December 12, 2018

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


Dear Sir or Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, we are pleased to submit these comments in response to the Food and Drug Administration’s (FDA’s) invitation for comments on FDA’s Discussion Document on Patient Engagement in Medical Device Clinical Trials.

The Advanced Medical Technology Association (AdvaMed) is the world’s largest trade association representing medical device and diagnostics manufacturers. AdvaMed’s member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed’s member companies range from the smallest to the largest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

AdvaMed has a number of comments on the draft discussion document which are detailed below.

Section 1: Proposed Definition

The proposed definition of “patient engagement” requires greater detail and clarification as there are multiple interpretations of the proposed definition. Areas to consider for clarification include:

- Whether the definition includes both patient advisors and patient research participants and whether patient advisors includes patient advocacy groups. Research participants would presumably be well-placed to help disseminate research results, but it is not clear they are included in the definition.
The meaning of the term implementation – for example, does this include implementation of the product design, the development of the protocol and conduct of the trial, input on the risk-benefit equation, and/or later elements of the product life-cycle?

The meaning of the term dissemination – the draft definition suggests that patients would disseminate medical product development and assessment, but it is unclear how they could do this. Consider separating dissemination of research results from medical products development and assessment.

Patient Advisors and Patient Research Participants

FDA should clarify whether research participants can also serve as patient advisors. For example, we believe patients who are interested in participating in a specific trial may be effective advisors since they will likely have a very good understanding of the disease or condition the device will treat or diagnose. Research participants may also be effective at disseminating trial results since they will have personal knowledge and experience with the investigative device. However, any draft guidance should also delineate situations in which patients serving as both advisors and participants could present a conflict of interest e.g., where the research participant/advisor is expected to assist with trial recruitment or where the research participant/advisor could bias or unmask trial results. We recommend that FDA highlight the potential for conflicts of interest and identify several COI (Conflicts of Interest) examples but allow sponsors to make these determinations on a case-by-case basis. The draft guidance should also explain that advisors can transition between participants and advisors depending on the stage of the trial.

For purposes of the draft guidance, we also recommend that FDA not use the term “patient” to include both patient advisors and patient research participants as was done for the discussion document. A patient advisor could be a caregiver or family member and referring to them as a “patient” in the draft guidance could easily become confusing.

Section 2: Value and Impact

As FDA describes the value and impact of patient input and feedback, we recommend use of clearer language. With respect to patient retention, FDA could say “Greater patient commitment resulting in better patient retention.” With respect to protocol deviations, FDA could say “Greater patient compliance resulting in fewer protocol deviations or violations.” With respect to demonstrating value, FDA could say “Help demonstrate value to payers and healthcare systems” since payers consider multiple factors in determining whether to cover and reimburse medical products (e.g., cost) in addition to patient benefit.

Section 3: Challenges

Clarify that with respect to the “perception that FDA does not allow patient engagement since it could be perceived as illegal marketing of devices” that the perception exists only with respect to the perceived “illegal marketing of investigational devices.”
Other challenges that exist and should be identified include legal interpretations that paying for hotels or transportation may be considered an improper inducement to participation in the trial or that obtaining patient input may be interpreted by other authorities, such as the Centers for Medicare and Medicaid (CMS), as a violation of the Anti-Kickback Statute (AKS). AKS requires sponsors to detail the “value of the exchange” with patients. Such contracts may discourage patient participation. It may also be challenging to detail the value of patient input for all the numerous aspects of a trial. Lack of clarity in this area can pose AKS liability for sponsors. Development of an explicit AKS Safe Harbors for patient input on clinical trials will be important.

Barriers associated with the perception that payments for hotels or transportation may be an improper inducement to trial participation could be surmounted in part, if FDA were to issue updated guidance clarifying acceptable compensation and reimbursement for patient advisors and patient research participants. Although the recent update to FDA’s Information Sheet on Payment and Reimbursement to Research Subjects clarifying that reimbursement for travel expenses to and from the trial site was helpful, overall the guidance continues to be vague and many device companies, particularly smaller device companies, are unclear as to what, if any, expenses may be acceptable reimbursement and compensation to human subjects. Such updated guidance should provide a level of flexibility to ensure that patient input can be sought from a broad range of patients. For example, travel costs may be higher in rural areas and/or some locales may only have one higher priced hotel as opposed to a moderate-priced hotel.

We would also bring to your attention the Harvard Clinical and Translational Science Center guidance entitled “Paying Research Participants: Ethical Guidance for IRBs and Investigators.” We believe the Harvard Catalyst guidance establishes an ethical, reasoned and updated approach to human subject reimbursement and compensation which acknowledges “considerations of fairness and appropriate recognition of the expenses, time, and burdens borne by research participants, as well as the importance of facilitating recruitment in IRB-approved studies.” Importantly, the Harvard Catalyst and FDA information sheet guidance appear to start from different places with the Harvard guidance emphasizing the acceptability of appropriate participant reimbursement and compensation and the FDA guidance emphasizing the potential for undue influence or coercion. As you undertake the patient engagement in clinical trials initiative, we believe clarifying appropriate participant reimbursement and compensation, both in clinical trials and in development of design of device trials and related product development will greatly facilitate this effort.

