForm, Medidata RAVE, etc.) were designed assuming a 100% SDV monitoring strategy. They are not able to distinguish between a) data that is not to be monitored, as opposed to b) data that has not been monitored yet but will be. Therefore, these systems will run programmed edit checks and generate queries on un-monitored data and send to sites for resolution. This essentially creates a de facto 100% SDV process, but in a less efficient way (rather than queries being issued to discover errors missed by monitoring). For example, on a Phase III osteoporosis trial, the use of a "targeted SDV"

approach lead to three times more queries being issued to investigator sites which created a tremendous additional workload for both the Pharma and site staff. The targeted approach actually increased timelines, efforts, and the overall study budget, with no resulting benefit in terms of patient safety or data quality.

The more rational approach would be for data queries to be generated and reviewed by statisticians and medical staff to uncover trends (fraud, systematic error, etc.), but not sent to sites if not deemed a priori as "critical".

Again, thank you for inviting feedback.

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November 28, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear Sir or Madam:

We submit these comments on behalf of Cook Group Inc. (Cook). Cook is a holding company of international corporations engaged in the manufacture of diagnostic and interventional products for radiology, cardiology, urology, gynecology, gastroenterology, wound care, emergency medicine, and surgery. Cook pioneered the development of products used in the Seldinger technique for angiography, and in techniques for interventional radiology and cardiology. Our products benefit patients by providing doctors with a means of diagnosis and intervention using minimally invasive techniques, as well as by providing innovative products for surgical applications. Cook sells more than 15,000 different products, which can be purchased in more than 60,000 combinations. Our company employs more than 10,000 people around the world. Eight thousand of those are based in the United States. While 50 percent of our products are sold outside the United States, 85 percent are manufactured in this country.

We appreciate the opportunity to comment on the *Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring*. Many of our products have required clinical data to support a regulatory approval in the United States from which these data were collected during a clinical study with regulatory and Institutional Review Board (IRB) oversight. Cook currently sponsors more than 75 clinical studies in 30 countries. It is primarily for this reason that we are keenly interested in providing our comments for consideration.

Cook would like to commend the FDA on revising the agency's guidance document on monitoring. As a sponsor of global clinical studies, Cook has for many years used a risk-based approach to monitoring that has provided alternative mechanisms to evaluate the overall scientific integrity of the studies while protecting the rights, welfare and safety of patients treated. This approach has lead to an improved use of resources (both human and financial) for

all parties involved including the sponsor, the Contract Research Organization (CRO), the monitor, and the investigative sites.

Any organization that implements a risk-based approach to monitoring must recognize the potential consequences of unforeseen outcomes and build in mechanisms to identify the risk(s) early and to frequently monitor to determine when the sources of the risks have reached a meaningful threshold requiring further mitigation. Recognizing this, Cook would like to offer additional considerations for developing a comprehensive and balanced risk-based plan for monitoring clinical studies that complement the utilization of on-site and centralized monitoring, training of research staff and physicians and the use of qualified and trained monitors.

Vendor Assessment

It is common practice for a sponsor or CRO to outsource specific areas of clinical research to a vendor that has the expertise and personnel to perform the clinical research services. It is strongly recommended that vendor assessments be encouraged as a part of the overall monitoring plan. The assessment should not be limited to outsourced responsibilities of the sponsor or CRO but should include assessments of the proposed investigative sites, the proposed principal investigators, the IRBs and core laboratories utilized by the hospital, sponsor or CRO.

Safety Monitoring

In addition to on-site and centralized monitoring as defined in the guidance, consideration should be given to the use of a Data Safety Monitoring Board and/or Clinical Events Committee to assist with the overall monitoring of the study with a focus on patient safety and outcomes. These committees, comprised of independent physicians and researchers, can be useful in some studies to provide perspective that may not be provided by those closely involved in the conduct of the study.

Data Protection/Patient Privacy

Although access to source data for use during central monitoring could lead to more frequent review of the clinical data, challenges exist at the investigative site, hospital or laboratory to ensure that adequate procedures and infrastructures (i.e., electronic medical records) are in place to allow non-employees access to patient level data while adhering to data protection laws and regulations. The data protection and patient privacy policies vary from site to site and the reliance on accessing these systems to augment or even replace the on-site monitoring must be realistically balanced with the increasing emphasis on data protection, patient privacy, and the local interpretation of the regulations.

Escalation

Emphasis should be placed on mechanisms by which potential concerns related to compliance with the regulations, protocol, and agreements, especially those related to the rights, welfare and patient safety, are quickly identified and subsequently escalated to the investigators, research staff, IRB(s), sponsor and/or FDA as appropriate. The mechanism for the escalation should also identify potential corrective action(s) to secure future compliance.

Auditing

As part of a sponsor's quality system, consideration should be given to performing periodic audits of the sponsor (functions involved in the oversight of the study), CRO, monitor and site(s) throughout the clinical study to evaluate adherence to the regulations, protocol, agreements, procedures and stipulations imposed by FDA and the IRB. The results of the audit should provide opportunities for preventative or potential corrective action(s) to be implemented by the audited function.

Harmonization

We would encourage the FDA to reference the recently published ISO14155:2011, *Clinical investigation of medical devices for human subjects – Good clinical practice* and further clarify its relationship to the proposed guidance. A large percentage of clinical studies conducted today to support regulatory submissions to FDA include data from outside the United States. Recognition of international consensus standards leads to efficiencies for all stakeholders, collaboration, and increases the confidence in the data and the processes used to gather the data.

We welcome the opportunity to work further with the FDA on revising this guidance. In our view, any steps that clarify and expedite the conduct of high-quality research are of great importance to our common goal of helping patients.

Thank you for considering our views and comments.

Respectfully,

Stephen L. Ferguson
Chairman of the Board

BIO
BIOTECHNOLOGY
INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

November 28, 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2011-D-0597: Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring; Availability

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring."

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO supports the goals of the guidance to assist sponsors of clinical investigations in developing risk-based monitoring strategies and to enhance human subject protection and the quality of clinical trial data. Biotechnology companies are at the forefront of biomedical innovation and welcome proposed strategies for monitoring activities that will assist them in conducting clinical investigations in a more modern, risk-based manner.

