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Re: ***Docket No. FDA-2011-D-0597: Comments on Updated Draft Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring***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We commend and support the FDA on updating the proposed draft guidance entitled *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.* We believe that this updated guidance will be helpful in aligning the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,

		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 .