Some companies have reported that their IRBs do not allow sites or sponsors to interact with subjects or communicate with subjects between visits out of concern that the sponsor is attempting to influence patient participants in the trial. Others have reported their IRBs allow such interactions if the planned interactions are identified in the initial protocol that is reviewed and approved by the IRB. In the former situation, sponsors may not have direct knowledge of patient issues outside of the clinical data collected and may have limited ability to address issues in a timely fashion or at all (e.g., subject doesn’t want to do the imaging study because s/he can’t take a day from work but can do the office visit for an hour). Even worse, the sponsor will make the same mistake in the next study due to lack of insight. Clarification by FDA to both sponsors
and IRBs that such communications and interactions are allowable and indeed, encouraged, would be helpful.

**Section 4: Approaches**

FDA should define new terms or use existing, well understood terminology consistently in the draft guidance. For example, FDA uses the language “clinical trial development plan” and “development process” in the discussion document. Does this refer to the development process of the clinical trial protocol and related materials, the device development process, or to both? Is a clinical trial development plan a specific FDA expectation when companies choose to pursue patient advisor or patient input and feedback?

In addition to the patient engagement examples listed in the discussion document, we suggest inclusion of a bullet on engaging disease-specific patient groups such as the Juvenile Diabetes Research Foundation and heartfailurematters.org, among others. We also suggest an additional bullet regarding patient feedback based on the progression and severity of the disease and the amount of risk and/or severity of side effects they may be willing to accept. Lastly, we suggest a bullet on the concept of providing trial results to specific trial patients for review then dissemination to the patient community or public as their feedback may impact the manner in which results are further communicated. The draft guidance should specify that all of these approaches or suggestions are optional, and sponsors should be able to select those which make sense for the particular trial or situation.

In response to continued concerns and challenges in recruiting women to cardiovascular trials, AdvaMed created a working group and reached out to leading women cardiologists to begin a dialogue and obtain their insights and recommendations and obtain their help developing targeted recommendations. Based on our dialogue with these leading cardiovascular clinicians, we believe greater efforts must be made to identify alternative clinical trial follow-up requirements that encourage participation of women and other demographic subgroups. We encourage FDA to include the following specific examples of ways to improve patient participation in clinical trials in the draft guidance:

- Requiring fewer follow-up visits;
- Allowing phone follow-up or home visits by nurse trial coordinators (in lieu of in-person visits by patients/subjects);
- Allowing for on-line follow-up options;
- Permitting the patient’s/subject’s primary care provider to perform some of the follow-up requirements and to reimburse for such;
- To provide transportation reimbursement; and
- To allow for weekend hours for required follow-up visits.

**Section 5: Timeframe**

With respect to the dissemination of trial results referenced in Section 5, we believe the draft guidance should include a section which encourages sponsors of medical device clinical trials to develop lay person summaries of clinical trial results. The lay person summary for applicable
trials (as defined in ClinicalTrials.gov) may be developed by sponsors and shared with clinical trial investigators who can make them available to the patients who participated in a clinical trial. Patient advisors could assist in development of such lay person summaries.

In order to make ClinicalTrials.gov as helpful as possible for the lay audience – for which the database was initially created – we recommend that FDA work with the National Library of Medicine (NLM) which manages ClinicalTrials.gov to encourage NLM to include lay person summaries of results of applicable clinical trials in ClinicalTrials.gov. Since such summaries may not be able to capture every detail about the trial important to a particular patient, patients could be encouraged to thoroughly review the ClinicalTrials.gov database information and the Summary of Safety and Effectiveness Data (SSED) or 510(k) summary and discuss any questions they have with their health care practitioner. Warnings can be included identifying additional precautions concerning interpretation of results (e.g., trial findings should be considered within the larger context of studies and the body of knowledge in a given area). We believe the inclusion of these additional warnings address concerns that have previously been expressed by NLM representatives, i.e., that sharing lay person summaries of trial results on ClinicalTrials.gov may be subjective (e.g., based on the perspective of the sponsor or the investigator) rather than objective, may fail to include appropriate contextual information and thus potentially misrepresent trial findings, and that a particular study “…is really hardly ever the meaningful unit of analysis,” rather “…it’s the body of evidence that really is more informative than the evidence of any one particular study.”

The discussion document also suggests patient advisors could play a role in developing and disseminating study findings. We suggest that patients who participated in the trial are also a possibility and may be better placed to assist in providing input on the communication of the study findings. Since sponsors will not have direct access to patients, the draft guidance should clarify that investigators should assist in disseminating study findings to trial participants.

In closing, thank you for this opportunity to provide input on the Discussion Document on Patient Engagement in Medical Device Clinical Trials. Please don’t hesitate to contact me if I can help respond to any questions.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs