November 2, 2018

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

Re: Docket No. FDA-2018-D-0787: Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank; Draft Guidance for Food and Drug Administration Staff, Responsible Parties, and Submitters of Certain Applications and Submissions to the Food and Drug Administration; Availability

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pleased to submit these comments in response to the Food and Drug Administration’s (FDA’s) Federal Register Notice on Draft Guidance for Food and Drug Administration Staff, Responsible Parties, and Submitters of Certain Applications and Submissions to the Food and Drug Administration: Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank.

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 has more than 400-member companies, ranging from the largest to the smallest 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AdvaMed has both general and specific comments on the draft guidance below.

General Comments

AdvaMed raised significant concerns with the proposed rule on Clinical Trials Registration and Results Submission and on the National Institutes of Health (NIH) Policy on Dissemination of NIH-Funded Clinical Trial Information. Many of the device industry’s concerns were discounted in the final rule. We have attached AdvaMed’s comments on the proposed rule for your information.
AdvaMed Position on ClinicalTrials.gov

AdvaMed strongly supports clinical trial registration of applicable device trials and reasonable disclosure of device trial results to ensure patient and clinician access to important information about the health benefits and risks of medical devices.

Importantly, AdvaMed also supports results disclosure associated with clinical trials for certain medical devices that are not approved under Section 515, 520(m) or deemed Not Substantially Equivalent (NSE) under 510(k). Specifically, AdvaMed supports results disclosure on ClinicalTrials.gov (CT.gov) for both Significant Risk (SR) and Non-Significant Risk (NSR) device trials for PMA or 510(k) products if a trial were stopped prior to approval or clearance for safety issues. Similarly, AdvaMed supports results disclosure for products that are not approved under Sections 515, 520(m) or cleared under Section 510(k) for safety reasons where the sponsor decides to discontinue the approval or clearance process.

Disclosure of results for device trials stopped due to a safety issue meets both the spirit and the intent of Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Disclosure of results in these instances serves the function of informing trial participants and the general public, and importantly, would potentially act to protect future human subjects from participation in trials for similar products that may present analogous risks.

However, AdvaMed is concerned about the impact on patient access to new device innovations of the final rule on Clinical Trials Registration and Results Submission, the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information and certain elements of the underlying statute. Elements of the final rule and the NIH Policy on Dissemination will disclose confidential, commercial information, or trade secret information that would otherwise be protected under the Federal Food Drug and Cosmetic Act (FFDCA) and the Freedom of Information Act. The final rule also undermines the delayed disclosure protections that were put in place by Congress to protect device innovation.

In addition, when Congress established new prohibited acts related to submission of information to ClinicalTrials.gov to which strict liability civil and criminal misdemeanor violations of the Act apply, it did not foresee the way in which the National Library of Medicine (NLM) would implement Title VIII of FDAAA – as an exceedingly complex database with potentially hundreds of data entry fields and related timeframes depending upon the complexity of the clinical trial protocol. As a result, device companies could potentially be fined for relatively insignificant deviations or unintentional data entries.

AdvaMed Concerns with the Final Rule
Disclosure of Confidential, Commercial, Trade Secret Device Information

The statute allows NIH to disclose in ClinicalTrials.gov confidential commercial information, trade secret or financial information that would otherwise be protected under the Freedom of Information Act and the final rule will disclose trial information related to products that were not approved or cleared by FDA. NIH will also require all device studies funded in whole or in part by NIH to disclose their information, thus depriving small companies from access to the device delayed disclosure provision.
The disclosure of proprietary, confidential commercial, trade secret or financial information associated with the clinical trials for products which are not approved, licensed or cleared will have a negative impact on development of new and innovative devices in the U.S. Companies and venture capital firms will be reluctant to fund device development in the U.S. if disclosure of clinical trial information enables competitors to gain a significant advantage for competing products with disclosure on ClinicalTrials.gov of research and development plans (full protocols, statistical plans and analyses) without the ability to protect trade secrets.

Small device companies account for the vast number of device innovations and contribute greatly to maintaining strong price competitiveness across the industry. Disclosure of proprietary, trade secret, confidential clinical trial information may, in particular, disadvantage small device companies or have the unintended consequence of eliminating many small device companies from the marketplace and have a corresponding negative, long-term impact on patient access to innovative technologies.

Developing innovative technology requires a great deal of time and a large capital investment. If a company or investor cannot achieve a fair return on investment, interest in pursuing device innovation will diminish. Making clinical trial information which is trade secret available to potential competitors will minimize the time and investment it will take for competitors to develop and market a similar device.

Congress made clear in 402(j)(5)(A)(i) of FDAAA that grantees who received federal funding in whole or in part were subject to 420(j)(2) and (3) of FDAAA. The device delayed disclosure provision is in Sec. 402(j)(2). It is clear Congress intended that device delayed disclosure and other elements of Title VIII of FDAAA would apply to federally funded studies whether they were funded in whole or in part. NIH does not have authority to exceed the scope of disclosure permitted under the FFDCA or under the FDA’s regulations to disclose trade secret or confidential commercial or financial information associated with device clinical trials that may be funded in part by a grant from NIH (including funding through SBIRs (Small Business Innovation Research programs) and STTRs (Small Business Technology Transfers) where the responsible party has ownership of certain trade secret or confidential commercial or financial information.

AdvaMed believes that disclosure of confidential commercial trade secret information should be limited to what is allowed under the FFDCA and the Freedom of Information Act.

**Final Rule Exceeds Statutory Definition of Clinical Trial**

The final ClinicalTrials.gov rule ignores the definition of an applicable device clinical trial in Title VIII – Clinical Trial Databases in the Food and Drug Administration Amendments Act and expands the definition of clinical trial to include all feasibility studies except for “early” feasibility studies.

Further, the plain language of the statute defines applicable device clinical trials as interventional trials. The final rule could be inappropriately interpreted to expand the definition of “Intervention” to include certain In Vitro Diagnostic (IVD) devices. Using commonly understood definitions of interventional, many IVD studies are not interventional because the study results are not used to treat or manage subjects whose clinical samples are tested for purposes of the study. These
samples are tested according to established laboratory standards (e.g., Clinical and Laboratory Standards Institute or ISO standards) to demonstrate compliance to IVD product verification and validation requirements. In short, these evaluations are only used to assess the performance of the IVD: individual test results are not provided to clinicians and do not inform patient diagnosis or treatment. Interpretation of intervention to include the registration of IVD studies is contrary to the transparency purpose and objectives of the ClinicalTrials.gov and may add confusion rather than clarity for patients. Subjecting these types of IVD evaluations to the registration and results requirements also adds unnecessary cost and burden to the completion of IVD studies.

AdvaMed believes that feasibility studies whose primary outcome is not intended to demonstrate the safety or effectiveness of a device should be exempted from submission in CT.gov and that IVD studies should not be an applicable device trial unless research subjects are assigned to a treatment or other intervention by the investigator based on the investigational in vitro diagnostic result and the research subjects’ outcomes are measured.

**Misinterpretation of Congressional Intent for Device Delayed Disclosure Provision**

In the final rule, NIH misinterprets congressional intent with respect to the applicable device delayed disclosure provision by preventing use of the device delayed disclosure for new uses of a previously approved or cleared device. The delayed disclosure provision was included in FDAAA 2007 with strong bipartisan congressional support and with no opposition in recognition that disclosure of the existence of an IDE through ClinicalTrials.gov could provide significant advantages to device competitors who could potentially speed a competing device into clinical trials and obtain final FDA clearance or approval in order to take advantage of the benefits associated with being first to market. Requirements to reveal clinical trial designs and primary and secondary endpoints could be even more devastating as device companies expend significant resources designing clinical trials and selecting the appropriate endpoints – intellectual property that would then be revealed to competitors through required disclosure in a clinical trial registry. Information related to the device design and to the design of the trial and its endpoints for a new indication is trade secret information. The delayed disclosure provision was intended by Congress to protect patient access to device innovation.

AdvaMed believes that delayed disclosure applies to all PMAs and 510(k)s both for an initial use and for a new indication of a previously approved or cleared device.

**Prohibited Acts Under the FFDCA and Submission of Truthful Information**

FDAAA amended the FFDCA to establish new prohibited acts related to submission of information to ClinicalTrials.gov. Specifically, the failure to submit, knowingly submitting false certifications, failing to submit required information or submitting information that is false or misleading in any particular to ClinicalTrials.gov will constitute strict liability civil and criminal misdemeanor violations of the Act. Strict liability applies to every prohibited act under FFDCA, except felony violations which require an intent showing. The question is whether strict liability is appropriate for insignificant deviations from the ClinicalTrial.gov reporting requirements that require interpretation of the highly complex and voluminous data entry required by the final rule.
In light of the significant number of deadlines for data submissions and the complexity of the reporting requirements, AdvaMed believes FDA should avoid criminalizing insignificant deviations or exposing individuals or companies to civil remedies for them. This is particularly appropriate in the device sector which is populated by a significant number of small or start-up companies that are frequently the industry’s innovators. Their contribution to the public health should not be threatened by civil liability or criminal prosecution for relatively minor and easily correctable reporting deviations.

Recommendations for Enforcement

Due to the ongoing concerns AdvaMed has with the final rule on Clinical Trials Registration and Results Submission, on the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information and with certain elements of the underlying statute, AdvaMed has the following recommendations to improve the final guidance on civil money penalties. Given the complexity of the final rule, we recommend that enforcement be limited to those cases where there was clear intent to avoid submission of relevant clinical trials.

- Both the proposed and final rule were extremely lengthy, complex and challenging to comprehend what was being required of sponsors. We recommend that FDA work with the NLM, which manages CT.gov, to develop easy to understand guidance for data submitters – similar to the type of guidance FDA routinely develops for sponsors – that clarifies in simple, easy to understand language the specific requirements where failure to submit information will be subject to civil or criminal penalties. Such guidance will also be important for bioresearch monitoring (BIMO) inspectors to guide responsible inspections of sponsors.

- Given the potential for significant fines associated with violations of CT.gov and the numerous data elements which are required to be submitted by sponsors to the data bank, FDA should work with NLM to identify which specific data elements are critical to be entered. This approach could be similar to other on-line data entry programs which designate or highlight via asterisk or other mechanisms, which items – when left blank – could therefore be viewed as deficient.

- FDA should also develop and attach an appendix to the guidance which clearly outlines medical device study types which are outside the scope of the guidance and which do not require registration in CT.gov.

- Given the lack of clarity and confusion regarding interpretations of the final rule, the final guidance should clarify that the civil monetary penalties will only be applicable prospectively following the finalization of the guidance.

Specific Comments

AdvaMed’s specific comments are included in the attached table.
In closing, thank you for considering AdvaMed’s comments on FDA’s Draft Guidance on Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank. Please don’t hesitate to contact me if you have any questions.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs

cc: Jeffrey Shuren, M.D., J.D., Director, Center for Devices and Radiological Health

Attachment
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<td>As referenced in the guidance, applicable clinical trial is defined at 42 CFR 11.10(a). This definition includes “applicable device clinical trial,” which means:</td>
<td>We recommend the guidance provide additional clarity regarding the definition of applicable device clinical trial to avoid misapplication of the guidance. During the nine-year period between enactment of the law establishing clinical trial registration and results posting for medical devices and publication of the final regulations, confusion resulted in certain areas. We recommend the guidance address these areas to avoid inappropriate expenditure of FDA and industry resources.</td>
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<td>P. 3</td>
<td>III. Discussion A. Definitions</td>
<td>Part 1 of the definition contains critical terms as it pertains to medical device studies. Specifically, the focus on a prospective study comparing an intervention with a device product. Interventional means, with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health-related outcomes. Clarity in the final guidance regarding these studies as outside the scope of applicable device clinical trial is important to avoid expenditure of FDA resources in areas that are outside the scope of the guidance and to prevent misapplication of an alleged compliance failure, which ultimately will be costly and time-consuming for both FDA and industry to resolve.</td>
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<td>(1) A prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360(j)(m)) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes);</td>
<td>For these reasons, we recommend the final guidance document include an appendix which clearly outlines medical device study types which are outside of the scope.</td>
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<td>(2) A pediatric postmarket surveillance of a device product as required under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 3601); or</td>
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<td>(3) A clinical trial of a combination product with a device primary mode of action under 21 CFR part 3, provided that it meets all other criteria of the definition under this part.</td>
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<td>P. 4</td>
<td>“The Centers generally intend to identify violations of the FD&amp;C Act’s requirements relating to the ClinicalTrials.gov data bank through evidence collected during inspections conducted as part of FDA’s Bioresearch Monitoring Program (BIMO).”</td>
<td>FDA response to these questions will provide clarification to sponsors regarding the process and how enforcement or notifications may or may not occur through the BIMO inspection process.</td>
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<td>Once a BIMO inspector identifies an issue, what administrative process will be followed thereafter? Will there be further review of the BIMO findings by any other entities within FDA and if so, by whom?</td>
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March 20, 2015

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

RE: Docket No. NIH-2011-0003 and RIN 0925-AA52; Clinical Trials Registration and Results Submission; Proposed Rule; Request for Comments

And


Dear Sir or Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, we are pleased to submit these comments in response to the National Institutes of Health (NIH) Proposed Rule and Request for Comments on Clinical Trials Registration and Results Submission and the NIH request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.