As an active member of the Clinical Trials Transformation Initiative (CTTI), BIO commends the work that the Agency and CTTI have done to survey current monitoring practices while compiling recommendations. BIO looks forward to continuing to

articulate and build support for these concepts through CTTI and among clinical trial stakeholders, including industry, contract research organizations, academia, and regulators.

Approaches such as centralized clinical trial monitoring and a focus on the most critical data elements can help Sponsors and FDA to deploy resources to the areas that will best promote the integrity and quality of clinical trial data. Conceptually, the approaches detailed in the guidance should enhance the efficiency and effectiveness of clinical trial monitoring, but great care should be taken in implementation of these approaches to reduce the potential for duplicative or burdensome monitoring requirements.

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Kelly Lai
Director, Science & Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
II. BACKGROUND		
Line: 134	"as long as the adequacy of the scientific evidence can be assured."	We recommend clarifying and elaborating on this statement.
Lines: 156-158	"Several publications suggest that data anomalies (e.g., fraud, including fabrication of data, and other non-random data distributions) may be more readily detected by centralized monitoring techniques than by on-site monitoring."	We request that the Agency provide examples of centralized monitoring techniques to identify data anomalies. We also recommend that the Agency include language stating that sponsors should establish criteria for on-site monitoring. These criteria and examples should clarify the expectation that Industry would provide to the regulatory agencies a detailed monitoring plan, including type of monitoring; intervals in which it would occur; and exact data to be monitored, and would reach agreement with the agencies on the outlined plan before the study begins enrolling patients. It is also the expectation that the Agency and industry would agree on data that would be inspected at a site visit, as this would potentially affect the monitoring plan, to assure that expectations between industry and regulatory agencies are clear.
Lines : 182-183	"Will consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans…"	While BIO agrees that a process for sponsors to prospectively submit a detailed monitoring plan should be established within CDER, we request that the Agency include a clearer definition and explanation of what will be the focus and intent of CDER's review. In addition, for this review to be a value added exercise for both CDER and sponsors, it would be beneficial to have CDER staff in the reviewing position that had previous experience at sites with monitoring.

III. FACTORS THAT INFLUENCE STUDY QUALITY AND INTEGRITY		
Lines : 245-248	"On-site monitoring can also provide a sense of the quality of the overall conduct of the trial at a site (e.g., attention to detail, thoroughness of study documentation, appropriate delegation of study tasks, and appropriate investigator supervision of site staff performing critical study functions)." Informed consent by the subject may be implicit in the sentence that begins on line 242 that states: "… provide assurance that study documentation exists…"	We believe that informed consent should be explicitly included in this list. Equally, in the list of tasks that can be performed remotely, remote training could be included.
Lines: 249-251	"Therefore, on-site monitoring ordinarily should be devoted to assessing the critical study data and processes and evaluating significant risks and potential site non-compliance identified through other sponsor oversight activities."	In addition, on site monitoring should be used to assess critical study data that cannot be assessed remotely (such as valid consent and appropriate consent procedures).
Lines: 258-260	Centralized monitoring is defined beginning on line 258: "Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) at which the clinical investigation is being conducted."	We believe that the Agency needs to be clear about the intent of the centralized monitoring. Additionally, we suggest additional wording: "Centralized monitoring could be considered to ensure more timely feedback and identification of protocol deviators and completeness and accuracy of data. It also allows identification of issues at sites."
Lines: 271-276	"Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data	Data management, clinical science, and other functions may be well placed to facilitate the analysis of data trends. We suggest including the following:

	trends not easily detected by on-site monitoring)" and "Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at a site"	"Data management, clinical science, and other functions may be able to facilitate this type of process working with a centralized monitoring group."
Lines: 277	"Verify source data remotely, provided that both source data…"	We suggest rewording the statement to read: "Verify CRF data from source data remotely, provided that both source data and CRFs can be accessed remotely."
Lines: 279-280	"Conduct aggregate statistical analyses of study data to identify sites that are outliers relative to others and to evaluate individual subject data for plausibility and completeness"	We suggest changing the statement to read: ~~"Conduct aggregate statistical analyses of study data to~~ Identify sites that are outliers by evaluating the site data statistically ~~relative to others and to evaluate individual subject data for plausibility and completeness~~."
Lines: 322-323	"A sponsor's monitoring activities should focus on these critical measurements and on preventing important and likely sources of error in their collection and reporting."	We suggest editing the statement to read: "A sponsor's Monitoring Plan should focus on these critical measurements and on preventing important and likely sources of error in their collection and reporting of study data."
Lines: 353-355	"…versus targeted or random review of certain data (less than 100% data verification) of monitoring activities will depend to some extent on a range of factors, considered during the risk assessment, including the following"	The phrase "considered during the risk assessment" is redundant per lines 350 and 351: "A monitoring plan ordinarily should focus on the critical data and processes identified by the risk assessment." We suggest deleting "considered during the risk assessment" so the statement reads: "…versus targeted or random review of certain data (less than 100%

		data verification) of monitoring activities will depend to some extent on a range of factors ~~considered during the risk assessment,~~ including the following."
Lines: 375-377	"Sites in geographic areas where there are differences in standards of medical practice or subject demographics or there is a less established…"	Please add "where" so the statement reads: "Sites in geographic areas where there are differences in standards of medical practice or subject demographics, or where there is a less established…"
Lines: 375-377	"Sites in geographic areas where there are differences in standards of medical practice or subject demographics or there is a less established clinical trial infrastructure may require more intensive monitoring, including some level of on-site monitoring."	We request the statement be edited to read: "Sites in geographic areas where there are differences in standards of medical practice or subject demographics or there is a less established clinical trial infrastructure may require more intensive monitoring, including a greater level of on-site monitoring."
Lines: 422-423	"For example, if it is determined that an investigator deviates significantly from other sites in making safety-related findings or other key safety metrics, the site should be considered for targeted on-site visits. …"	Investigators do not deviate from sites, but rather from other investigators. We request the statement be edited to read: "For example, if the safety findings at a particular site deviate significantly from safety findings at other sites, a targeted on-site monitoring visit to the outlier site should be considered."
Lines: 427-428	"Identification of possible deviations or failures that would be critical to study integrity and how these are to be recorded and reported"	This is unclear. Would this include failures and/or errors? Please provide clarification. We suggest adding the following text: "Any site that has been identified to be collecting information that in any way adversely affects the study integrity would need a full evaluation. The results of this evaluation would need to be collated and reported."
Lines: 433-434	"The study monitoring plan should also describe how various monitoring activities will be documented, regardless of whether	We suggest changing "centralized" to "centrally" so the statement reads:

