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This letter consolidates FDA's inspectional findings during the above-mentioned audits and, therefore, is intended to provide more global information to assist you in pursuing correction of study monitoring inadequacies and deficiencies that are not solely those of one Medtronic product area.

The following enumeration and discussion of violations and deviations from the regulations is not intended to be an all-inclusive list of problems encountered during our reviews. Information pertaining to the [] products will be discussed at the end of each of the following sections.

1. Failure to ensure proper monitoring of the clinical investigation(s) -- 21 CFR 812.40

For the [] study, your clinical site monitoring was conducted according to []

According to the []

[] Even though monitoring visits were conducted throughout the clinical investigations, they were inadequate to identify under-reporting of adverse events and system complications, informed consent deficiencies, and other problems.

Based on our review of the records at the investigational sites, some adverse events and system complications were not reported to Medtronic, and were subsequently left unreported in an original Premarket Approval (PMA) application to the Agency [] . For example, we noted consistent under-reporting of adverse events, system complications, and interim visits (over [] unreported events out of the [] subjects enrolled at the [] .

You addressed some of the under-reporting, particularly that from the [] , during monitoring visits conducted at the clinical sites immediately prior to the FDA inspections. According to your July 1996 monitoring site visit report for the [] , clinic and hospital charts for all patients were reviewed. Medtronic determined that the casebooks reflected consistent under-reporting in two areas: []

[] . To correct this problem, your firm recommended that the investigators document []

Updated clinical information was provided to the Agency in a PMA Amendment [] .

It should be noted that [] written response following FDA's July 1996 inspection states that, prior to Medtronic's July 1996 monitoring visit, no concerns had been raised regarding the reporting of adverse events. In fact, a December 1995 monitoring report and follow-up correspondence for this site noted that clinic and hospital charts for three participants were reviewed and CRFs were compared to those on file at Medtronic. These documents stated that the investigator and staff continue to adhere to the clinical protocol, with no significant deviations found, and that overall the center was doing an excellent job in conducting the study.

At the [] [], adverse events were identified for [] patients ([]) but were not recorded in the patients' case report forms (CRFs). For at least [] subjects' files reviewed ([]), numerous [] identified in progress notes were not reported. No Form [] [], was observed for these [] subjects. For Subject [] []. Form [] was completed for the [] visits. The [] forms for these two visits indicate that [] []; however, for the other visits, no [] were noted.

We noted that your monitoring procedures had provisions for [] [].

These visits could include verification of data or case report forms with the patient records or source documents. There was no evidence that audit site visits were conducted in accordance with the procedure. Detailed site audits of the data, had they been performed, might have detected the violations noted above.

During the inspection of Dr. [] [], the FDA investigators were told that Medtronic had never visited the site for the purposes of monitoring/auditing, but that a technician was present for some of the [] [], and in some cases completed case report forms. Monitoring of the study progress reportedly was conducted primarily through telephone calls with the study investigator. Further, for [] [] (Drs. [] []), [] [] (Dr. [] []), [] [] (Drs. [] []), [] [] (Dr. [] []), and [] [] (Dr. [] []) numerous examples of incidents of inadequate informed consent, protocol deviations, inadequate device accountability, and the failure to report adverse events were noted. Many of the examples noted above could have been prevented through a comprehensive and adequate monitoring plan.

2. Failure to ensure investigator compliance -- 21 CFR 812.46

Medtronic failed to ensure investigator compliance with the investigational plan. For example, investigators failed to maintain accurate, current, and complete study records (which, in part, led to the under-reporting of adverse events and system complications in the [] study as described above), failed to [], and deviated from the protocol.

The protocol required that all []. The most current [] showed that, of the [] in the [] study, only []. A May 1996 monitoring report for the [] site indicated that only a few [] to Medtronic and little documentation existed regarding reasons that []. This failure to [] did not allow Medtronic the opportunity to [].

For the [] IDE studies, you failed to ensure that clinical investigators met the requirements for obtaining informed consent in accordance with 21 CFR Part 50. Although monitoring visits generally confirmed that consent forms had been signed by patients prior to device [], the IRB-approved consent forms actually used were not reviewed for adequacy by Medtronic. FDA review of those consent forms found that some did not identify all potential risks, that they minimized risks, and/or they did not contain required elements. For example, the consent used at Dr. [] site minimized risks by including statements such as "treatment ... has been shown to have very small risks" and "[] requires a minor operation," and the consent did not include the risks of [] or the duration of the study. The consent used by Dr. [] did not, for example, include risks of [].

[] Dr. [] consent failed to include the risks of [].

In some instances Dr. [] failed to get consent forms signed prior to []. Problems with documentation of informed consent were also noted for Dr. [].

During the FDA's August and December 1996 inspections, Medtronic representatives stated that their past procedures for approving the informed consent document were not the same as they are now [i.e., for the [] study the clinical investigator was allowed to make changes as long as the consent form was approved by their Institutional Review Board (IRB)]. Medtronic

representatives explained that current consent forms are required to be approved by Medtronic and the IRB, thereby ensuring the inclusion of all potential risks associated with a study. However, in a compassionate use request submitted in November 1996 by Medtronic to the Agency ([redacted]), an informed consent document was attached which did not include all potential risks previously identified (e.g., [redacted]) and required elements (e.g., specification of alternatives and that FDA may inspect the records).

Medtronic took no significant actions during the [redacted] referenced studies to achieve investigator compliance. During our review of the monitoring files, it was obvious that several investigators failed to comply with the requirements of the investigational plan and/or federal regulations. For example, for the study there was a lack of required follow-up and late submission of data forms (e.g., they were not sent in for years) for Dr. [redacted] patients. Dr. [redacted] also exhibited delayed follow-up of patients, late forms submission, and protocol deviations. These deviations included [redacted]

For Dr. [redacted], there was a lack of required follow-up and complaints from patients regarding inadequate patient care. For the [redacted] study, problems regarding protocol deviations (inclusion/exclusion criteria and adverse event and routine study observation reporting) were noted for Dr. [redacted].

An inspection of Dr. [redacted] ([redacted]), ending on [redacted], revealed that he continued to [redacted] after receiving a study suspension notification from the sponsor and prior to notification of study resumption. Medtronic continued to allow access to the device after enrollment limits had been reached, and assisted in developing alternate procedures which included an Emergency Use Protocol to allow for such shipments. A letter at that time, from Medtronic to Dr. [redacted], informed him that FDA concluded that several of the cases did not qualify for consideration as emergency uses and the fact that the patient limit had been reached did not give investigators liberty to continue to [redacted] by designating them as "emergency uses." In this letter, Medtronic also references three other letters from FDA which stated that continued failure to comply with the IDE requirements regarding emergency use will result in FDA proposing withdrawal of approval of the IDE application.

Dr. [redacted] ([redacted]) allowed non-study physicians to [redacted]. Study data was transferred to case report forms by individuals not under his direct supervision. In addition, at the request of Medtronic, and following his

authorization, Dr. [] signature stamp was used on many of the case report forms. It remains unclear who actually used the stamp and whether or not Dr. [] reviewed the case report forms for accuracy as required by protocol.

Many of the examples listed under item #1 may also be considered as failures to ensure investigator compliance.

3. Failure to provide accurate, complete and current information
-- 21 CFR 812.150(b)

Certain data submitted in PMA [] were discrepant when compared to data in the case report forms and/or medical records. In addition, certain data within the PMA were contradictory.

Discrepant information was reported in the PMA and PMA Amendment regarding []. For example, inconsistencies were noted in the summary tables of [].
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During the FDA's August 1996 inspection, [] records from the [] were reviewed. Of these subject records, [], where the [] as described in the PMA tables [] differed. These subjects were identified as []. Further, discrepancies were identified with the data and reporting of the [] files []. For example, subject [] was reported in subject []; PMA Table [], while PMA []. Records for subject [] indicate []; PMA Table [], but PMA Table []. The PMA Amendment shows subject [] and [], the same as reported in PMA Tables [] and [], respectively. For these two study subjects, the data reported in the subject study records and the PMA not only conflicts, but the PMA contradicts itself in separate tables. Although these data discrepancies may not have negatively impacted the PMA application overall, it is your responsibility to ensure that accurate information is provided to the Agency.

Additionally, the FDA 483 issued following the December 1996 inspection identifies examples of complications for several patients in the [] study which were unreported to the Agency. For example, regarding patient [] your [] final report indicates that there was []

[] Under [] this patient is identified as [] What is not described in the report is that this patient []

[] The final report, under []

[] Case report forms indicate that []

[] What is not evident in the final report is that [] For patient [] according to annual reports and/or the final report this patient was []

[] What is not evident from these reports is that the patient had []

[] In addition, for the [] study, Dr. [] failure to report adverse events to you in a timely manner may have affected data submitted to the Agency in your annual reports.

Further, there were some problems noted with device accountability. For example, a listing [] of clinical product serial numbers at the [] site for study [] shows several [] unaccounted for (ship dates [] - []). In the [] study, a [] either unaccounted for or used for []

For PMA [], at Dr. [] site, raw data was missing or incomplete on several patient charts and follow-up forms. Some [] recorded on patient charts were different than those reported to Medtronic. At Dr. [] site, in some cases study data was incomplete or not available. For these two investigators, annual reports were not routinely submitted to the reviewing IRBs. For Dr. [] (PMA []) raw data was not available for all follow-up visits and, in two instances, incorrect data was reported on the CRFs to the sponsor. Additionally, there was no documentation of progress reports being made to the sponsor and IRB approval was never obtained because the study was represented as an amendment to another IDE study. This combining of studies resulted in disorganized study files, the use of an incorrect consent form for one patient, and the reporting of incorrect information to the IRB. Deviations noted at Dr. [] site (PMA []) included inaccurate

case report forms and lack of required follow-up exams for some subjects. It is unclear how these "problems" affected Medtronic's data reporting in the respective PMAs.

For each of the referenced cardiology/cardiovascular studies, device accountability was also inadequate. Records documenting the receipt and use of the devices were not maintained at the site, and for Dr. []'s study, Medtronic did not have an accurate listing of all [] sent to this site. The problem with device accountability may have, in part, been due to Medtronic's procedure for "hand delivering" the investigational devices []. However, this practice does not relieve the investigators of their recordkeeping responsibilities [21 CFR 812.140(a)(2)].

We acknowledge your October 1, 1996, letter to Edwin Dee, Director, Compliance Branch, Minneapolis District Office, which was forwarded to our office. The letter was in response to the observations identified during the August 1996 inspection of the []. While your response appears to satisfy some of our questions and observations because updated clinical information was provided, we remain concerned about the extent of unreported data resulting from Medtronic's failure to adequately meet its monitoring responsibilities. For example, the fact that you failed to adequately monitor early in the [] study affected the reporting of data in PMA []. Additionally, your auditing procedures were inadequate as evidenced by the consistent under-reporting of adverse events, system complications, and interim visits.

Your failure to obtain all study information led to incomplete information/clinical data being submitted in the original PMA []. The fact that you later supplemented this data with corrected information does not mitigate this observation. The monitoring visits which resulted in the collection of this corrected information were performed in every case just prior to our scheduled inspections. Moreover, your failure to ensure investigator compliance and [

[]. Your failure to review consent forms actually being used in studies led to patients receiving inadequate informed consent and possibly placing them at risk.

FDA will continue its review of information collected regarding the []. We will inform you of our findings when complete.

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It is your responsibility to ensure adherence to each requirement of the Act and regulations. Within 15 days of receipt of this letter, please provide this office with written documentation of the specific steps you have taken or will take to prevent the recurrence of similar violations in current or future studies. Should you require additional time to respond, please contact Mr. Kalins at the telephone number provided below.

Your response should be directed to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 2098 Gaither Road, Rockville, Maryland 20850, Attention: David R. Kalins. A copy of this letter has been sent to the Food and Drug Administration's Minneapolis District Office, 240 Hennepin Avenue, Minneapolis, Minnesota 55401. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Mr. Kalins at (301) 594-4720, ext. 137.

Sincerely yours,



Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health