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 has more than 400 member companies, ranging from the largest to the smallest 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.

We understand that the proposed rule provides for an expanded registry and results data bank and is intended to be responsive to 402(j)(3)(D) of Title VIII of the Food and Drug Administration Amendments of 2007 (FDAAA). We also understand that the NIH intends to require all NIH-funded device clinical trials to register and submit summary results whether they are funded in whole or in part by NIH per Notice Number NOT-OD-15-019.
AdvaMed has both general and specific comments below. Please note that our general and specific comments below also apply to device clinical trials that may be funded in part by a grant from NIH but where the responsible party has ownership of trade secret or confidential commercial or financial information.

**GENERAL COMMENTS**

**Disclosure of Proprietary and Confidential Commercial Information**

AdvaMed supports clinical trial registration of applicable device trials and reasonable disclosure of device trial results to ensure patient and clinician access to important information about the health benefits and risks of medical devices. However, we are gravely concerned about NIH’s proposal to require the submission of results information for applicable clinical trials of devices that are not approved, licensed, or cleared for any indication (regardless of whether the sponsor seeks approval, licensure, or clearance) as well as other proposals in the rule which will disclose or may have the effect of disclosing proprietary, confidential data (e.g., detailed intervention descriptions and NIH consideration of whether or not to disclose the full protocol).

The final rule must strike an appropriate balance between transparency on the one hand and protections for the proprietary and confidential device intellectual property and trade secrets that underline device innovation on the other. We believe the disclosure of proprietary, confidential clinical trial data associated with products which are not approved, licensed or cleared or other such disclosures of proprietary confidential information will chill interest in developing new and innovative devices in the U.S. Companies and venture capital firms will be reluctant to fund device development in the U.S. if disclosure of clinical trial information enables competitors to shortcut research and development for competing products.

Unlike the drug industry where entire molecules are patented and are frequently patented even before the first clinical trial begins, patents¹ provide little protection in the device industry. Competitors can easily negate device patents with simple engineering or design changes. This lack of patent protection explains the rationale for the statutory ban in the U.S. on the disclosure of any information related to an investigational device exemption (IDE) including even the existence of the IDE until the device has been approved by FDA. Additionally, because of the iterative nature of device innovation, the average life-cycle for many devices may be as short as 18 months. In many instances, relatively small populations receive each generation of the device. As a result, device companies may have a small market and a relatively short time from which to recoup the resources spent on the conduct of a clinical trial. In short, developing innovative technology requires a great deal of time and a large capital investment. If a company or investor cannot achieve a fair return on investment, interest in pursuing device innovation will diminish. Making clinical trial information available to potential competitors will minimize the time and investment it will take for competitors to develop and market a similar device.

¹ Medical device manufacturers do pursue patents on their products. However, due to the relative ease with which engineering changes can be made to design around device patents, patents do not play the same strong role of protecting intellectual property that they play in the development of drugs, for example.
Small device companies (sales of less than $100 million) account for a vast number of device innovations and contribute greatly to maintaining strong price competitiveness across the industry (nearly 70 percent of AdvaMed’s members are small companies). In many instances, small companies are willing to invest in developing technologies for niche, pediatric and orphan markets – patient communities that may otherwise be overlooked and underserved. Disclosure of proprietary, confidential clinical trial information may, in particular, disadvantage small device companies or have the unintended consequence of eliminating many small device companies from the marketplace and have a corresponding negative, long-term impact on patient access to innovative technologies.

For these reasons and as discussed in more detail in our specific comments, the final rule must appropriately allow for delayed disclosure of applicable device trials to account for situations where product development efforts (including clinical trials) may be delayed, put on hold or reprioritized due to funding issues or other business reasons. Further, companies often have intentions to continue product development and subsequent pursuit of device approval or clearance even after receiving an initial non-approval or not substantially equivalent finding from FDA. The final rule should only require disclosure of device trial results where companies have affirmatively declared they have abandoned development of the product. In addition, as described in more detail below, in order to promote continued device innovation in the U.S., the rule should not require disclosure of the full clinical trial protocol.

**Standardized Terms and Definitions**
Although we understand and are supportive of NIH’s desire to utilize standardized terms and definitions in the clinical trial registry and results data bank, in general, there is a need for more flexibility in the ClinicalTrials.gov database. Some of the proposed data elements are more appropriately directed toward drug trials and are difficult for device trials to complete (e.g., the proposed adverse event requirements by organ system). Submissions should rely on standardized terms when appropriate but all data elements should allow for the “other” category with an opportunity to describe unlisted data elements so as to appropriately and accurately describe trial information.

**Encouraging Voluntary Submissions to ClinicalTrials.gov**
Companies that would otherwise voluntarily submit clinical trials to ClinicalTrials.gov may forego the opportunity given the detailed, burdensome requirements and the associated overly aggressive timelines of ClinicalTrials.gov in this proposed rule. We believe NIH should scrutinize the ClinicalTrials.gov requirements and their corresponding reporting timelines to assess which data elements are essential in order to encourage voluntary registration of more trials that do not meet the “applicable” trial definition.

**Delayed Disclosure**
We are concerned that the proposed rule repeatedly interprets existing legal requirements (i.e., Federal Food Drug and Cosmetic Act and the Public Health Service Act) in such a way as to severely limit or undermine use of the device delayed disclosure provision in 402(j)(2)(D)(ii)(I) of the PHS Act – a provision that was added to FDAAA and which passed Congress with strong bi-partisan support. For example, NIH’s extraordinary interpretation of the Federal Food Drug
and Cosmetic Act (FD&C Act) allows NIH to treat all trials for 510(k)s as trials for “new” uses (as opposed to initial uses) and to treat all combination products as applicable drug trials under the proposed rule in an apparent effort to deny the PHS Act’s statutory protection of delayed disclosure to device products.

We also want to note for the record that AdvaMed provided extensive written comments in June 2009 to the National Institutes of Health’s request for comments on the expansion of the clinical trial registry and results data bank that we have attached to these comments. We are resubmitting them here because we believe they remain helpful in developing the final rule.

Specific Comments
AdvaMed’s specific comments follow below. All page references are to the pre-publication version of the NPRM with the exception of the first comment which references the NIH request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. We attempt to identify relevant page numbers and the relevant portions of the proposed rule in the pre-publication version of the NPRM where possible but given the length, complexity and repeated descriptions of various aspects of the rule throughout the proposed rule, we were unable to reference all applicable page numbers and changes to the regulation in every instance.

Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information – “This Policy applies to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of study phase, type of intervention, or whether they are subject to the FDAAA registration and results submission requirements set forth in Section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)).”

Comment
402(j)(5)(A)(i) of the Public Health Service (PHS) Act required NIH to certify that “if an applicable trial is funded in whole or in part [emphasis added] by a grant from any agency of the Department of Health and Human Services, including the Food and Drug Administration, the National Institutes of Health, or the Agency for Healthcare Research and Quality, any grant or progress reports forms required under such grant shall include a certification that the responsible party has made all required submissions under paragraphs (2) and (3) [emphasis added] before releasing any remaining funding for a grant or funding for a future grant to such grantee.”

From this, it is clear that Congress intended that device delayed disclosure and other elements of Title VIII of FDAAA would apply to federally funded studies whether they were funded in whole or in part. As noted in our comments below, NIH does not have authority to exceed the scope of disclosure permitted under the FD&C Act or under the FDA’s regulations to disclose trade secret or confidential commercial or financial information associated with device clinical trials that may be funded in part by a grant from NIH (including funding through SBIRs and STTRs) where the responsible party has ownership of certain trade secret or confidential commercial or financial information.
In contrast, where the federal government or NIH has wholly funded research, development and a product’s associated clinical trials, we believe NIH has authority to disclose and should disclose all information.

Submission of non-technical and technical summaries of results – we invite further public comment on methods we might employ to help answer this question [whether narrative summaries can be provided in a manner that is objective and not misleading] so that we can explore this issue more thoroughly before making a final determination. Pages 61 – 64 and elsewhere, and related proposed rule provisions.

Comment
AdvaMed provided detailed recommendations on this question (which we will not repeat here) in our June 2009 comments to NIH (see attached). In order to make ClinicalTrials.gov as helpful as possible for the lay audience – for which the database was largely created – we recommend that NIH rapidly develop a template for narrative non-technical summaries. Although not to be ignored, concerns that narrative non-technical summaries may be misleading can be addressed via added disclaimers that a narrative summary may not be able to adequately capture important details about the trial; patients should thoroughly review the ClinicalTrials.gov database information and the linked Summary of Safety and Effectiveness Data (SSED) and/or 510(k) Summary; and patients should discuss any questions they have with their health care practitioner.

We invite public comment on whether the registration and results information that is proposed for submission in this NPRM is sufficient to meet the statutory requirement in section 402(j)(3)(D)(iii)(III) of the PHS Act to provide “information on the protocol” as may be necessary to help evaluate the results of the clinical trial or whether submission of additional information, including submission of the full protocol, should be required. Pages 65, 66 and elsewhere, and related proposed rule provisions.

And

For which applicable clinical trials must results information be submitted? – §11.42 – Proposed §11.42 identifies the applicable clinical trials for which results information must be submitted to ClinicalTrials.gov, according to this proposed rule unless the requirement is waived under proposed §11.54. . . . For reasons described in section III.C.5 of this preamble, we also propose to require the submission of results information for specified applicable clinical trials of drugs or devices that are not approved, licensed, or cleared for any indication (regardless of whether the sponsor seeks approval, licensure, or clearance). This proposal is consistent with the requirement in section 402(j)(3)(D)(ii)(II) of the PHS Act that the Secretary establish through regulation whether or not results information must be submitted for applicable clinical trials of drugs and devices that have not been approved, licensed, or cleared by FDA, whether or not approval, licensure, or clearance is sought. Pages 247, 248, 413 and elsewhere, and related proposed rule provisions.
§11.48(a)(6) – Additional clinical trial results information for applicable device clinical trials of unapproved or uncleared devices. Page 430 and elsewhere, and related proposed rule provisions.

Comment
We do not support providing full protocols for approved, cleared or for unapproved, unlicensed, or uncleared products, or the disclosure of summaries that effectively compromise the confidentiality of such protocols. We also do not support inclusion of clinical trial results information for applicable trials of unapproved, unlicensed or uncleared devices. We believe disclosure in the ClinicalTrials.gov database should not exceed the scope of disclosure permitted under the FD&C Act and the FDA’s regulations for any number of reasons, including protecting incentives for companies and individuals to develop devices that the public needs. Interference with incentives to develop innovative devices undermines the public health, and is inconsistent with the purpose of the database to inform patients and physicians of clinical trials for new, innovative treatments and diagnostic products. In other words, the fewer the incentives for investment in innovation, the fewer innovative products will be available to patients and their physicians.