	conducted on-site or centralized."	"The study monitoring plan should also describe how various monitoring activities will be documented, regardless of whether conducted on-site or centrally."
Lines: 493-496	"Sponsors should consider what events may require review and revision of the monitoring plan and establish processes to permit timely updates where necessary. For example, a protocol amendment, change in the definition of significant protocol deviations, or identification of new risks to study integrity, could result in a change to the monitoring plan."	We agree that the sponsor needs specific ways to alter a monitoring plan after a study is underway. We suggest that CDER also needs a process to review and approve such changes in an expedited manner.
Lines: 510-511	"Monitoring documentation should be provided to appropriate management in a timely manner for review or, as necessary, follow-up."	Please remove "as necessary" so the statement reads as follows: "Monitoring documentation should be provided to appropriate management in a timely manner for review or~~, as necessary~~ follow-up."

Nancy Hutchinson, PhD
Head Drug Regulatory Affairs - North America

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NOVARTIS

November 28, 2011

FDA Dockets Management Branch (HFA305)
Food & Drug Administration
5630Fishers Lane
Rockville, MD 20852

Docket No. FDA-2011-D-0597: Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear Sir or Madam

Please find attached comments from Novartis Pharmaceuticals Corporation ("Novartis") on the Food and Drug Administration (FDA) Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.

Overall, Novartis fully supports and commends FDA on recognizing the value of alternative monitoring approaches and proposing a risk-adapted Monitoring Plan to determine the intensity, frequency and focus/scope of the monitoring activities, while ensuring patient protection, protocol and regulatory adherence, as well as data accuracy and integrity. Novartis has implemented risk-based monitoring approaches, as appropriate, for its trials and finds this Draft Guidance important and timely.

Novartis appreciates the opportunity to provide comments and respectfully requests that consideration be given to our comments and recommendations.

Kind regards,

Nancy Hutchinson, PhD
Head Drug Regulatory Affairs
- North America

Attachment

Submission of Comments For:

FDA Draft Guidance: Oversight of Clinical Trials - A Risk Based Approach to Monitoring

Comments Submitted by: Novartis Pharmaceuticals Corporation

Specific Comments		
Section / Line #	**Proposed content (regulation/guidance)**	**Novartis Comments**
I. Introduction ***(Lines 21-24)***	***"This guidance is intended to make clear that sponsors can use a variety of approaches to fulfill their responsibilities related to monitoring investigator conduct and the progress of investigational new drug (IND) or investigational device exemption (IDE) studies."***	It is suggested that the guidance be made applicable to any trial submitted to FDA. The Guidance specifically makes reference to IND and IDE clinical trials; however, there are many trials that are performed at the request of FDA as post approval trials. These studies are typically performed with a dose and patient population that is consistent with the approved labeling and as per the IND regulations would not meet the definition of investigational use of a drug, however maybe submitted to the IND.
II. D. Steps FDA is Taking to facilitate Wider Use of Alternative Monitoring Approaches ***(Lines 176-181)***	• ***"Will ensure that the bioresearch monitoring compliance program guidance manuals (CPGMs) for sponsors, CROs, and monitors (CPGM 7348.810) and for clinical investigators and sponsor-investigators (CPGM 7348.811) are compatible with the approaches described in this guidance*** • ***"Will ensure that all affected program areas within FDA are aware of the goals and purposes of this guidance and its compatibility with current CPGMs"***	Sponsors that have already begun to employ alternative monitoring approaches often have questions raised during FDA inspections because these processes deviate from the "traditional" approach to monitoring. Therefore, it would be helpful for the Guidance to outline the additional changes and communications that will be made by FDA to ensure the FDA inspection program is in alignment with this the final Guidance. Defining/committing to timeframes for implementing these additional changes and communications with respect to the finalization of the guidance would help to facilitate more robust and seamless implementation by sponsors and FDA.

Submission of Comments For:

FDA Draft Guidance: Oversight of Clinical Trials - A Risk Based Approach to Monitoring

Comments Submitted by: Novartis Pharmaceuticals Corporation

IV. A. 2. Centralized Monitoring ***(Line 286-289)***	***"FDA encourages greater reliance on centralized monitoring practices than has been the case historically, with correspondingly less emphasis on on-site monitoring. The extent to which centralized monitoring practices can be employed will depend to some extent on accessibility of electronic records and EDC systems."***	Novartis agrees with the concept of greater reliance on central monitoring activities along with reduced on-site monitoring. However, recognizing the privacy issues related to accessing electronic medical records that would be need to be addressed to verify patient source data against the submitted information, it may be helpful to denote that the use of "centralized monitoring practices" to conduct remote source data verification (SDV) may not always be feasible. Thus on-site monitoring may still be required in most instances to confirm the accuracy, and identification, of any deviations that would primarily be found during the review of patient source data. The same would also be true for the verification of informed consent forms since they also contain personally identifiable medical information.
II. D. Steps FDA is Taking to facilitate Wider Use of Alternative Monitoring Approaches ***(Lines 182-184)*** ***and*** **IV. D. 4. Training and Study-Specific Information**	***"Will consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans (see section IV.D.4). Sponsors of IDE studies wishing to solicit feedback on their monitoring procedures prior to the submission of the IDE application may either submit a pre-IDE, or contact CDRH's Division of Bioresearch Monitoring."*** ***"CDER intends to evaluate potential processes through which sponsors could***	Novartis supports the FDA proposal to establish processes for sponsors to submit and obtain the review of proposed alternative monitoring plans based on a risk based approach, and recommends that a mechanism and/or guidance include provisions that allow the sponsor to submit, discuss and obtain feedback on detailed, protocol-specific risk based monitoring plans. This process should also be applicable for any significant revisions to an existing risk based monitoring plan.

