



**Medtronic**

Medtronic, Inc.  
710 Medtronic Parkway NE, ms LC270  
Minneapolis, MN 55432.5604 USA  
www.medtronic.com

0306 '02 FEB 19 73:10

tel 763.505.2562  
fax 763.505.2613  
chuck.swanson@medtronic.com

Charles H. Swanson  
Vice President, Chief Quality and Regulatory Officer

February 15, 2002

Docket Management Branch  
HFA-305, Room 1061  
Food and Drug Administration  
5630 Fishers Lane  
Rockville, MD 20852

To Whom It May Concern:

Thank you for the opportunity to share comments on the FDA's draft "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees." As a key player in the medical device market, we understand and appreciate the need for constant vigilance when it comes to scientific integrity in research studies, and we support the FDA's efforts to ensure that results of clinical studies remain unbiased in order to maintain a high standard of patient safety. We have three main concerns, however, with the FDA proposal for data monitoring committees (DMCs) as they relate to industry-sponsored studies.

**Concern #1: Too many of the medical device trials will appear to require DMCs because there is not a clear distinction between public-sponsored studies (such as those conducted by the National Institutes of Health) and industry-sponsored studies (such as those conducted by Medtronic). The opportunity for misinterpretation of the guidelines is high.**

According to the FDA guidelines, the DMC concept was established for large, randomized, multi-site studies that evaluate intervention to prolong life or reduce the risk of a major adverse health outcome. The guidelines also state that DMCs are not needed for every clinical study, but they are recommended in the following situations:

- When there is high risk to the patient (section 2.1)
- In long-term trials (section 2.2)
- To assure scientific validity of the trial when changes (due to internal and external factors) can create biased results (section 2.3)
- Where interim analysis is planned (section 2.3, 4.41, 6.3, 6.6 and 7.2)
- In Phase I and early Phase II studies (section 4.4.2)
- For expedited regulatory review (section 5.2)

01D-0489

C17

Most of the clinical studies conducted by device manufacturers fall into one or more of these categories. Thus, if this guideline is enacted, most device companies will be compelled to use DMCs for their trials. In addition, the FDA already plays a significant role in reviewing scientific validity of device trials, which is different from NIH-sponsored studies. We believe this redundant use of DMCs for industry-sponsored device trials would result in duplication of efforts, possible overuse, and avoidable time and expense.

We believe the guidelines need to clarify the circumstances in which a DMC will be required and recommend that DMCs be established only for the first two situations in the case of industry-sponsored clinical studies. All other situations should be left to the sponsor's discretion, based on that company's cost/benefit analysis.

**Concern #2: The role of DMCs must be more flexible in order to acknowledge the unique needs inherent in industry-sponsored trials, including those related to blinded studies.**

The DMC guidelines, as currently expressed, assume that all information the DMC receives from studies must be masked (or blinded) from the sponsor, and the DMC must be totally independent from the sponsor. While this model prevails in NIH-sponsored clinical trials, the very nature of device studies makes it very difficult to ensure even single-blinded studies, because many elements of the data, beyond randomization assignment, might reveal the treatment group. In addition, there are regulations in place, such as 21CFR812, that require sponsors to isolate factors related to observed adverse events. Sponsor monitors must verify randomization and appropriate device functions at investigational sites.

J. Herson, in his 1993 article in *Statistics in Medicine*, pointed out the fundamental difference between NIH-sponsored trials and industry-sponsored trials in the table shown here.

**Table I. Characteristics of Clinical Trials by Sponsorship**

Characteristics	NIH-sponsored	Industry-sponsored
Purpose	Advance medical research	Get new product approved
Activity	Research	Development
Orientation	Science	Product
Example	Lipids Research Clinics	Lovastatin
Audience	Public	FDA
At design stage	Know the question	'Know' the answer
Type of trial (NHLBI)	Large number of patients, long duration, one trial	Small number of patients and of shorter duration than NHLBI, but the new drug application would consist of a whole collection of trials over a 7-10 year period

Source: Herson, J. (1993), Data Monitoring Board in the Pharmaceutical Industry, *Statistics in Medicine*, Vol.12, 555-561.

Because the FDA and device companies already share a vital role in assuring proper conduct and scientific validity of industry-sponsored studies, the DMC should have a more limited role in industry-sponsored trials than in public-sponsored studies. Depending on the criticality and risk level of a study, industry sponsors must have options for establishing DMCs with less independence than the one currently suggested. Although we recognize the value of a DMC in certain circumstances, we believe that in most studies, more practical measures can be taken to achieve the same results.

**Concern #3: Recognizing the need to balance the goal of patient safety with the need for independent evaluations, we believe that the use of independent statisticians should be an option, not a requirement, for sponsors.**

We disagree with the draft guideline recommending that independent statisticians perform interim analyses. Hiring statisticians independent from the sponsor may result in less reliable data, an increased chance of misinterpreting data and delayed submission of trial results. We recommend that the use of independent statisticians be described as one of many options available for the sponsor to minimize bias when DMCs are employed. It is the sponsor's responsibility to demonstrate that bias issues are adequately addressed, whether a DMC is used or not.

Section 6.4 of the draft guidance suggests "the integrity of the trials be best protected when the statistician preparing unblinded data for the DMC is external to the sponsor." We think it is naive to believe that DMCs are the panacea for bias. Issues of supply and demand of qualified DMC members, conflict of interest, the need for confidential handling of proprietary data by independent statisticians, lack of detailed knowledge of the device, and the financial relationship between contractor and sponsor can certainly introduce bias. Companies may need exclusivity clauses in contracts with DMC members who also work for competitors.

Based on the FDA's recommendation, the role of internal statisticians will diminish, and the activities of independent statistical consultants will increase. Companies may end up hiring contract research organizations to do work formerly managed in house. Because there is a finite supply of people qualified and available to serve in this role, and because larger drug companies may monopolize available resources, there may be additional costs and time delays for the submission of clinical device results.

The suggestion of independent statisticians may have come from the Data Coordinating Center model, which is becoming more competitive in large, long-term NIH studies. We suspect some of the motivation for having academic statisticians serve in the independent statistician/DMC role comes from a perceived opportunity, but we question whether clinical studies will be a top priority for academic statisticians with teaching or research responsibilities of their own.

We believe strongly in maintaining high standards of quality in our clinical studies and worry that the use of independent statisticians may compromise that quality. Device studies are very complex and need engineering experts to interpret device performance. Also, the development of technology moves very quickly, resulting in the need for clinical research to be conducted in a timely fashion. Statisticians and data coordinating activities must be fully integrated into the sponsor's organization in order to address these needs. In-house statisticians have an in-depth knowledge of the products and their possible clinical outcomes. Thus they are able to provide a better assessment of the quality of data and a more effective response to data management issues. Using independent statisticians will only create a heavier burden for sponsoring companies and slow down the submission process, thus compromising the speed with which new products get to market.

### **Summary**

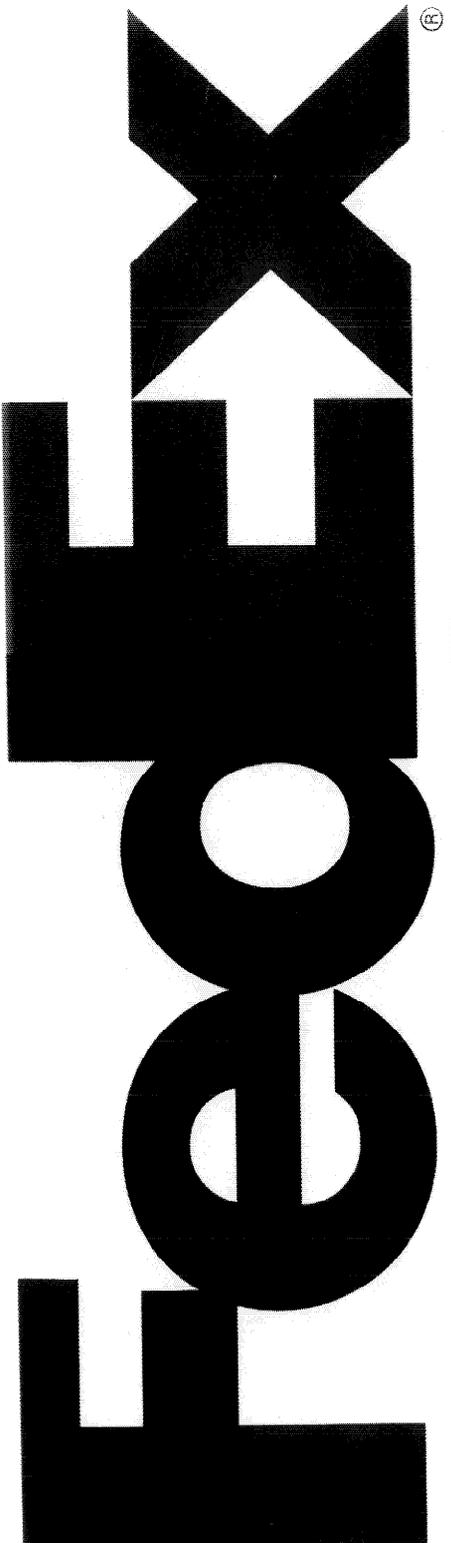
Patient safety is our main concern. By conducting safe, effective clinical trials and getting new, advanced products to market quickly, we can save lives. DMCs may, indeed, help us do that. We are not arguing that DMCs are not a good idea, but rather that they be used judiciously. They must be clearly defined. They must be flexible enough to acknowledge the differences between public-sponsored and industry-sponsored trials. They can't create a burden on industry by adding substantially to a company's cost or the time it takes a product to get to market. With those caveats in mind, we ask that you consider our suggestions for changes to the draft document "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees."

Sincerely,



Charles Swanson (:KS)

CHS:kls:DMCguidresponse.doc



Express

*The World On Time*®

Align top of

Chuck Swanson  
Medtronic, Inc.  
710 Medtronic Parkway, LC 270  
Fridley MN 554325604  
(763)505-2562

SHIP DATE: 15FEB02  
ACCOUNT # 184535998  
MAN-WGT: 1 LBS

TO: Documents Mgt Branch  
Food and Drug Administration  
HFA-305, Rm 1061  
5630 Fishers Lane  
Rockville MD 20852

(301)827-6880

343 2565 954

FedEx

POWERSHIP 3

343 2565 954

REF: 40276

STANDARD OVERNIGHT

MON  
A2

CAD # 638348

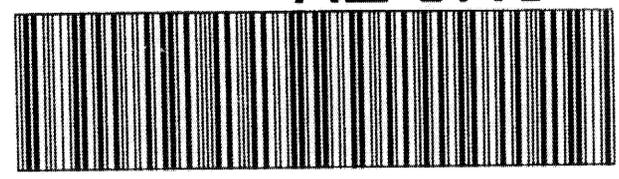
15FEB02

Trk# 343 2565 954

FedEx Letter

20852-MD-US

IAD  
NZ GAI



# 153077 077 SP G.T.I 1099::

Align bottom of Peel and Stick Airbill here.  
Select FedEx Letter or FedEx Envelope/Letter on your shipping document.