For these and other reasons, and consistent with the Freedom of Information Act, the FD&C Act and the FDA’s regulations thoroughly protect study protocols and results information for applicable trials of unapproved or uncleared devices submitted to the agency from the outset of product development. Where the existence of an investigational device exemption (IDE) has not been “publicly disclosed or acknowledged” all data or information in the IDE file is protected from disclosure with two very narrow exceptions. See 21 CFR 812.38(b)(3) stating “no data or information in the [IDE] file are available for public disclosure except [data or information related to banned devices, see 812.38(b)(1), or adverse events relating to a test subject who suffered from such an event].” Indeed, the fact of the existence of an IDE is confidential and may not be publicly disclosed by FDA as long as a product sponsor does not publicly disclose or acknowledge its existence. 21 CFR 812.38(a). This protection continues until “FDA approves an application for premarket approval of the device subject to the IDE; . . . .” [21 CFR 812.38(a)] or finds an IDE substantially equivalent to a predicate device [see 21 CFR 807.95(c)(2)].

The protections for PMA device data or information before approval or denial are as strong as those in the IDE context, if there has been no public disclosure or acknowledgement of the PMA’s existence. 21 CFR 814.9(b) & (c). After approval or denial, “any protocol for a test or study” [21 CFR 814.9(f)(2)] or “assay method or other analytical method” is protected from disclosure if the study protocol or test method is “trade secret or confidential commercial or financial information under [21 CFR] 20.61.” See 21 CFR 814.809(f)(2) and 814.9(f)(5). In other words, FDA’s regulations prohibit the scope of release of protocols suggested by the proposed regulation. The scope of protection applies to approved and unapproved devices. Indeed, the FDA’s confidentiality regulation in Part 814 specifically protects data or information in the file of unapproved devices when such information is trade secret or confidential.
commercial or financial information. In some instances, all data or information in an inactive PMA file is protected from disclosure. Specifically, the regulation states:

(g) All safety and effectiveness data and other information not previously disclosed to the public are available for public disclosure if any one of the following events occurs and the data do not constitute trade secret or confidential commercial or financial information under [21 CFR] 20.61.

(1) The PMA has been abandoned. FDA will consider a PMA abandoned if:

   (i)(A) The applicant fails to respond to a request for additional information within 180 days after the date FDA issues the request, or

   (B) Other circumstances indicate that further work is not being undertaken with respect to it, and

   (ii) The applicant fails to communicate with FDA within 7 days after the date on which FDA notifies the applicant that the PMA appears to have been abandoned.

(2) An order denying approval of the PMA has issued, and all legal appeals have been exhausted.

(3) An order withdrawing approval of the PMA has issued, and all legal appeals have been exhausted.

21 CFR 814.809(f)(2) & (3) (emphasis added).

Simply put, in Part 814 the FDA repeatedly limits disclosure consistent with the FD&C Act and Freedom of Information Act. Nothing that is exempt under the Freedom of Information Act, see 5 U.S.C. 552(b)(4), and FDA’s regulation implementing that statutory provision, see 21 CFR 20.61, may be released to the public, even for unapproved devices. Moreover, even when FDA has grounds to believe that a PMA has been abandoned, the FDA may not disclose any data or information in the PMA that has not already been made public, if the applicant communicates with the agency within seven days of notice from the agency the applicant’s intent to continue pursuit of approval. This is consistent with maintaining confidentiality of the existence of PMAs under review and reflects the reality that companies, particularly smaller companies, often stop pursuit of approval for any number of reasons, including for example, a shortage of funds.

The foregoing regulatory protections from disclosure directly reflect the FD&C Act. Under section 520(c), “[a]ny information reported to or otherwise obtained by the Secretary or his representative under section 513, 514, 515, 516,518,519, or 704 or under subsection (f) or (g) of this section which is exempt from disclosure pursuant to subsection (a) of section 552 of title 5, United States Code, by reason of subsection (b)(4) of such section shall be considered confidential and shall not be disclosed and may not be used by the Secretary as the basis for reclassification . . . establishment or amendment of a performance standard . . . , except (1) in
accordance with subsection (h), . . . .” Section 520(c) prohibits any disclosure of trade secret and confidential commercial or financial information obtained under the device provisions, including of course, devices cleared through the premarket notification and premarket approval processes, and the inspection provision of the FD&C Act and restricts the use of PMA information to the extent specified in section 520(h)(4).

Consistent with section 520(c), disclosure of PMA data or information pertaining to a device approval or denial is limited to a “detailed summary” that by definition would exclude trade secret or confidential commercial or financial information. See 520(c) & (h)(1)(A). Even FDA’s use of PMA data or information is significantly constrained under section 520(h)(4) that permits FDA’s use of PMA data six years after approval. See id. This use for approving or reclassifying devices, or establishing performance standards, does not permit disclosure of any data or information in the PMA file, except through the detailed summary required by 520(h)(1)(A). Under (h)(4), FDA may never use trade secrets in the PMA file. Additionally, any disclosure by the agency in the context of approving a device, establishing a performance standard or classifying a device is limited to the detailed summary of safety and effectiveness data that accompanies device approvals and denials, and those summaries cannot contain trade secret or confidential or commercial or financial information. See 520(c).

In light of the very forceful prohibitions against disclosure in the FD&C Act and the FDA’s implementing regulations, we believe that HHS’s disclosure of trade secret and confidential commercial information would constitute a taking in violation of the Fifth Amendment. See Ruckelshaus, Administrator, United States Environmental Protection Agency v. Monsanto Co. 467 U.S. 986, 1003-1004 (1984). Specifically, the Court in Ruckelshaus stated that trade secret property, although intangible, is protected by the Taking Clause of the Fifth Amendment, and is compensable when a regulatory action interferes with a “reasonable investment-based expectation,” see Ruckelshaus v. Monsanto Co. at 1010 - 1014. In Ruckelshaus, the Court found that during the period from 1972 to 1978, when the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) specifically permitted persons submitting applications for registration to protect their trade secret data or information by declaring the information as trade secret, EPA’s use of that trade secret information would be a taking that had to be justly compensated or else it would result in violation of the Fifth Amendment. See Id.

Under the FD&C Act, a regulated person’s claim of a reasonable investment-based expectation exceeds that of regulated persons under FIFRA. There, disclosure and EPA use of trade secret data or information were protected, unless a subsequent applicant provided fair compensation to the person whose property would be affected. The Court fully understood that “[o]nce the data that constitute trade secret are disclosed to others, or others are allowed to use those data, the holder of the trade secret has lost his property interest in the data. Ruckelshaus v. Monsanto Co, at 1011.

As we state above, here under the FD&C Act, disclosure of trade secret data or information is absolutely prohibited whether the data are received in the context of a premarket notification submission or a premarket approval application. Under these circumstances, the proposed rule should not and cannot undermine statutory, regulatory and Constitutional protections, and we
respectfully request that the final rule exclude the trade secret information that is prepared and intended for submission to FDA that the law legally protects from disclosure. Accordingly, to the extent a protocol is trade secret or confidential commercial information, we strongly recommend that only information about the protocol that will not destroy its confidential character be disclosed in the ClinicalTrials.gov database. The proposed rule should parallel FDA’s device law and regulations to avoid undermining Congressional choices, and ultimately, the public health. This can be accomplished by not requiring the disclosure of information that would compromise the confidentiality of clinical protocols.

For applicable trials of cleared or approved devices, we believe relevant clinical trial information is currently captured in the full listing of ClinicalTrials.gov’s protocol registration data elements and basic results reporting requirements; the current listing of these data elements provides extensive information on clinical trials and enables interested parties to appropriately evaluate each reported trial.

Disclosure of a full clinical protocol, or information that compromises the confidential character of a protocol such as disclosure of clinical trial information for applicable device trials of unapproved or uncleared devices, will reveal confidential proprietary information about new devices, including their development, e.g., early pilot or feasibility testing, pre-clinical and clinical data development information, and materials, design and construction of the device. Moreover, such disclosure would reveal the culmination of the intellectual process that determined how to study the safety and effectiveness of a device, information which is of considerable value to competitors and, thus, protected confidential commercial information. Disclosure of this information would be very damaging to small company innovators, an economically fragile group, yet enormous contributors to the public health. In effect, receipt of disclosed information like the confidential clinical protocol could have the unintended consequence of eliminating many small device companies from the marketplace and could have a negative long-term impact on patient access to innovative technologies.

The current structure of ClinicalTrials.gov presents understandable information that is consistently formatted for comparison purposes and does not reveal confidential or proprietary information of device sponsors. Additionally, the FDA’s laws and regulations controlling disclosure of device information obtained by the FDA under the FD&C Act prohibit disclosure of trade secret and confidential commercial or financial information; additionally, for unapproved devices the existence of IDEs and PMAs, if not publicly disclosed by their device sponsors, may not be disclosed by FDA. Likewise, to the extent IDEs and premarket notifications are not made public by device sponsors, their existence is protected until after FDA issues a substantial equivalence order. Moreover, these regulatory prohibitions against disclosing trade secret and confidential commercial information create a reasonable investment-based expectation of protection from disclosure. As a result, if the government discloses such information, it must justly compensate the affected person, or the disclosure of the information would be an unconstitutional taking under the Fifth Amendment.

Accordingly, we recommend that any requirement to disclose full clinical protocols, or summaries that are tantamount to such a disclosure, or disclosure of clinical trial information for
applicable device trials of unapproved, unlicensed or uncleared devices, be removed from the final rule. Maintenance of the confidential character of protocols developed to demonstrate device safety and effectiveness is critical to encouraging device development and we believe that any advantage from disclosing confidential protocols would be significantly outweighed by the loss of investment in smaller companies, who are often the leading innovators in the device industry.

Completion date – Proposed §11.44(a)(1) provides that clinical trial results must be submitted no later than 1 year after the completion date of the clinical trial, unless a certification for delay is submitted or a request for extension is granted. In accordance with the statutory definition in section 402(j)(1)(A)(v) of the PHS Act, the term “completion date” is defined in proposed §11.10 – for a clinical trial – to mean “the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. Pages 67, 145, 146, 383 and elsewhere, and related proposed rule provisions.

Comment
AdvaMed recommends expanding the one-year period for submission of basic results information to 18 months as allowed by 402(j)(3)(D)(iv)(I). Doing so would more closely align with global clinical trial reporting requirements which define completion date as last patient, last visit for all protocol endpoints. It would also allow sponsors greater ability to collect and analyze study data according to the plan specified in the protocol rather than artificial deadlines imposed by NIH.

Whereas a 12-month deadline may make sense for “serious and life-threatening disease” drug trials in which regulatory submissions are made based on primary efficacy, it does not make sense for the numerous other types of trials registered in ClinicalTrials.gov that are not designed for an analysis of incomplete information that would effectively constitute an interim analysis. Device trials often collect secondary outcome data collection well past the primary completion date (e.g., mobility functional score at 12 months with the primary outcome measured at 3 months). For these and other trials, an interim analysis with the associated activities (i.e., monitoring visits, data query resolution, table generation, output validation, incomplete safety reporting) represents an inappropriate intrusion by NIH into the design of the protocol and the conduct of the study. Furthermore, the requirement to provide interim results has direct consequences for human subjects by requiring sponsors to enroll more subjects than needed to conduct the trial in order to power the analysis and accommodate the interim database lock.

Extending the deadline for submission of basic results information from 12 to 18 months would allow more sponsors to collect and analyze study data in full prior to the reporting deadline, or to complete the critical processes associated with the interim database lock. This extension would also reduce the burden for both companies and NIH associated with requests for “good cause” extensions to complete data analysis.
In short, requiring a de facto interim analysis specifically to submit data to ClinicalTrials.gov can have the unfortunate and unintended consequence of requiring sponsors of clinical trials to enroll more human subjects than absolutely needed for the trial. For these reasons, NIH should extend the one-year period for submission of results information to 18 months as allowed by the statute.

Adverse Event Reporting – Our proposed definition of adverse event derives from the OHRP definition. We propose to define an adverse event as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.” We do not intend for our proposal to cause an investigator to collect adverse event information of a type or in a way that is not specified in the protocol. We propose to maintain the requirement under the statutory default provisions in sections 402(j)(3)(I)(iii)(I) and (II) of the PHS Act to submit two tables of information summarizing anticipated and unanticipated adverse events that were collected in accordance with the protocol, i.e., one table for all serious adverse events and one table for other adverse events that exceed a frequency of 5 percent within any arm of the trial. Consistent with the statutory default provisions, our proposal would require submission of information on all such adverse events, not only those that are unanticipated or considered attributable to interventions studied in the clinical trial, to the extent that the collection of these data was specified in the protocol for the trial. We also propose to require responsible parties to submit the total number of participants affected by an adverse event at the organ system level. This information would be required for each arm of the clinical trial and for each adverse event table (serious adverse events and other adverse events).