Submission of Comments For:

FDA Draft Guidance: Oversight of Clinical Trials - A Risk Based Approach to Monitoring

Comments Submitted by: Novartis Pharmaceuticals Corporation

(Lines 487-489)	***voluntarily submit their monitoring plans to the appropriate review division and request feedback from the clinical trial oversight component for the Center."***	
IV. D. 1. Description of Monitoring Approaches ***(Line 420-421)***	***"Definitions of events or results that trigger changes in planned monitoring activities for a particular clinical investigator."***	The use of tolerance ranges or establishing acceptable variations has not been addressed in this Guidance document. It is recommended that tolerance ranges be established "per protocol" for trial procedures and data (based on statistical components). These in turn would act as a "trigger" to initiate increased monitoring activities. These Tolerance ranges have been proposed by the EMA (Draft EMA Reflection Paper on Risk Based Quality Management in Clinical Trials, dated 14 June 2011.
IV. D. Monitoring Plan **(Lines 436-460)**	***"2. Communication of Monitoring Results"*** ***and*** ***"3. Management of Noncompliance"***	Since many of the components of the monitoring plan recommendations in these two sections are often addressed in applicable Sponsor SOPs and written processes related to monitoring activities, it may be helpful to denote that these recommended components of the monitoring plan can be addressed within individual study monitoring plans or, more generally, in related sponsor SOPs or other written general monitoring processes.
III. D. 4. Training and	***"A monitoring plan may reference***	It is suggested that a statement be added denoting that if the sponsor

Submission of Comments For:

FDA Draft Guidance: Oversight of Clinical Trials - A Risk Based Approach to Monitoring

Comments Submitted by: Novartis Pharmaceuticals Corporation

Study Specific Information *(Lines 482-485)*	***existing policies and procedures (e.g., a standard operating procedure describing issue investigation and resolution). In this case, the sponsor should take appropriate steps to ensure that monitors, whether sponsor or CRO employees, are aware of and are trained on these policies and procedures as well as on the monitoring plan."***	proposes to use the CRO's procedures, the sponsor should review and agree to the adequacy of those procedures prior to use
V. Documenting Monitoring Activities *(Line 501)*	***"Documentation of monitoring activities should include the following:*** • ***The date of the activity and the individual(s) conducting it*** • ***A summary of the data or activities reviewed*** • ***A description of any noncompliance, potential noncompliance, data irregularities, deficiencies identified*** • ***A description of any actions taken, to be taken, and/or recommended, including responsible for completing actions and the anticipated date of completion"***	The section for documenting monitoring activities appears to be focused on the typical "on-site" methods of monitoring. When using the "central" or "remote" monitoring method, we recommend the acknowledgement that the use of alternative electronic or automated documentation methods; to demonstrate and document data review activities and follow up actions should be acceptable provided they meet appropriate controls regarding access, back up and audit trails, which will ensure the data integrity and ability to retrieve the information using validated systems. Also since FDA inspectors are required to review monitoring logs during pre-approval inspections, the guidance should include a recommendation that both on-site monitoring and centralized monitoring activities are documented in some form of monitoring log.

Personnel from the Duke Clinical Research Institute (DCRI) met in two sessions to discuss the *Draft Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.* Comments of the 14 participants have been summarized below.

We support the FDA's efforts to encourage the clinical research industry to re-assess monitoring practices so that resources are better allocated to meet the requirements of each specific trial.

DCRI is proud of it broad experience with cost effective, targeted monitoring and respectfully submits the following comments on the draft Guidance.

1) Assessing risk

There has been much buzz in the research community that the Guidance will be used only to reduce, not to increase, the amount of monitoring for a study. We do not agree with this assessment: we believe the Agency has clearly laid out an expectation for a comprehensive monitoring strategy that—while it may reduce the time a monitor spends on-site—will increase the frequency at which issues are identified and markedly improve both the time to resolution and the quality of the data from the site.

Some have remarked that FDA has lowered its expectations for monitoring to effect "cost savings" for industry. We do not believe this to be true. While adopting a risk based approach to monitoring may lead to cost savings, cost should not be a primary factor in the risk assessment procedure. Initially it may be difficult for sponsors to have confidence that any monitoring plan based on a "new" approach will comply with the expectations of FDA inspectors, and sponsors may resist stepping down from what's perceived to be the "gold standard": on-site 100% source document verification. Alternatively, the pendulum could swing too far, and a bare bones approach to monitoring—one based solely on a desire to cut study costs—could become the vogue.

We believe contract research organizations can, and should, guide their sponsors through the process by including risk based monitoring plans in project bids, supported by a documented risk assessment. Documentation of the risk assessment may never have been part of the overall project plan in the past, but the draft guidance seems to encourage its development. The protocol remains the most important project document, and it is from the protocol that the monitoring's plan initial risk assessment will be drawn. However; the relationship between the two – the protocol and the monitoring plan – has historically not been a documented piece of the overall project planning. Incorporating this logical connection between the protocol and the monitoring plan as part of the initial project planning will be an important step in ensuring that the adequacy of the monitoring plan and its compliance to the Guidance.

2) Submitting monitoring plans to FDA for review

With all due respect, we do not believe that submitting monitoring plans for FDA review is a good way to achieve compliance. We believe it's rare that an FDA reviewer has experience as an inspector and, therefore, able to recognize potential compliance pitfalls. Furthermore, the persons designing the investigation and those responsible for its proper conduct should not rely on regulatory oversight as a

safety net for the propriety of their monitoring. If the sponsor or CRO is in doubt that the plan is sufficient, they should re-think the plan, not just send it along to FDA and hope for the best. We are loath to think that an inspector's finding that study monitoring was inadequate would be laid at a reviewer's doorstep with the assertion, "But FDA approved our plan."

In any event, it seems unlikely that the FDA has the resources to spare for this additional workload. To layer this additional responsibility on the Agency is contrary to one of the objectives of the new Guidance: the most beneficial allocation of resources.

3) Monitoring for omissions or misconduct

Questions have arisen as to how centralized monitoring can uncover the non-reporting of safety data. In a webinar presented by FDA on 24 October 2011, a presenter described using electronic data capture (EDC) in real time to spot anomalies across sites as one of the best ways to uncover reporting omissions. We agree and would go further: it is our experience that the training of monitors—whether those monitors visit a site or contact the site remotely by phone or web conference tools—is key to detecting errors of negligence or those that raise suspicions of malfeasance. For those who do not have an EDC system, one is not required: centralized monitoring can be accomplished with adequately trained personnel. It should be emphasized that training includes development of what are termed "soft skills"; those interaction skills that, as face time with sites decreases, will help monitors establish and maintain the most productive working relationship with sites.

In addition, the notion of "breaking down silos" raised by the FDA in its October 2011 webinar is important here. Biostaticians or data managers may be the first to detect trends, aberrations, and outliers. Good and open communication among all the members of a project team is fundamental. The adoption of the concept of risk based monitoring will provide the opportunity for sponsors and CROs to review their internal operating procedures and look for ways to modify other areas to make them risk appropriate.

4) IRBs

Neither the Guidance document itself nor the FDA's October 2011 webinar addressed the role of the Institutional Review Board (IRB) in a risk-based monitoring approach. A study site's IRB is on the front line of human subject protection. The experience of the site's IRB, its resources and how they are allocated to the study are all factors that should be included in a risk assessment procedure for a site and for the study overall.

In addition, if source documents are to be scanned or photocopied to be sent off-site for monitoring, this activity must be approved by the site's IRB and the site's privacy officer and disclosed in the informed consent document.

5) Relevance to small studies

Establishing and carrying out a monitoring plan that utilizes different modalities –i.e., centralized monitoring and on-site visits, live training and remote training resources – is common practice for

"mega" trials, which enroll thousands of subjects at hundreds of sites. Adapting these procedures to smaller trials can present more of a challenge, particularly when there may be technological challenges on either (or both) the site and sponsor side. We believe that the final Guidance should address this issue by emphasizing that monitoring plans are fluid documents, expected to be amended as needed. Smaller sites will certainly require closer, "customer service" oriented monitoring at the outset. It is our policy to establish good relations with our sites initially, having found that this ultimately saves time and money over the course of the trial. The intensity or tenor of the initial monitoring need may change as the trial progresses: it may become more focused, it may become less frequent, it may result in more on-site training sessions. Regardless of how the monitoring changes over the course of a study, we urge the Agency's assurance that it will not to ascribe the change to initial error or fault.

6) Paper records

A question was raised in the October 2011 webinar concerning sites or sponsors that do not have the advanced technological resources that larger entities enjoy. The concern was that limited technology would impair or preclude the ability to adapt monitoring beyond the customary on-site reviews. We have conducted studies, even large trials, relying on paper records rather than EDC. It is our experience that you can successfully conduct remote monitoring of a site that has solely paper records; however, sites often propose that they receive added payments to compensate for additional time and resources spent making copies or scans of study documents, such as IRB approvals, for the purposes of remote monitoring. Perhaps this is the only point at which cost considerations should play a role in determining the parameters of the monitoring plan: the project team should take a hard look at what must be photocopied or scanned. As an FDA commentator noted in the October 2011 webinar, it is common to collect more information than is actually needed for a study. Copying every document and record at a site is counterproductive to focusing monitoring on critical items based on a documented risk assessment. Establishing the remote monitoring piece for sites that utilize paper files may be a good way for the sponsor to evaluate not only its monitoring plan but its recordkeeping policies overall. In any event, just because a site is using paper files does not mean that every piece of paper they collect or generate should be copied and sent to a remote monitor. If a site balks at the requirements to enable remote monitoring, the site's reasons should be explored objectively and with an eye to mutual education and collaboration in problem-solving.

7) The monitor as trainer/educator/mentor

Frequent communication with a site—i.e., at time intervals less than the 6-8 week span between customary visits to sites—gives in-house monitors the opportunity to assess how well site personnel understand the protocol and study procedures, and to offer guidance and training, as needed. The combination of centralized monitoring and study visits that are focused on review of critical variables will increase confidence in the accuracy and completeness of the data.

Some have expressed concern that sponsors will reject research naïve sites in favor of experienced sites that are more easily monitored remotely. On the contrary, an experienced in-house monitor build a

relationship with and mentor site personnel to ensure that increasingly more sites are capable of conducting clinical research.

November 28, 2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

Docket No. FDA–2011–D–0597

Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear Ms. Meeker-O'Connell:

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 70,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO applauds the issuance of the above-titled Draft Guidance, which is meant to allow study sponsors and their representatives to develop risk-based monitoring strategies and plans for investigational studies of medical products, using a "modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively." ACRO member companies have long supported the idea that risk-based monitoring, if appropriately supported by robust operating procedures and best practices, meets the FDA and ICH GCP requirement of "adequate monitoring" and we agree that effective implementation of appropriate risk-based monitoring strategies and plans has the potential to result in more effective oversight of complex, modern trials.

ACRO appreciates the opportunity to offer the following comments.

Section II. Background

At lines 62-64 the Draft Guidance states that, "Quality is a systems property that must be built into an enterprise and cannot be achieved by oversight or monitoring alone." While ACRO agrees with this principle, and with the corollary statement that in the realm of clinical research quality begins with a well-designed and executed protocol, we believe that in regard to *monitoring* per se the appropriate focus of *quality management activities* should be on human subject protection and the quality and integrity of research data. A wide range of activities may lead in the direction of research that is less costly or more efficient or faster, but the goal of

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ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

At lines 197-198, the Draft Guidance indicates that the complete absence of on-site monitoring will likely continue to be unusual, consistent with ICH E6. ACRO agrees that there will continue to be value in some level of "triggered" on-site monitoring. However, the degree to which triggered monitoring is employed will depend on the clinical trial design. While some trials, such as interventional studies, may require little on-site monitoring, other clinical trials may more typically require on site review of data collection and entry, investigator supervision, site compliance, critical data review, investigational product management and suitability of the research facility. Thus, appropriate planning for site visit triggers will be a key element of risk reduction. Design elements such as predictive algorithms and historical data can be used to pre-determine a schedule of monitoring site visits and predict an expected work volume and resourcing needs. As data is obtained and centrally monitored for sites on an on-going basis, the schedule of visits and other monitoring activities can be adjusted and an in-person monitoring visit may be triggered to occur sooner or later than the pre-determined schedule.