For each organ system class that has one or more adverse events listed in either table, the overall number of participants affected, by arm or comparison group, by any adverse event in that organ system class (see proposed §11.48(a)(4)(ii)(D)), and (4) for each organ system class that has one or more adverse events listed in either table, the number of participants at risk, by arm or comparison group, for any adverse event in that organ system class.

Comment
Section 402(j)(3)(I)(i) and (ii) of the PHS Act required NIH to issue a regulation not later than 18 months after enactment of FDAAA on the best method for including serious adverse events in the database and if NIH failed to do so within 24 months, Congress specified default reporting requirements for serious and frequent adverse events reporting. 402(j)(3)(I)(iii) does not specify reporting total number of participants affected by any adverse event within each organ system for which adverse event data were collected. As a result, NIH does not have authority to require this proposed report and must use the statutory default reporting requirement.

In AdvaMed’s June 22, 2009 comments to NIH (see attached), we recommended many improvements to the ClinicalTrials.gov Adverse Event (AE) reporting requirements including that AE reporting for devices be consistent with the definition of serious adverse event used by
the international standard for clinical investigations of medical devices in human subjects (ISO 14155).

NIH failed to issue regulations on AE reporting by the 18- to 24-month deadline required in the statute. This regulation is attempting to create law where there is no longer a legal basis to do so. Further, if this proposed regulatory change becomes final, it will have a negative impact on medical device trials. NIH’s proposal to require reporting of the total number of participants affected by any adverse event within each organ system for which adverse event data were collected is a non-standard data element that would not be specified in the protocol and that sponsors would have to generate solely for ClinicalTrials.gov purposes which would be burdensome for device companies. In contrast to drugs which are chemical entities that are metabolized and often have systemic effects (and where it might make sense to report by organ systems), many devices are designed to replace or augment a function of the body and typically act locally, providing readily identifiable physical effects. Due to their local effect, device protocols typically require AE reporting only on organ systems that might be impacted by the experimental device.

What are the requirements for the submission of truthful information? – §11.6 – Section 402(j)(5)(D) of the PHS Act specifies that “clinical trial information submitted by a responsible party under this subsection shall not be false or misleading in any particular.”

Comment
We do not believe a new attestation requirement is needed because ClinicalTrials.gov already requires verification of the record when data is submitted.

In the context of whether clinical trial data or information are false or misleading, NIH should also clarify in guidance that it will consider “intent” including whether the:

- responsible party promptly corrects the noncompliance when provided notice;
- responsible party has engaged in a pattern or practice of noncompliance; or the noncompliance involved may have significantly misled health care providers or patients concerning the safety and effectiveness of the device involved.

NIH should clarify that inadvertent omission of information pertaining to “Other Intervention Names” and “Secondary IDs” would not be considered falsification of data.

FDAAA placed new strict liability prohibited acts that relate to conduct under the registry and results data bank requirements in Section 301 of the FD&C Act. This could subject device companies to significant penalties for minor omissions or inadvertent errors in data entry.

Strict liability is a very unforgiving standard that we do not believe was intended to apply to the highly complex and voluminous data entry that the proposed regulation requires. In light of the significant number of deadlines for data submissions required by the proposed regulation, under
a strict liability standard, companies and their employees could be subject to the charge of making false or misleading statements for unintentional omissions or errors and be exposed to civil, criminal or administrative liability for small, minor mistakes or failures to meet ClinicalTrials.gov deadlines or for unintentional omissions. This is particularly concerning in the device sector which is populated by a significant number of small or start-up companies that may face significant challenges meeting the requirements of the proposed rule. Again, we recommend that NIH clarify in guidance that they will consider intent when determining whether clinical trial data or information is false or misleading.

Principal Investigator (PI) is a term used in the definition of responsible party in section 402(j)(1)(A)(ix) of the PHS Act. For purposes of this proposed rule, principal investigator means “the individual who is responsible for the scientific and technical direction of the study.” . . . We would expect a principal investigator to have full responsibility for the treatment and evaluation of human subjects in the study and for the integrity of the research data for the full study. In keeping with this approach, an investigator for an individual site in a multi-site clinical trial would not be considered the PI unless he or she also has overall responsibility for the clinical trial at all sites at which it is being conducted. Page 144 and elsewhere, and related proposed rule provisions.

Comment
NIH should add a qualifier to designate the PI of the overall trial (e.g., Overall Study PI) and the PI at the individual site. The term PI is typically used both to describe the investigator who has responsibility for a multi-site trial and to refer to the investigator at the individual site. The proposed definition of PI will cause confusion and will result in inaccurate entries.

Combination Products – . . . any applicable clinical trial that studies a combination product would be treated as an applicable drug clinical trial under this proposed rule. Page 169 and elsewhere, and related proposed rule provisions.

Comment
NIH should follow FDA’s determination of the primary mode of action for combination products. Thus, if FDA determines a combination product has a device primary mode of action, the combination product is subject to FDA’s device regulations, and it should be considered a device for ClinicalTrials.gov purposes. The proposal to treat all applicable trials for combination products as drug trials is arbitrary and is inconsistent with the FD&C Act and ignores Congressional intent on the determination of the regulatory pathway of combination products.

In addition, for laypersons, health care providers and researchers who may be interested in more detailed information on the product and may be relying on FDA’s summaries of safety and effectiveness or 510(k) summaries, it will be confusing to see such products categorized as drugs by one government website and as devices on another.
It should be noted that NIH’s extraordinary interpretation to treat all combination products as applicable drug trials under the proposed rule denies the PHS Act’s statutory protection of delayed disclosure to combination products whose primary mode of action is device-related.

Interventional Study Model characterizes the approach used for assigning groups of human subjects to interventions during the clinical trial. In proposed §11.10(b)(5)(i), the data item is defined as “[t]he strategy for assigning interventions to human subjects.” In ClinicalTrials.gov, responsible parties would be required to select an entry from the following limited set of proposed options: “single group” (i.e., clinical trials with a single arm), “parallel” (i.e., participants are assigned to one of two or more groups in parallel for the duration of the study), “cross-over” (i.e., participants receive one of two alternative interventions during the initial phase of the study and receive the other intervention during the second phase of the study), or “factorial” (i.e., two or more interventions, each alone and in combination, are evaluated in parallel against a control group). No “other” option is proposed. Page 178 and elsewhere, and related proposed rule provisions.

Comment
NIH should create an “other” category with a free text box to allow adequate description of alternative study designs. Although NIH provides a number of choices for study design, an “other” category would recognize other possible study designs and allow adequate description of such study designs. This is especially needed for device trials given the diversity of study designs used to evaluate the safety and effectiveness of devices. As the science around design of clinical trial protocols advances, FDA is also accepting newer trial designs (i.e., adaptive trial designs) and allowing for more flexibility including multiple phase designs that transition from three to two arms, for example. Two other scenarios that would fit better under an “other” category than within the short list provided include enrichment designs that employ multiple randomizations during the trial (neither “parallel” nor “cross-over” would adequately describe all variants of this approach), and designs using adaptive borrowing of historical data that permit the case of a single arm of data collected prospectively yet base the analysis on comparisons between purely historical data and a mix of prospective and historical data. This second scenario would be poorly described by either “single group” (which ignores the historical data used in the analysis) or by “parallel” (which improperly addresses the fact that new data is only being collected from a single arm). Modern trial designs such as these are frequently intended to reduce the number of human subjects needed to demonstrate safety and effectiveness. ClinicalTrials.gov should reflect and encourage this trend. As a side note, it would be straightforward to create new categories over time by tracking the examples used in the “other” category. If the “other” category were not used, then the meaning of the existing categories could actually evolve over time with the changing prevalence of different designs that were forced into inappropriate categories.

Intervention Description – The term “intervention description” is not used in section 402(j) of the PHS Act, but we propose it as an additional data element to be submitted as clinical trial information at the time of registration. Based on prior experience, we recognize that
the Intervention Name(s) and Other Intervention Name(s) data elements, whether providing information on brand or non-proprietary names, do not always provide enough information to allow potential human subjects or other users to differentiate among similar interventions used in different arms of a clinical trial, or to distinguish the intervention used in one clinical trial from a similar intervention used in another clinical trial, or to understand the differences between interventions studied in a clinical trial and those used in routine medical practice . . . . To reduce this ambiguity, additional descriptive information is needed about the intervention, such as information about the dosage, dosage form, frequency of administration, route of administration, and/or duration of administration of a drug, or a general description of the device, including how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as its key components and general types of materials used . . . . If an experimental device uses different material than previous versions of the device, or than other marketed devices, the responsible party could provide a general description of the new material without including its specific formulation. Page 190 and elsewhere, and related proposed rule provisions.

Comment
As currently described, this field may require device companies to disclose confidential, proprietary business information. As a result, this field should remain optional and should be generic in nature (e.g., “new material” as opposed to a “general description of the new material”).

As described, the intervention description is too detailed and may require sponsors to disclose confidential proprietary information about devices. Requiring companies to disclose proprietary, confidential business information such as how the device functions, its scientific concepts, physical and performance characteristics of the device, and its key components and materials, will inevitably chill and slow innovation on new products for patients as device companies may conduct studies outside the U.S. or reduce the number of trials they conduct in the U.S. in order to protect this important information as long as possible. Disclosure of this information is also likely to disadvantage small device companies who typically account for the vast majority of device innovations and contribute greatly to health care price competitiveness across the industry.

The field should remain optional and should focus on generic descriptions that will not result in disclosure of proprietary information. Moreover, the need for intervention description information may duplicate the description of the study arm that generically describes the study device. To the extent an adequate generic description of the intervention is included in the arm description, there is no need to duplicate that information. To the extent the information is not present in that description, it can be added to this new element in the proposed rule. No matter where it appears, it should not compromise trade secret or confidential proprietary commercial information.
Determination of applicable clinical trial and U.S. FDA Approval, Licensure, or Clearance Status [and delayed disclosure provision for devices] – We propose U.S. FDA Approval, Licensure, or Clearance Status to be submitted as clinical trial information to indicate whether any intervention regulated by FDA and studied in the clinical trial has been approved, licensed, or cleared for any use. Such information would help in ensuring that the data bank operates in compliance with statutory requirements. For example, knowledge of the approval or clearance status of a device is necessary to determine when clinical trial registration information submitted for an applicable device clinical trial may be posted publicly in the data bank. (See section 402(j)(2)(D)(ii) of the PHS Act.) This information also would be helpful for users of ClinicalTrials.gov, including potential participants, who might wish to know whether or not the product(s) under study have been approved, licensed, or cleared for the use studied in the clinical trial. Requiring submission of the approval, licensure, or clearance status for each drug or device studied in an applicable clinical trial would therefore improve and not reduce the clinical trial information available in the data bank, consistent with section 402(j)(2)(A)(iii) of the PHS Act for proposed modifications to clinical trial registration information. Pages 43, 166, 167, 197 and elsewhere, and related proposed rule provisions.

Comment
To determine an applicable device clinical trial, it appears that NIH proposes to utilize a series of questions, in effect an algorithm, which is not described. We would note that applicable device trials are entitled to delayed disclosure under 402(j)(2)(D)(ii). We further understand NIH proposes to eliminate the check box that is currently used by sponsors to denote delayed disclosure of trial information associated with device trials (see footnote on Table 1 of NIH document titled “What Changes from Current Practice Are Proposed in the NPRM?”) and that NIH believes the statute prohibits sponsors who so desire to voluntarily disclose the existence of their clinical trial prior to clearance or approval (p. 43). AdvaMed’s June 22, 2009 comments to NIH (see attached) provided a legal analysis which stated that companies could voluntarily waive the statutory requirement to delay posting of a trial until after FDA clearance or approval. The check box option accomplished this objective and has worked well. We object to NIH’s proposed removal of the check box. If NIH proceeds with an algorithm to determine an applicable device trial, it should be Beta tested with the device industry to ensure that no trial information is released in violation of 402(j)(2)(D)(ii)(I) and (II) which provides for delayed disclosure of clinical trials.

We would also note that NIH’s interpretation that the statute prohibits responsible device parties who so desire, to voluntarily disclose the existence of the trial via the delayed disclosure checkbox, conflicts with congressional intent to encourage voluntary registration of clinical trials [402(j)(4)(A)].

Enrollment Section – 402(j)(2)(A)(ii)(I)(kk) of the PHS Act expressly requires submission of “the target number of subjects” to be enrolled in an applicable clinical trial, but this phrase is not defined. We believe this data element is intended to describe the intended or estimated size of the clinical trial, in terms of the estimated total number of human subjects...
(including healthy volunteers) or target number of human subjects who will be enrolled in the clinical trial. We therefore propose in §11.28(a)(1)(xviii) to require the submission of enrollment information at the time of registration, which is described in proposed §11.10(b)(18) as “the estimated total number of human subjects to be enrolled or target number of human subjects in the clinical trial.” We expect that the estimated or target enrollment in a clinical trial might change either before or during the clinical trial, e.g., as recruitment continues. Consistent with section 402(j)(4)(C) of the PHS Act and proposed §11.64(a)(1), a responsible party would be required to update the Enrollment data element not less than once every 12 months, if the anticipated or target enrollment in the clinical trial changes. This update would be in addition to the requirement in proposed §11.64(b) that a responsible party submit the Actual Enrollment data element when recruitment for a clinical trial has ended, i.e., when the Overall Recruitment Status of the trial is changed to “active, no longer recruiting” or “terminated.” This latter requirement is intended to provide users of ClinicalTrials.gov with additional information about the total number of participants enrolled in the clinical trial, which may differ from the target enrollment. (See proposed §11.64(b) and the discussion below of “Overall Recruitment Status” for a discussion of this requirement.) Our proposal for Enrollment is similar to procedures in place for ClinicalTrials.gov prior to FDAAA. Overall Recruitment Status. We propose that the Overall Recruitment Status data element be updated not later than 30 days after a change in the overall recruitment status of the clinical trial. This proposal is consistent with section 402(j)(4)(C)(i)(III) of the PHS Act. We believe that changes in recruitment status should be communicated promptly so that potential human subjects can know whether or not a clinical trial is currently recruiting subjects. Pages 203, 214, 323, 324 343, 443, 444 and elsewhere, and related proposed rule provisions.

Comment
NIH links changes to overall recruitment status to required updates to the actual enrollment data element and apparently will require an update of actual enrollment 30 days after recruiting ends which will be highly problematic. Previously, actual enrollment was updated 30 days after overall study completion. The proposed definition requires the sponsor to account for all screening failures by the time recruiting ends in order to provide an accurate enrollment number. Upon providing “actual” enrollment data to ClinicalTrials.gov, you may find that more patients are needed (e.g., five patients failed to come back for follow-up visits and thus recruitment must begin again to find five additional patients). Depending on how the trial data are collected and verified for any given study, the actual enrollment number may not be available until after study close out monitoring visits are conducted and the study database is locked. Locking the database will be well after the proposed requirement to provide the information “when recruitment has ended,” making it impossible to correct certifications and certify the truthfulness of information any sooner.

It should be noted that the definition of enrolled in ClinicalTrials.gov will be inconsistent with many device studies as they are presented in the Summary of Safety and Effectiveness or the 510(k) Summary, which is publicly available on FDA’s website and to which ClinicalTrials.gov is required to link. It is common for device trials to include screening failure in the trial design and for the patients that are enrolled in the study to be those that have passed screening. All
patients would be accounted for in the participant flow module of ClinicalTrials.gov. Allowing this inconsistency will lead to confusion, especially for the lay person.

In general, the PHS Act requires reporting after overall study completion rather than prior to study completion. Additions of more and shorter reporting timeframes add complexity and confusion to the reporting requirements. In general, we believe the proposed rule should define **enrolled** such that it takes into consideration how most device trials are designed. Moreover, NIH should look for ways to streamline and add consistency to reporting requirements and timeframes for required clinical trials which will also encourage more voluntary reporting of clinical trials.

**Eligibility Criteria**

Clinical trial protocols typically contain lengthy, detailed descriptions of inclusion and exclusion requirements for participants, including, for example, specific laboratory test result values. The requirements are often complex and must be assessed by a clinician or researcher involved in the clinical trial. We believe the submission of all eligibility criteria would be burdensome for responsible parties and, instead of helping prospective participants, would instead prove confusing or overwhelming. Therefore, in proposed §11.10(b)(21), Eligibility Criteria is described as “a limited list of criteria for selection of human subjects to participate in the clinical trial, provided in terms of inclusion and exclusion criteria and suitable for assisting potential human subjects in identifying clinical trials of interest.” Page 205 and elsewhere, and related proposed rule provisions.

**Comment**

We concur that listing all eligibility criteria would be burdensome for responsible parties and confusing for participants. We recommend that NIH add a statement that not all the inclusion/exclusion criteria will be listed in ClinicalTrials.gov so that participants understand that they may meet all the listed eligibility criteria but may not ultimately be eligible for the trial because of an enrollment criterion in the protocol that was not listed in ClinicalTrials.gov. The statement should also remind potential participants that they can reach out to the trial facility contacts for complete inclusion/exclusion criteria.

The Agency believes that for applicable device clinical trials of devices that previously were approved or cleared it is permissible and appropriate to post registration information prior to the deadline. Posting this information prior to the deadline would be consistent with the objectives of expanding the registry and results data bank by rulemaking, facilitating enrollment in clinical trials and providing a mechanism to track subsequent progress of clinical trials. (See sections 402(j)(2)(A)(i) and (3)(D)(i) of the PHS Act.) Conversely, waiting to post registration information for applicable device clinical trials of devices that previously were approved or cleared until after results information is required to be posted would delay access to information about such clinical trials and would eliminate the possibility for the data bank to be used to facilitate enrollment in such trials and to allow the public to track such trials while they are ongoing. The Agency proposes in §11.35(b)(1)
to post registration information for an applicable device clinical trial of a device that previously was approved or cleared “not later than 30 calendar days after clinical trial results information is required to be posted in accordance with §11.52 of this part.” However, in light of the objectives of the data bank discussed above we intend, in practice, to post registration information for such applicable device clinical trials as soon as practicable after submission, but not later than 30 calendar days after clinical trial results information is required to be posted. Page 245 and elsewhere, and related proposed rule provisions.

Comment
The proposal to post registration information as soon as practicable after submission but not later than 30 calendar days after trial results are required to be posted fails to distinguish between a new trial for the same product that has been cleared or approved with the same indication/use and a trial for a product that has been cleared or approved for a new un-cleared or unapproved indication/use. As a result, the proposal is in direct contravention of the statute [402(j)(2)(D)(ii)(I) of the PHS Act] which provides for delayed disclosure of device clinical trials for a device that was not previously cleared or approved. To comply with the statute, NIH must provide for delayed disclosure for trials for cleared or approved products for new uncleared or unapproved indications/uses.

The statute is very clear that trials for products that have not been previously cleared or approved (i.e., new products or new indications for existing products) are subject to the delayed disclosure provision. As a result, NIH should make this distinction in the rule.

Applicable device clinical trials of devices that have not been approved or cleared previously – Section 402(j)(2)(D)(ii)(I) of the PHS Act provides that for applicable device clinical trials of devices that have not previously been approved or cleared (i.e., unapproved or uncleared devices), registration information must be posted publicly not earlier than the date of approval or clearance of the device and not later than 30 days after such date. Proposed §11.35(b)(2) reflects this statutory provision. In order to help us meet the posting deadline and identify the set of applicable device trials for which registration information needs to be posted after approval or clearance of a device, we have included a requirement in proposed §11.64(b)(2) for the responsible party to update the U.S. FDA Approval, Licensure, or Clearance Status data element not later than 15 calendar days after a change in status has occurred. The responsible party would be required to update that data element for all applicable clinical trials that study the device that was approved or cleared. Pages 245 – 246 and elsewhere, and related proposed rule provisions.

Comment
As stated above, to comply with the statute, the rule needs to distinguish between a new trial(s) for the same product that has been cleared or approved with the same indication/use and a trial(s) for a product that has been cleared or approved for a new uncleared or unapproved indication/use. Further, in general, the statute makes clear that updates to ClinicalTrials.gov by the responsible party are on an annual (12-month) or on a 30-day basis, not 15-day increments.
The statute does not specify that reporting requirements by responsible parties must factor in NIH time. As a result, the rule should change the update requirement to 30 days.

**Submitting results information following initial product approval, licensure, or clearance** – Proposed §11.44(a)(2) would require that results information be submitted by the earlier of 1 year after the completion date, or 30 calendar days after FDA approves, licenses, or clears the drug or device for any indication studied in the applicable clinical trial. Page 250 and elsewhere, and related proposed rule provisions.

**Comment**
The proposed rule is inconsistent with the statute because it leaves out the statutory language of “not later than 1 year.” 402(j)(3)(E)(i) states that results for applicable trials are due not later than 1 year after the earlier of the estimated completion date or the actual completion date except in the case of devices seeking approval of a new use [402(j)(3)(E)(v)] in which case it states that results are due not later than 1 year after the earlier of the date that is 30 days after the new device is cleared or approved, or after the Secretary issues a not substantially equivalent (NSE) or not approvable letter, or the 510(k) or PMA is withdrawn. The proposed rule could result in the perverse situation where a trial that ends 3 months prior to FDA approval or clearance would not have sufficient time (i.e., the statutorily mandated 1 year) to post results after the study completion date.

**Delayed results with certification – §11.44(b) and (c).** Pages 251 – 255 and elsewhere, and related proposed rule provisions.

**Comment**
For results submissions associated with applicable trials for devices seeking approval, licensure or clearance of a new use (versus an initial use), the proposed rule appears to indicate it will require results submissions 30 days after FDA issues an NSE or not-approvable letter. The proposed rule appears to assume that responsible parties would not continue with product development, or to assume that the product has been abandoned once FDA sends the NSE or not approvable letter. However, the statute provides companies with up to 210 days to resubmit the application or PMA (see 402(j)(3)(E)(v)(I)(cc)). It is incorrect to assume that the product has been abandoned and the rule should be changed to allow responsible parties to continue with product development without disclosure of trial results even after receiving an NSE or non-approvable letter for products associated with a new use. Trade secret or confidential commercial information could be prematurely disclosed both in trials for devices for new uses and for initial uses and no distinction should be made between the two approaches. Importantly, FDA’s regulations prohibit FDA disclosure of NSE results because an NSE classifies a device into Class III, requiring a PMA. See 21CFR 807.95(c)(2).

The proposed rule should also be changed to allow related good cause extensions for delayed disclosure of device trial results for both initial and new uses as well as for products that have received an NSE or non-approvable letter.
“We do not believe that results submission should be delayed for applicable clinical trials of products that the sponsor has no intention of marketing or for which product development has been abandoned.” Page 254 and elsewhere, and related proposed rule provisions.

Comment
The proposed rule fails to account for situations in which product development may be delayed or put on hold due to funding issues or priority setting within a company (e.g., a company pursues other products where the opportunity for FDA clearance or approval is judged to be faster before returning to the product in question). Companies may also decide to pursue the product outside the U.S. before returning to the U.S. market – in which case the product has not been abandoned. The device industry in particular must frequently put device development on hold because funding has run out and a new round of funding must be sought from investors. In each of these scenarios, there is a continued need for protection of companies’ confidential, proprietary business information.

We also take issue with the trigger that NIH proposes to use to determine whether results submissions should be delayed for products which are under development. The proposed trigger appears to be that the responsible party is conducting subsequent clinical trials on the product. The conduct of subsequent clinical trials is not the only marker for determining whether a product remains under development. For example, a company may have determined that certain design changes are appropriate before conducting a subsequent clinical trial. It should be noted that for the vast majority of products, sponsors will have invested millions of dollars in the research and development of the product including non-clinical and clinical trial data. In order to promote continued device innovation in the U.S., the rule should continue to protect companies’ confidential, proprietary business information.

Since NIH cannot intuit a company’s intentions, in order to require submission of results, the rule should create a mechanism by which responsible parties can affirmatively declare that they have abandoned product development and that as a result, trial results will not be posted. The process should also allow companies to indicate that the project was abandoned before results were obtained so no results will be posted.

NIH states “for purposes of proposed 11.44(c), the first 510(k) cleared for a particular device type would be considered ‘initial clearance’ of the device. For example when a device is reclassified from Class III to Class II, then the first 510(k) that is cleared as having demonstrated substantial equivalence to the reclassified device would be considered the initial clearance of the device. Consequently, for purposes of proposed 11.44(b), all other 510(k)s cleared for a device type other than the first one, would be considered clearance of a new use.” Page 260 and elsewhere, and related proposed rule provisions.
Comment
NIH appears to cite the infrequent example of a device being down-classified from Class III to Class II to misinterpret the PHS Act and the FD&C Act. The rule should be consistent with long-held legal interpretations of the FD&C Act. Congress defined an applicable device trial in 402(j) in terms of the FD&C Act (i.e., a prospective study of health outcomes comparing an intervention with a device subject to 510(k), 515 or 520(m)). Although FDA reviews 510(k) submissions under the substantial equivalency review standard, each sponsor’s 510(k) is treated independently from a previous sponsor’s “predicate” 510(k) as a new 510(k) (i.e., initial use or initial clearance of the new 510(k)). All 510(k)s are considered an initial use or initial clearance, therefore, it is inappropriate to treat all other 510(k)s cleared for a device type as clearance of the same use. Even in the example cited by NIH of a Class III down-classified to Class II, all subsequent 510(k)s by different sponsors would be for an “initial clearance or initial use” not a “new use” as that term is used in the PHS Act. In short, every 510(k) is an initial clearance by operation of the FD&C Act. We would also note that Congress intended delayed disclosure to apply to trials for new uses of an existing device.

It should be noted that it appears NIH’s extraordinary interpretation of FFDCA allows NIH to treat virtually all trials for 510(k) devices as trials for new uses (as opposed to initial uses) under the PHS Act and thus not subject to the statute’s delayed disclosure provision, in contravention of this statutory protection for devices.

Two-Year Limitation of Delay – §11.44(b)(2) and (c)(2). Pages 256, 257, 416 and elsewhere, and related proposed rule provisions.

Comment
There are many legitimate reasons a company may be delayed in pursuing product development including but not limited to loss of funding or reprioritization of projects in order to obtain what may be judged to be a faster FDA clearance or approval on another product (to provide a stream of income for the delayed product). The rule is unclear as to whether good cause extensions can exceed the two-year limitation. NIH should clarify that good cause extensions are in addition to the 2-year limitation.

We invite public comment on these specific situations and on more general criteria that could be used to determine what constitutes good cause for an extension. Pages 264-266 and elsewhere, and related proposed rule provisions.

Comment
There are many legitimate reasons a company may wish to file for a good cause extension to delay results while pursuing product development. The following are legitimate reasons for good cause extensions and should be included on in the rule:

1. Device trials supporting product deemed not approvable or not substantially equivalent;
2. Device trials stopped for reasons unrelated to safety which remain under product development;
3. Good cause extensions for device trial results for initial 510(k) clearances, again to include each and every 510(k) clearance, and for initial PMA use and for new PMA uses;
4. Trials with a primary completion date in advance of the overall completion date for which an interim analysis is not included in the protocol;
5. Device trials certifying initial approval that, if approval has not been granted at the end of the 2-year period and the responsible party intends to continue with product development, a good cause extension should be granted;
6. Device trials certifying a new use that, if the responsible party has not filed the application within 1 year and still intends to file, a good cause extension should be granted; and
7. Device trials supporting a product that has been stopped but development of the product has not been abandoned.

In these situations, disclosure of information related to the trial may disclose confidential commercial information or technology. There may be other appropriate reasons for good cause extensions that are not listed above. In general, companies should be granted good cause extensions where product development has not been abandoned.

**Posting of information about certifications for delayed submission and about good cause extensions.** In order to provide responsible parties with insight into the general types of reasons that have and have not been considered to constitute good cause for an extension, we propose to post and update periodically on the ClinicalTrials.gov website a generalized list of reasons for which extensions have and have not been granted. Pages 268 – 271 and elsewhere, and related proposed rule provisions.

**Comment**
We concur with NIH’s analysis that posting information about the reasons used to delay results submission could result in the posting of information that might be considered confidential. However, even the proposed rule’s generalized list might disclose confidential information (i.e., “. . . we would attempt [emphasis added] to remove from the list any information that might allow a user to identify a specific applicable clinical trial.”). The way NIH proposes to implement this element, it is not clear NIH could remove enough information to prevent a particular reason from being traced back to a particular trial. If NIH wants to create such a generalized list, it should be presented to users of the website as a standardized list of possible reasons trials may be delayed as opposed to a list that could relate to a specific trial or trials.

We invite comments on whether or not we should require the submission of additional demographic or baseline characteristics that were collected during the clinical trial, the advantages and disadvantages of requiring the submission of such information, and, if so, how such information can be specified in the rule. Page 277 and elsewhere, and related proposed rule provisions.
Comment
Submission of additional demographic or baseline characteristics (e.g., country of origin/residence) that were collected during the trial should not be required as these subsets of data may not be statistically significant, and may be misleading and cause confusion. Making public these subsets of data may also be seen as promotional beyond FDA approved labeling.

Although we understand the theoretical benefit that providing additional demographic and baseline data could provide, this benefit must be balanced against the documented burden associated with meeting the requirements of registering trials and posting basic results. The assumption that certain additional baseline and demographic information is typically collected in protocols is not accurate. Requiring sponsors to design studies for the purpose of collecting additional information strictly to fulfill ClinicalTrials.gov reporting purposes stands in stark contrast to NIH’s stated general consideration, “It is important to note that this proposed rule does not impose any requirements for the design or implementation of a clinical trial or for the collection of information during a clinical trial” (p. 34).

§11.48(a)(3)(v) – We specify in proposed §11.48(a)(3)(v) the information that a responsible party must submit for any scientifically appropriate analysis: (A) Statistical Analysis Overview: The responsible party would identify the arms or comparison groups compared in the statistical analysis (by selecting the arms or comparison groups already defined for the outcome measures) and specify the type of analysis conducted. The type of analysis conducted would be selected from the following limited set of options: “superiority,” “non-inferiority,” “equivalence,” or “not applicable,” where “not applicable” would be appropriate for a single group analysis, for example. No “other” option is proposed. Pages 283, 284, 425 and elsewhere, and related proposed rule provisions.

Comment
NIH identifies a limited set of options that would be available (i.e., superiority, non-inferiority, equivalence, or not applicable). We recommend that the proposed rule be expanded to include two new categories: “Estimation” and “Descriptive.” It can be that certain analyses are simply about estimating certain quantities (such as the rate of events in a given arm, rather than a comparison between rates in two arms). Also, many safety analyses in particular are inherently descriptive rather than inferential, and would be better captured with a “descriptive” moniker.

§11.48(a)(3)(v)(A), (B) and (C) – The proposed rule states “Statistical analysis results of scientifically appropriate statistical analyses, if any, include any statistical analysis that is: A) pre-specified in the protocol and/or statistical analysis plan that was performed on the outcome measure data, B) made public by the sponsor or responsible party prior to the date on which results information is submitted for all primary and secondary outcome measures studied in the clinical trial, or C) conducted in response to a request made by the FDA prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial.” Pages 282, 283, 285, 425 and elsewhere, and related proposed rule provisions.
Comment
§11.48(a)(3)(v)(C) should be revised in the following manner:

(C) Conducted on the primary outcome measure in response to a request made by the U.S. Food and Drug Administration prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial.

We believe the scope of (C) is extremely broad and could be quite burdensome as currently proposed. The requirement to report statistical analyses should be restricted to FDA requests for statistical analyses on primary outcome measures only. It is not unusual for there to be extensive questioning and dialogue between the responsible party and FDA during the course of the trial, during the submission process, or as part of preparation for an FDA Advisory Panel meeting. Such requests can include analyses on different analysis sets, examinations of numerous subgroups, or applications of methods not originally specified in the protocol or analysis plan. These analyses are frequently ad hoc or exploratory in nature and many are not investigated further after initial examination. The fact that many of these findings are not deemed relevant can be inferred from their broad exclusion from the product labeling. An appropriate balance between transparency of information that is accessible to the public and the volume of data that can be requested by FDA would be achieved by restricting the scope of (C) to primary outcome measure analyses only.

Administrative Information – Results point of contact telephone number and email address. §11.48(a)(5). Pages 271, 396, 429 and elsewhere, and related proposed rule provisions.

Comment
§11.48(a)(5) requires the name or official title of the point of contact and the telephone number and email address of the point of contact. This is defined as the name, official title, organizational affiliation, physical address, mailing address, phone number and email address of the individual who is the responsible party or of a designated employee of the organization that is the responsible party.

We agree that it is very important to name a contact point, however, naming individuals or employees can be problematic. This information is also held private in other government databases. In lieu of naming an individual, we recommend allowing responsible parties to list a function (e.g., clinicaltrials@companyabc.com) rather than an individual point of contact. There are personal privacy reasons that individuals or designated employees may not want their work address and email listed in a public U.S. government database. In addition, individual points of contact may change frequently, requiring responsible parties to update ClinicalTrials.gov too frequently.

§11.48(b) – Redacted final report required to be submitted. This section requires a redacted final report be submitted to NIH. . . . for each pediatric postmarket surveillance of a device that is not a clinical trial, we believe that the final report would contain a
suitable summary of the surveillance results, and we propose that it be submitted to ClinicalTrials.gov in a form that can be made available to the public. Pages 44 – 45 and elsewhere, and related proposed rule provisions.

Comment
This should be revised to allow the manufacturer to alternatively submit a suitable summary of the pediatric postmarket surveillance of the device rather than a full final report that is redacted. NIH itself acknowledges that “pediatric postmarket surveillances under section 522 of the FD&C Act can take various forms [other than a clinical trial], including a detailed review of the complaint history and the scientific literature, non-clinical testing, observational studies . . . .” FDA’s Guidance for Industry and FDA Staff entitled Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act provides examples of postmarket surveillance which “illustrate a range of surveillance methods” including “telephone or mail follow-up of a defined patient sample,” “non-clinical testing” including “analysis of devices explanted from animal models . . . .”, and “use of secondary data sets (e.g., Medicare), registries (e.g., Society for Interventional Radiology stent registry), internal registries, or tracking systems.” Redacted reports of such postmarket surveillance methods might be confusing and virtually unreadable. We believe a summary of pediatric postmarket surveillance studies that are not clinical trials would be much more useful and helpful to the intended audience of ClinicalTrials.gov than a redacted report.

Definition of “Enroll or enrolled.” Page 384 and elsewhere, and related proposed rule provisions.

Comment
The definition of enroll or enrolled should be expanded to add “unless specifically defined differently in the protocol.” Not all studies consider the point of enrollment the signing of informed consent. Further, in some limited circumstances, the signing of informed consent is not required.² The preamble of the proposed rule has stated, with respect to other data elements, that

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² Part 50, Protection of Human Subjects requires:
Sec. 50.27 Documentation of informed consent.
(a) Except as provided in Sec 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject’s legally authorized representative at the time of consent. A copy shall be given to the person signing the form.
Part 56, Institutional Review Boards allows:
Sec. 56.109 IRB review of research.
(c) An IRB shall require documentation of informed consent in accordance with Sec. 50.27 of this chapter except as follows:
(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject’s legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context, or
(2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an exception from informed consent for emergency research are met.
it is not NIH’s intention to require collection of data beyond those required by the protocol. We agree with that and believe it should be applied in this instance as well. While presumably unintentional, this definition appears to place NIH in the position of dictating study design which is within the sponsor and FDA’s purview. The current definition may also result in a situation in which enrollment numbers for a specific trial will be different on the ClinicalTrials.gov website than in FDA’s 510(k) Summary or Summary of Safety and Effectiveness to the cleared or approved product, respectively, to which ClinicalTrials.gov is required to link. Also see our comments on enrollment on pages 16–18 above.

**Definition of “Gender.”** Page 392 and elsewhere, and related proposed rule provisions.

**Comment**
Replace “gender” with “sex” everywhere that it appears in the proposed rule in order to be consistent with FDA guidance. FDA recently issued guidance entitled *Evaluation of Sex-Specific Data in Medical Device Clinical Studies* which included a discussion of the terms “gender” and “sex” referencing an Institute of Medicine (IoM) study by the Committee on Understanding the Biology of Sex and Gender Differences. Per FDA and IoM, “sex” refers to classification by reproductive organ while ”gender” refers to a person’s self-representation as male or female based on the individual’s gender presentation.

**Definition of “Why Study Stopped.”** Page 393 and elsewhere, and related proposed rule provisions.

**Comment**
The definition of why the study stopped should be limited to whether the study was stopped for safety reasons, i.e., why study stopped means, for a clinical trial that is suspended or terminated or withdrawn prior to its completion as anticipated by the protocol, a brief explanation of the reason(s) why such clinical trial was stopped, if the study was stopped for safety reasons.

We believe safety reasons (e.g., adverse events, new safety information about a class of therapies) should be noted. However, all other reasons are a subset of ‘business reasons’ which should not require disclosure to avoid disclosing confidential commercial information about the strategic and financial operations of the company.

**Adverse Event Information – Page 426 and elsewhere, and related proposed rule provisions.**

**Comment**
Change: “collected during” to “collected per protocol during.”
As stated in the preamble, it is not the intention of this regulation to require collection of adverse events beyond those required by the protocol. Also see our comments on Adverse Events on pages 11-12 above.

§11.66 Requirements for corrections of clinical trial information. Page 446 and elsewhere, and related proposed rule provisions.

Comment
Companies cannot enter corrected data until it is available. Thus, paragraph (a) should be revised to read:

Correction of errors. A responsible party who becomes aware of errors in any clinical trial information submitted under this part or is informed by NIH that such clinical trial information contains errors shall correct such errors not later than 15 calendar days after the date on which the corrected data becomes available responsible party becomes aware of the errors or on which NIH informs the responsible party of the errors, whichever is earlier.

In closing, thank you for this opportunity to provide comment on NIH’s Proposed Rule and Request for Comments on Clinical Trials Registration and Results Submission and the NIH request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. Please do not hesitate to contact me if you have any questions.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs
June 22, 2009

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Bethesda, MD 20894

Docket No. NIH-2009-0002: Notice of Public Meeting on Expansion of the Clinical Trial Registry and Results Data Bank; Request for Comments

Dear Dr. Zarin:

On behalf of AdvaMed, the Advanced Medical Technology Association, I am pleased to submit these comments in response to the National Institutes of Health’s (NIH) request for input on issues the Agency will consider as it develops regulations to expand the clinical trial registry and results data bank (ClinicalTrials.gov) per Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA).

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. AdvaMed’s members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent of the health care technology purchased annually around the world. AdvaMed members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have fewer than $30 million in sales annually.

AdvaMed Comments on NIH Topics and Questions
In response to the topics and questions posed in the NIH’s March 23, 2009 Federal Register Notice, AdvaMed has prepared the following responses below. AdvaMed also raises a number of important additional areas of concern to device manufacturers associated with the implementation of Section 801 of FDAAA in our response to Question 11.
1. Whether to require submission of results information for applicable clinical trials of drugs, biological products, and devices that are not approved under sections 505, 515, or 520(m) of the FDC Act, licensed under section 351 of the PHS Act, or cleared under section 510(k) of the FDC Act (whether or not clearance, approval or licensure was sought). Please comment on issues such as the potential advantages and disadvantages to the public and public health of disclosing results information for trials involving drugs, biological products, and devices that are not approved, licensed, or cleared; the effects (if any) on the development of drugs, biological products, and devices; the reporting burden on data submitters; and the appropriate timing of submission and public disclosure of information, taking into account the certification process established by the FDAAA when approval, licensure, or clearance is sought for a product under study in an applicable clinical trial. In particular, consider scenarios involving trials of different types of unapproved products: (a) Applicable clinical trials of products for which marketing applications or premarket notification submissions are never submitted to the (Food and Drug Administration (FDA); (b) applicable clinical trials of products for which marketing applications or premarket notification submissions are submitted, but a decision is pending; and (c) applicable clinical trials of products for which marketing applications or premarket notification submissions are submitted and the FDA decides not to approve, license, or clear the product for marketing.

**AdvaMed Response**

**Trials Stopped for Safety Issues**

AdvaMed supports results disclosure associated with clinical trials for certain medical devices that are not approved under Section 515, 520(m) or deemed Not Substantially Equivalent (NSE) under 510(k). Specifically, AdvaMed supports results disclosure on ClinicalTrials.gov for both Significant Risk (SR) and Non-Significant Risk (NSR) device trials for PMA or 510(k) products if a trial were stopped prior to approval or clearance for safety issues. Similarly, AdvaMed supports results disclosure for products that are not approved under Sections 515, 520(m) or cleared under Section 510(k) for safety reasons where the sponsor decides to discontinue the approval or clearance process. Disclosure of results for device trials stopped due to a safety issue meets both the spirit and the intent of Section 801 of FDAAA. Disclosure of results in these instances serves the function of informing trial participants and the general public, and importantly, would potentially act to protect future human subjects from participation in trials for similar products that may present analogous risks.

There are other scenarios involving medical devices that are not approved under Sections 515, 520(m) or cleared under Section 510(k) in which AdvaMed does not believe it is appropriate to disclose clinical trial results until after approval or clearance. In a small subset of medical device trials, it may never be appropriate to disclose results.

**Trials Deemed Not-Approvable or Not Substantially Equivalent**

Specifically, in situations in which a PMA or 510(k) application is submitted to FDA and it is deemed not approvable or not substantially equivalent (NSE) but the company
intends to resubmit the application, then we believe the results should not be required to be submitted until 30 days after the product is approved or cleared. There are important device distinctions that are relevant in this scenario. Many devices are engineered products designed to replace, repair or augment a function of the body. Thus, an engineering or design change may rectify a problem with the device enabling a new and successful FDA application. Additionally, in these instances, we believe a good cause extension should apply. Further, AdvaMed recommends the creation of a text box in ClinicalTrials.gov enabling a company to briefly explain the reasons for the delay in results information. See also the last bullet in our response to Question 9 section “g.”, involving trials where the company intends to resubmit the application.

**Trials Stopped for Reasons Unrelated to Safety**

Finally, in a small subset of incompleted medical device trials, AdvaMed believes it is inappropriate to disclose results. Medical device trials may be stopped for reasons unrelated to safety but rather due to an inability to obtain continued financing, or due to changed company priorities, as examples. In these circumstances, disclosure of information related to the trial may disclose confidential commercial information or technology in violation of the FDC Act, FDA regulation and Freedom of Information Act bans on disclosing information related to an Investigational Device Exemption (IDE). It may also disclose confidential or proprietary information to a company’s competitors preventing the original company from successfully pursuing the affected technology later. Because the product was never FDA approved or cleared, the device cannot be marketed and thus cannot present risks to patients or the public. In these rare instances, we believe the incomplete trial results should not be released.

In sum, except in the two different situations described above, AdvaMed supports results disclosure on ClinicalTrials.gov for both Significant Risk (SR) and Non-Significant Risk (NSR) device trials for PMA or 510(k) products if the trials were stopped prior to approval or clearance for safety issues.

2. Whether narrative summaries of the clinical trial and its results can be included in the data bank without being misleading or promotional. Comment on issues such as the potential advantages and disadvantages to patients, research subjects, and the public of requiring responsible parties to submit narrative summaries that are written in non-technical, understandable language for patients; the utility to the scientific community of requiring responsible parties to submit narrative summaries written in technical language; the content and structure of any such narratives; and procedures that could be established to help ensure the content is not misleading or promotional.

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1 The protocol is part of the Investigational Device Exemption (IDE) which is protected confidential commercial information under the Freedom of Information Act (5 U.S.C. §552), the FDC Act and FDA regulations (21 C.F.R. Part 20).
AdvaMed Response

AdvaMed’s responses to questions 2 and 3 are combined in the response to Question 3.

3. What additional information, if any, that is written in non-technical, understandable language for patients should be required to be submitted to the data bank or should be provided in the data bank to assist patients in understanding and interpreting the information available in the data bank. Please consider the types of information that would best assist patients and other members of the public in understanding and interpreting results information in the data bank, including information on adverse events. Comment on issues such as the types of information that might assist patients and the public in understanding the results of individual clinical trials and of clinical trials in general. Identify existing sources of explanatory information that are oriented toward patients and the public and could be included in or linked to the data bank.

AdvaMed Response to Questions 2 and 3

AdvaMed supports the provision of both technical and non-technical summaries of results for trials associated both with approved or cleared and unapproved or NSE devices (subject to the exceptions noted in our response to Question 1 for trials associated with certain unapproved or NSE devices) in ClinicalTrials.gov.

As a practical matter, many patients will likely read both the technical and the non-technical summary. Thus, to ensure transparency and reduce confusion for patients reading both the technical and non-technical summaries, data elements between the two summaries should be consistent.

AdvaMed supports the use of a structured summary in abstract form for both the technical and non-technical summaries. The sole difference would be the level of language used in the summaries, to ensure that non-technical summaries will be accessible to general users of the database. AdvaMed recommends the summaries should be no more detailed than what one commonly finds in a journal abstract and include a word limit (e.g., 250-300 words as suggested in the CONSORT Statement for reporting randomized trials in journal and conference abstracts\(^2\)). AdvaMed has recommended a list of data elements or sections of a summary in Table A below. Some of the data elements may be automatically populated by the database (as ClinicalTrials.gov has done for other results data elements) where the information was previously required (e.g., registration data elements). This structured format would ensure consistent presentation of clinical trial information and would facilitate a review or quality check by ClinicalTrials.gov.

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\(^2\) CONSORT for Reporting Randomised Trials in Journal and Conference Abstracts, [www.thelancet.com](http://www.thelancet.com), Published online January 22, 2008.
**Table A: Proposed Data Elements To Be Addressed in Technical and Non-Technical Summaries**

<table>
<thead>
<tr>
<th>Study Title</th>
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<tbody>
<tr>
<td>Study Device/Therapy/and or Components</td>
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<tr>
<td>Study Population</td>
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<tr>
<td>Indication/Intended Use Studied in Trial</td>
</tr>
<tr>
<td>Study Design Overview</td>
</tr>
<tr>
<td>Study Objective(s)</td>
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<tr>
<td>Primary Endpoint(s)</td>
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<tr>
<td>Secondary Endpoint(s)</td>
</tr>
<tr>
<td>Summary of Clinical Study Results including Sample Size</td>
</tr>
<tr>
<td>Risks and Benefits (includes Adverse Events)</td>
</tr>
<tr>
<td>Warnings/Precautions/Contraindications if applicable</td>
</tr>
</tbody>
</table>
  - Please list any warnings, precautions or contraindications for previously cleared or approved device |
| Approval or Clearance Status |
| Please list any indications previously cleared or approved for this device |

As discussed above, the requirement to provide technical and non-technical results summaries for unapproved or NSE products would apply only to those clinical trials that were not completed due to safety reasons or to those products that are not approved or cleared under Section 515, 520(m) or 510(k) for safety reasons where the sponsor decides to discontinue the approval or clearance process.

If the trial were stopped for reasons other than a safety issue (e.g., lack of funding), the summaries would not be required. For example, medical device trials may be stopped for reasons unrelated to safety such as changed company priorities. In these circumstances, disclosure of information related to the trial may disclose confidential or proprietary information or technology in violation of the FDC Act and other bans on disclosing information related to an Investigational Device Exemption (IDE). Because the product was never FDA approved or cleared, the device cannot be marketed, and thus, cannot present risks to patients or the public. In these rare instances, the requirement to provide technical and non-technical summaries would not apply.

In situations where products are not approved under Section 515, 520(m) or are deemed NSE under 510(k) and the sponsor intends to continue the approval or clearance process,
the sponsor should be given an opportunity to seek a good cause extension, thus enabling technical and non-technical summaries to be submitted after approval or clearance. The requirement to provide the summaries would apply to unapproved or NSE products where the applicant is continuing to seek approval or clearance only after the product is cleared or approved.