Section III. Factors that Influence Study Quality and Integrity

In line 221 at footnote 28, the Draft Guidance encourages sponsors to seek consultation with the appropriate review division regarding quality aspects of clinical trial design. While we are mindful that the FDA's resources are limited, ACRO suggests that prospective review of the proposed monitoring plan by the appropriate Agency division would significantly advance the transition from current outmoded, retrospective practices to alternative monitoring approaches that more efficiently focus on patient safety and data integrity.

A second way that the Agency could facilitate and accelerate a transition to risk-based monitoring approaches, would be to issue an Addendum to the Draft Guidance that includes Use Cases to illustrate a "modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively" across studies of varying size, therapeutic areas, design complexities, etc.

Section IV. General Monitoring Recommendations

ACRO agrees with the guidance provided in lines 248-254, regarding the utility of on-site assessment of site-critical study data and processes and evaluating significant risks and potential site non-compliance at an early stage of the study. We encourage the FDA to provide further guidance regarding the critical activities of site selection and site initiation.

At lines 277-278, the Draft Guidance suggests that remote monitoring can be accomplished when source data can be verified remotely, provided that both source data and CRFs can be accessed remotely. While we appreciate this encouragement for remote monitoring of electronic data, we do have some concerns that such a straightforward model of the relationships between and among sponsor, CRO, study site, and data seldom exist in today's world. It is not at all uncommon for one CRO to be charged with site monitoring while another does data storage and a third performs data analyses; simply, to say that one participant has remote access to electronic data does not mean that all participants do.

At lines 299-308, the Draft Guidance mentions, but does not provide detail on, the issues of prospective quality planning and upfront site risk assessment. In its similar draft reflection paper (Reflection Paper on Risk-Based Quality Management in Clinical Trials), the European Medicines Agency (EMA) notes that risks might be anticipated especially at the interfaces of quality systems or the points of movement of information/data across systems. ACRO believes it would be useful for the FDA to elaborate further on differing methods that might be used to assess risk at both the site and system interface levels.

At lines 322-327, the Draft Guidance mentions that the sponsor's risk assessment "should consider the impact and likelihood of error, and the extent to which error would be detectable, for identified data and processes." Perhaps the biggest issue with centralized monitoring is in the identification of what it is important to know (what are the greatest risks?) as well as the level of risk in being uncertain about what you don't know. Referring again to the EMA's Draft Reflection Paper, it would be helpful if the FDA would further discuss methodologies for establishing the acceptable variation or tolerance limits for particular clinical trial procedures.

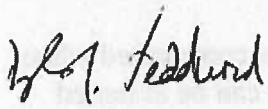
At line 417, the Draft Guidance suggests that the description of monitoring approaches would include criteria for determining the timing, frequency, and intensity of planned monitoring activities. Again, ACRO thinks it would be helpful if the Draft Guidance would provide examples of such criteria across commonly conducted phase II-III trials (e.g. cardiovascular, diabetes, oncology, central nervous system).

Conclusion

ACRO thanks the FDA for issuing this Draft Guidance, and we appreciate the opportunity to provide these comments. We believe that this Draft Guidance will help define and provide encouragement for alternative monitoring models that leverage centralized monitoring as a more efficient and effective resource as part of the overall monitoring plan. Having several times referenced the EMA Draft Reflection Paper, ACRO encourages the Agency to consider how it may work with European regulators to standardize the concepts of risk-based monitoring approaches put forth in order to ensure harmonization of approaches used in running global clinical trials.

Please feel free to contact ACRO at any time for additional input.

Respectfully submitted,



Douglas Peddicord, Ph.D.
Executive Director

invivodata Response

FDA Draft Guidance: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring

invivodata is pleased to have the opportunity to respond to the FDA Draft "Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" (referred to here as the 'draft Monitoring Guidance').

Please find below a table of the responses to sections of the draft Monitoring Guidance.

Draft Guidance Line/Statement	invivodata response
General	invivodata commends FDA for encouraging industry to consider centralized monitoring procedures, especially those that are enabled by technology. It is clear from FDA's current thinking that such processes may enhance patient safety and data integrity.
General	FDA uses the acronym 'EDC' for electronic data capture throughout the draft Guidance. It appears that FDA is referring generically to any technology enabled system that captures any type of data in the context of clinical trials. However, it is the observation of invivodata that EDC is synonymous with electronic CRF systems. While such systems are central to clinical trials, they represent only one potential venue for collecting electronic data. Other examples include electronic patient report outcomes (ePRO); clinical data management systems (CDMS); clinical trial management systems (CTMS); etc. invivodata recommends that FDA either more clearly specifies the range of technology enabled systems covered by the term EDC, or preferably that FDA consider the use of the term eClinical systems.
General	In a number of places in the draft Guidance FDA refers to 'non-compliance.' It is presumed that this refers to non-compliance of the investigative site with the investigation plan. However, non-compliance can also occur by patients, possibly based upon inappropriate training by the investigative site. It is recommended that in this context, where centralized monitoring may be used to track patient and investigative site activities, that FDA more clearly specifies the types of non-compliance that may occur in a clinical trial.
Lines 156-158	FDA refers to centralized monitoring helping to detect data anomalies such as fraud or fabrication of data. invivodata suggests that some ePRO data collection systems track patient and site behavior in such a way that they can help to detect fraud or

Draft Guidance line/statement	invivodata response
	fabrication of data. It is suggested that FDA consider indicating that data collections systems may already assist for detecting such fraud through central monitoring and/or analytic processes.
Line 335-336	FDA states that "adherence to protocol eligibility criteria intended to include only subjects from the targeted study population..." is subject to more intensive monitoring. invivodata notes that technology enabled screening systems already exist that can execute screening calculations, which in turn ensures that only subjects that meet the screening criteria are enrolled in the study.

In order to provide specific examples where "EDC systems" would include ePRO systems that perform appropriate monitoring tasks, and therefore support invivodata's recommendation to broaden the terminology, the following specific sections of the draft Monitoring Guidance are noted:

Draft Guidance line/statement	FDA Statement
Lines 265-267	"Replace on-site monitoring for monitoring activities that can be done as well or better remotely (e.g., standard checks of range, consistency, and completeness of data and checks for unusual distribution of data within and between study sites, such as too little variance)[31]"
Lines 268-270	"Target on-site monitoring by identifying higher risk clinical sites (e.g., sites with data anomalies or a higher frequency of errors, protocol violations, or dropouts relative to other sites)"
Lines 271-273	"Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data trends not easily detected by on-site monitoring)"
Lines 274-276	"Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at a site"
Lines 279-280	"Conduct aggregate statistical analyses of study data to identify sites that are outliers relative to others and to evaluate individual subject data for plausibility and completeness"

Draft Guidance Statement	FDA Statement
Line 281-283	"Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility violations, and delays in reporting data), and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance"
Lines 363-366	"Endpoints that are more interpretative or subjective may require on-site visits to assess the totality of subject records and to review application of protocol definitions with the clinical investigator."

November 17, 2011

Division of Dockets Management (HFA–305)
Food & Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852.

Submitted electronically to http://www.regulations.gov

Re: Docket FDA-2011-D-0597
Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear FDA,

This letter represents the views of RTI Biologics, Inc. (RTI) concerning **FDA's request for** comment on the draft Guidance for Industry, *Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring*. RTI is the leading provider of sterile biological implants for surgeries around the world with a commitment to advancing science, safety and innovation. RTI prepares human donated tissue and xenograft tissue for use in orthopedic, dental, hernia and other **specialty surgeries. We appreciate the opportunity to respond to FDA's** request for input. Please see the following pages for our comments.

Respectfully Submitted,

Robin Waite
Director Clinical Projects
RTI Biologics, Inc.

Balancing On-Site and Centralized Monitoring in the Monitoring Plan

We appreciate FDA acknowledging that industry has the perception that the frequent on-site **monitoring visit model, with 100% verification of all data, is FDA's preferred way** for sponsors to meet their monitoring obligations (lines 96-99). We also appreciate FDA recognizing that it is important for the Agency to clearly articulate your recognition of the value of alternative **approaches to facilitate change in industry's monitoring** practices (lines 148-149). This guidance has much practical **insight which appears to be based, at least in part, on FDA's** experience (lines 216-220). It would be very helpful if FDA could provide some case study examples of monitoring plans, to step the reader through an example risk assessment process, taking into consideration the relevant factors when developing a monitoring plan, and articulating these decision points in the monitoring plan itself.

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22 November 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
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Re: Docket No. FDA- 2011-D-0597

To Whom It May Concern:

Triangle PEERS is pleased to submit comments on the *FDA Draft Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.* Triangle PEERS (**P**art **E**leven & **E**lectronic **R**ecords **S**takeholders) is an association based in Research Triangle Park, North Carolina, whose membership represents over forty organizations, including pharmaceutical companies, clinical research organizations, academic research organizations, validation and IT systems consultants, and technology vendors. PEERS members possess expertise in a variety of perspectives such as technology, process engineering, quality assurance, regulatory affairs, data collection and management, legal, and data security. PEERS members focus primarily on the practical implementation of regulations, guidance and standards pertaining to electronic records, including 21 CFR Part 11, particularly as this applies to Good Clinical Practices (GCPs) in the conduct of clinical trials.

PEERS applauds the Agency for its willingness to recognize a variety of approaches to monitoring clinical sites and to consider risk assessment as a key component of determining monitoring methodology. PEERS appreciates the Agency's flexibility in allowing technology to enhance the effectiveness of clinical monitoring. PEERS recommends, however, that the Agency emphasize that risk-based monitoring

methodologies should be implemented with care and, in particular, that remote monitoring should enhance or complement but not necessarily replace on-site monitoring,. The Guidance, when finalized, should clarify that risk-based monitoring does not suggest any less vigilance in clinical monitoring. To that end, PEERs recommends that the risk-based approach to clinical monitoring be clearly documented and justify how alternative monitoring methodologies will adequately protect patient safety, data integrity, and product quality.

PEERS also agrees with the Agency in line 203 that clinical monitoring should be one part of an overall quality management system and recommends that the Agency emphasize this aspect more or add cross-references to other available resources and industry Guidance on the topic of quality management systems.

Increasingly, this industry is conducting global trials, with clinical investigational sites located in several different countries. The appendix to the European Medicines Agency draft "Reflection paper on risk based quality management in clinical trials" (04 August 2011) addresses privacy concerns related to remote access to site/study records and controls to consider. For harmonization of a global clinical trial, PEERS requests that FDA address privacy with respect to considerations of other global regulatory agencies and data protection authorities in terms of balancing of the interests, namely safety and data integrity with privacy standards.

The specific comments of PEERS follow, organized sequentially by the sections and lines of the draft Guidance.

Lines	Comment
Section II.A. Lines 93-110	PEERS recommends that the Agency delete Section II.A. altogether. Instead, the surveys and white papers cited could be referenced in a new Section VII as additional resources. If the Agency elects to retain Section II.A., lines 93 -110 in particular should be clarified; lines 93-110 may be misconstrued as standards for monitoring frequency. Instead, lines 93-110 should be used as illustrative examples with the caution that monitoring frequency should be based on such factors as type of study, patient safety considerations, subject enrollment time frame, and critical assessments.
Section II.B. Lines 125-127	PEERS recommends that the Agency give examples of when reliance entirely on centralized monitoring would be appropriate. Further, what kind of technical processes would be expected to

	be in place?
Section II.C. Lines 144-166	PEERS recommends that the Agency clarify what types of centralized monitoring are alluded to in this draft Guidance. For example, is this a reference principally to electronic centralized monitoring based on electronic data capture, or does this also include more traditional monitoring means, such as reviewing paper document, spread sheets, and queries? Additionally, an elaboration on acceptable processes and technical measures of centralized monitoring would also be helpful.
Section II.C. Lines 156-158	PEERS agrees that data anomalies can more effectively be assessed, and outliers become more obvious, as long at timely data from the sites is available. Remote access to data also makes it easier to more quickly determine whether a site is following the protocol in terms of both timing and data collection, or whether the clinical site may need additional education. However, it should be noted that this ability to review the data implies a dependency on implementation of an electronic data capture (EDC) system. Traditional data entry of paper case report forms will not be timely enough to catch issues early.
Section II.C. Lines 163-166	PEERS recommends moving this important sentence into the Introduction (Section I) of the Guidance since it is a key concept: "This guidance is therefore intended to clarify that risk-based monitoring, including the appropriate use of centralized monitoring and technological advances (e.g., e-mail, webcasts, and online training modules) can meet statutory and regulatory requirements under appropriate circumstances." PEERS also recommends that the examples be broadened to include videoconferencing, Skype for real-time interviews and meetings with study site staff.
Section IV.A Lines 231-295	Although this Section distinguishes the differences in types of monitoring, the content should be expanded to emphasize that centralized monitoring really is data monitoring, and possibly checking on accuracy of subject inclusion/exclusion at sites. The Section should also clarify that there are some activities (e.g., verification of accurate drug storage, potential sharing of passwords) that, without further technological advancements, may be difficult to determine remotely and that relying on one,

	or very few, on-site monitoring visit(s) could raise concerns.. For example: • In the case that there is no access to electronic source documentation and subject charts, verification of exclusion/inclusion criteria and detection of adverse events and other safety issues may be difficult without on-site monitoring visits. • Assessing study drug accountability may also be difficult in many cases remotely. • Verification that products are properly stored and secured as per Good Manufacturing Practice or protocol requirements would be difficult, as would verify some instrument calibrations. • Assuring that subject and study records are properly secured would be a challenge remotely. • Evaluating the informed consent process may also pose some problems, especially when there is no access to electronic clinical management systems. • There is also the aspect of human nature which causes many individuals, including Principal Investigators and site study staff, to conduct themselves in a more appropriate manner if they perceive that they are being directly observed. The clinical site monitor can also get a better understanding of the dynamics and relationships among site study staff. • There is an element of human relationships and trust between the clinical site monitor and site study staff that cannot be fostered and developed as successfully without some face- to- face interactions. On-site monitoring visits may foster an awareness of compliance issues, and a willingness to discuss concerns or report evidence of potential misconduct that may not be as readily achieved with centralized monitoring.
Section IV.A.1 Lines 240-241	PEERS recommends revising the definition of on-site monitoring: "*On-site monitoring* is an in-person evaluation during the course of the study carried out by sponsor personnel or representative(s) during the course of the study at the site(s) at which the clinical investigation is being conducted. (Additions

	underlined for ease of identification.)
Section IV.A.1. Lines 249-251	PEERS recommends revising the language to read as follows: "Therefore, on-site monitoring ordinarily should be devoted to assessing the critical study data and processes and evaluating significant risks and potential site non-compliance, <u>including data anomalies or patient safety or other quality concerns</u>, identified through other sponsor oversight activities." (Additions underlined for ease of identification.)
Section IV.A.2. Lines 268-270	PEERS recommends adding unusually high rates of enrollment at a site as another factor for identifying higher risk clinical sites.
Section IV.A.2. Lines 277 -278	The draft Guidance notes that source data verification can also occur remotely, provided the electronic source data and the collected trial data (case report forms) can be accessed remotely. It should be noted that accessing electronic source at a clinical site or institution may not be that feasible, as some institutions will have data privacy concerns, potentially incompatible network protections in place, and administration of use accounts may be problematic. Also, electronic source systems, such as electronic health records (EHR) systems need to be set up to segregate subject- specific files with remote access in order to facilitate remote source data verification. PEERS recommends that the Agency reiterate that to trust the electronic source there must be an appropriate level of verification or validation of the electronic source system.
Section IV.A.2. Lines 286-287	PEERS understands that industry has been looking to the Agency for encouragement in the use of risk-based monitoring approaches. It is also recognized that focusing limited resources on high risk sites can actually increase patient safety. PEERS recommends that the Agency reinforce the concept of documenting the study and site risks and linking those directly to criteria for when on-site monitoring visits will or will not occur.
Section IV.C. Lines 348 – 401	PEERS agrees with the factors noted playing into whether to conduct on-site monitoring. PEERS suggests that an additional factor of past experience of a less than positive nature with an investigator may also be a reason to conduct on-site monitoring.
Section IV.C.	PEERS agrees that additional monitoring should be undertaken

Lines 371-373	in vulnerable populations, but recommends that it should be clarified that the criteria for classification of vulnerable populations can encompass aspects other than health risks, and include issues such as coercion or social, privacy and/or legal risks.
Section IV.D. Lines 403-496	PEERS agrees that it is advisable to create a monitoring plan, to proactively define the approach to be taken and the rationale, to avoid the appearance of monitoring visits being solely based on cost and timing factors once a trial begins. PEERS recommends also that metrics be defined to access the effectiveness of the monitoring plan and that a backup plan be documented in the event the monitoring plan is determined not to be effective. The monitoring plan should also include criteria for triggering on-site monitoring visits when centralized monitoring is utilized more heavily. There should also be predefined triggers that would lead to revision of the documented monitoring plan.
Section IV.D.2 Lines 436-447	PEERS agrees with the Agency with the emphasis on timely reporting from monitoring visits, in order to identify and respond to issues in a timely manner, and mitigate further risks.
Section IV.D.3 Lines 449 - 460	PEERS strongly agrees with the Agency that clear procedures are necessary to address site non-compliance in a consistent and prompt manner. Identifying the root cause for issues is a critical activity to ensure that corrective action truly addresses the problem, and that adequate preventive action can be implemented to prevent recurrence.
Section IV.D.4. Lines 462-489	PEERS recommends that training also include any computer systems that will be used to analyze data, including for outliers, potential noncompliance. This training would extend not only to the EDC system, but also to potential analysis software, and EHR systems at the clinical sites, if electronic source will be accessed. In situations of centralized, remote monitoring, PEERS recommends that training also include enhanced subject protection and ethics training.
Section VI.B Lines 539-545	PEERS recommends that there be procedures in place for timely reporting between the Contract Research Organization (CRO) and sponsor regarding site issues that are identified via

	monitoring conducted by the CRO. The procedures should also identify responsibility for site issue resolution and escalation, including how communications will be handled.
New Section VII.	PEERS recommends that the Agency include a new Section VII to list additional resources and references. PEERS recommends deleting Section II.A. Current Monitoring Practices altogether from the Guidance and retain this information and foot notes as references within the new Section VII.

In closing, Triangle PEERS appreciates the opportunity to comment on the draft FDA *Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring*.

Sincerely,

Triangle PEERS

Research Triangle Park

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