AdvaMed is however, concerned about the possibility that posted summaries of results may jeopardize the ability to publish the clinical study results in the scientific literature if the International Committee of Medical Journal Editors (ICMJE) or other journal editors view such summaries as prior publication. The ICMJE updated their Uniform Requirements for Manuscripts Submitted to Biomedical Journals in October 2008 indicating: “The ICMJE does not consider results posted in clinical trial registries as previous publication if the results are presented in the same, ICMJE-accepted registry in which initial registration of trial methods occurred and if the results are posted in the form of a brief structured abstract or table.” Additionally, the ICMJE posted an FAQ document on Clinical Trials Registration in October 2008 reporting: “. . . thus the ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. However, . . . [ICMJE] may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov to be prior publication.” (See www.ICMJE.org). AdvaMed encourages the National Library of Medicine (NLM) and FDA to work closely with ICMJE to ensure that the inclusion of technical and non-technical summaries of results information in the data bank is not considered prior publication.

We understand that some organizations have indicated they support the use of the ICH E3 Annex 1 Synopsis as a format for trial result summaries. ICH E3 is tailored for drug trials. If a structured format tailored to devices is technically unachievable, AdvaMed could support the use of the ICH E3 format if modifications were made to it to reflect data elements that are relevant to device trials.

The following are specific topic headings in the ICH E3 Synopsis format with proposals for modified headings to ensure applicability to device clinical trials. We propose expansion of the headings versus replacement considering the increase in combination therapy trials (e.g., drug and device combination product).

- “Name of Active Ingredient” – with respect to devices, add Note: N/A or not applicable for device clinical studies.
- “Phase of development” – with respect to devices add Note: N/A or not applicable for device clinical studies.
- “Test product, dose and mode of administration, batch number” – with respect to devices add “Test product, therapy, device, or components (for combination drug/device products include dose, mode of administration and batch number for drugs)”
• “Reference therapy, dose and mode of administration, batch number” – with respect to devices add “Reference product, therapy, device, or components (for combination drug/device products include dose, mode of administration and batch number for drugs)”

Since the ICH E3 Synopsis format can be up to three pages long, it will also be important to ensure that use of this format does not jeopardize publication in the scientific literature.

See our response to Question 6 below for recommendations on the timeline for technical and non-technical summaries.

4. **Whether to require submission of the full clinical trial protocol or only such information on the protocol as may be necessary to help evaluate the results of the trial.** Comment on the value of the full clinical trial protocol versus partial information from the protocol in evaluating the results of a trial and the completeness of results data submission.

**AdvaMed Response**

AdvaMed supports providing complete information on clinical trials for approved and unapproved products (subject to the exceptions identified in our response to Question 1). We believe full and complete clinical trial information is currently captured in the full listing of ClinicalTrials.gov’s protocol registration data elements (as reflected in the August 20, 2008 Draft Protocol Data Elements Definitions document) and in basic results data elements (as reflected in the March 9, 2009 Draft “Basic Results” Data Element Definitions document). By “full listing,” AdvaMed means all data elements in both documents including those identified as required or conditionally required by ClinicalTrials.gov and required/may be required to comply with Section 801 of FDAAA. We believe the full listing of protocol registration and basic results data elements provides extensive information on a clinical trial and enables interested parties to appropriately analyze a trial. Please note that we are recommending that one additional data element be added to the Adverse Events (AE) data elements (see the AdvaMed Response to Question 9 below).

AdvaMed does not support providing the **full protocol** for approved and unapproved products for a number of reasons. Disclosure of the full protocol would violate existing FDC Act and other requirements. The protocol is part of the Investigational Device Exemption (IDE) which is protected confidential information under the FDC Act and Freedom of Information Act. In the device arena, disclosure of the full protocol will reveal proprietary and confidential information about the actual device including device development (e.g., early pilot or feasibility tests, and pre-clinical and clinical data development background), materials, design, and construction of the device. This information will not be useful or helpful to the vast majority of patients but it will expose confidential and proprietary information to competitors.
Small companies account for a vast number of device innovations and contribute greatly to maintaining strong price competitiveness across the industry (nearly 70 percent of AdvaMed’s members are small companies). In many instances, small companies are willing to invest in developing technologies for niche and orphan markets – patient communities that may otherwise be overlooked and underserved.

Disclosure of the full protocol would essentially provide a roadmap (both on the design of the trial and on the actual device) for competitors to follow and could provide significant advantages to competitors who could speed a competing device into clinical trials and obtain FDA approval or clearance in order to take advantage of the benefits associated with being first to market. Such disclosures could have the unintended consequence of eliminating many small device companies from the marketplace and could have a negative long-term impact on patient access to innovative technologies.

In addition, protocols are often hundreds of pages in length and may quickly over-burden the data bank. Protocols will also be uniquely formatted according to the sponsor’s standards making clarity and transparency challenging for the public. In conclusion, we support FDAAA’s purpose of providing transparent and complete information to the public on clinical trials and we believe – in keeping with the current structure of ClinicalTrials.gov – the full listing of data elements referenced above presents understandable information that is consistently formatted for comparison purposes and that does not reveal confidential or proprietary information of device sponsors.

5. Procedures the agency might consider for quality control, with respect to completeness and content of clinical trial information, to help ensure that data elements are not false or misleading and are non-promotional. Consider the effect of different approaches on the workload of both data submitters and the agency and on the quality of data available to the public, as well as suitable means for the agency to communicate information about its quality assurance processes to data submitters and the public.

AdvaMed Response
With respect to the first part of Question 5, AdvaMed concurs that reports of clinical trial data elements should not be false, misleading or promotional. We would note that existing law (Section 502 of the FDC Act) prohibits manufacturers from disseminating false or misleading product information which would include false or misleading clinical trial information. In addition, FDA regulations prohibit manufacturers from promoting an investigational device (21 C.F.R. §812.7). FDA already applies these standards to clinical trial information that is provided by manufacturers in written materials, such as press releases about clinical trial results and press releases about advisory panel decisions on PMA submissions. Since manufacturers are familiar with, and are currently held to these legal standards, we do not believe new quality control requirements or procedures or guidance are necessary for postings on ClinicalTrials.gov. Of course, it will be important for FDA and NLM to ensure consistent interpretation and implementation of these existing regulatory requirements across and within the Agencies when these
requirements are applied to materials posted on the data bank, such as technical and non-technical summaries of trial results.

With respect to the second part of Question 5, concerning suitable means for the Agency to communicate information about its quality assurance processes to data submitters and the public, AdvaMed appreciates that ClinicalTrials.gov has posted a Draft Quality Assurance/Quality Control Review document for public review. Transparency of this information is very useful to sponsors entering information into the data bank.

6. Whether the 1-year period for submission of basic results information should be increased to a period not to exceed 18 months. Comment on the advantages and disadvantages of increasing the period for submission of clinical trial information from 1-year after the completion date to a period not to exceed 18 months. Consider the implications for all stakeholders, including governmental bodies, data submitters, and users of ClinicalTrials.gov; the extent to which such a change would affect public health or the utility of the data bank; the possible effect on the number of requests that responsible parties would submit to the NIH requesting an extension of the results reporting deadline; and the possible improvements to the quality and or completeness of initial submissions of results data to the NIH. Consider the implications of delay periods of different lengths between 12 and 18 months.

AdvaMed Response
AdvaMed supports expanding the one year period for submission of basic results information to 18 months from the “Primary Completion Date” as allowed for in FDAAA. Some secondary outcomes may require longer-term follow-up data on the primary outcomes (e.g., mobility functional score at 12 months where the primary outcome measured the same outcome at 3 months). This means many trials are incomplete at the time basic results are now required to be entered by FDAAA due to planned secondary outcomes. As a result, analysis at the point in time now required by FDAAA for submission of “basic results” introduces a “partial or additional database lock” process which requires verification of the data in the database (i.e., complete data monitoring and resolution of data queries), analyses, validation of the analyses, and interpretation of results. Expansion to 18 months reflects a more reasonable timeframe to complete these critical processes so as to meet the basic results reporting requirements, and to ensure that the most complete data are available for posting. This may also minimize the number of requests for “good cause” extensions to complete data analysis.

Further, we believe a common timeframe for updating secondary results and for providing technical and non-technical summaries (which should include complete information on primary and secondary outcomes) would provide clarity to trial sponsors and to the public on when such updates are expected. By design it is common for a clinical trial to be ongoing for secondary endpoint data collection after the “Primary Completion Date” and even following the time when basic results are due. An update
process may cause confusion as the required updates may appear to be ad hoc updates versus planned data collection.

For updating results related to secondary outcomes and for providing technical and non-technical summaries, AdvaMed proposes the timeline should be 18 months following the “Study Completion Date” (i.e., last data collected for primary and secondary outcomes on last subject) as defined in the data bank Protocol Data Element Definitions document (August 20, 2008 draft). We interpret “Study Completion Date” (versus “Primary Completion Date”) as the final date on which all primary and secondary data were collected on the last study subject. This may or may not be the same date as the “Primary Completion Date” depending on the scientific protocol design.

This proposed 18 month timeline provides clarity and consistency where secondary outcomes may be later than primary outcomes (e.g., specified health outcomes at 12 months where the primary outcome measured the same outcomes at 3 months). It allows sufficient time to accomplish data verification and analysis processes that drive quality reporting of data presented in the summaries. It enables a reasonable timeframe for presenting information to the public while recognizing the complexity of the continuum of clinical trial designs. In addition, this timeline minimizes the need for “good cause” extensions as well as updates and modifications to the results information, thus reducing confusion to users of the data bank.

Please see AdvaMed’s response to Question 9, section “g.” for suggested additions to data elements in the data bank that will assist users in understanding the results status of a particular trial.

7. **Whether the clinical trial information required by the regulation should be required to be submitted for applicable clinical trials for which “basic results” information is submitted before the effective date of the regulation. Consider the advantages and disadvantages to data submitters and users of the data bank, including patients, prospective human subjects, care providers, and researchers.**

**AdvaMed Response**

AdvaMed believes it is too burdensome for both sponsors and ClinicalTrials.gov staff to require sponsors to submit data for all the likely expanded data elements that will be required by the new rule for clinical trial entries that were entered prior to the effective date of the regulation. Such a requirement may cause an extensive backlog of results data requiring review and will result in a significant delay in release of results to the public. Although FDAAA specifically asks ClinicalTrials.gov to review the possibility of requiring expanded results for trials entered prior to the effective date, we would also point out that applying regulations retroactively is contrary to typical legal standards of due process which favor prospective rather than retroactive application.
8. The appropriate timing and requirements for updates of clinical trial information and procedures for tracking such updates. Please comment on the advantages and disadvantages of requiring more frequent updating of information submitted to the clinical trial registry and results data bank, which elements (if any) would benefit from more frequent updating, and what would be the optimal frequency of such updates.

AdvaMed Response
Please see the AdvaMed response to Question 6 for our comments on the appropriate timing for updates of clinical trial information.

9. The standard format for the submission of clinical trial information required by the regulation, including adverse event information, and additions or modifications to the manner of reporting of the data elements established under the basic results reporting provisions of the FDAAA.

AdvaMed Response
Section 801 of FDAAA directs ClinicalTrials.gov to expand basic results reporting to serious and frequent adverse event (AE) information by regulation within 18 months of enactment. If the Secretary fails to issue AE reporting regulations in this area by 24 months after date of enactment, FDAAA establishes two default statutory reporting requirements or data elements for AEs (Section (j)(3)(H)(I)(ii) and (iii)): Serious Adverse Events (all anticipated and unanticipated SAEs grouped by organ system); and Frequent Adverse Events (anticipated and unanticipated AEs that are not included in the SAE section) that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system.

In order to enhance patient understanding and to ensure such Adverse Event sections do not mislead patients, AdvaMed recommends improvements to the statutory AE default reporting requirements as implemented on ClinicalTrials.gov described below. AdvaMed also has recommendations on Additions or Modifications to Basic Results Data Elements.

a. Adopt the ISO 14155 definition of Serious Adverse Effect for use in reporting Serious Adverse Events for medical devices.
b. Replace “Other (Not Including Serious) Adverse Events” with “All (Including Serious and Non-Serious) Frequent Adverse Events.”
c. Include an additional “AE Reporting Criteria” data element.
d. Include additional data elements that will describe whether the adverse event is attributed to the medical device.
e. Calculate percentages automatically.
f. Require entry of “Number of Participants at Risk” once per study arm, rather than repeating it for every AE term.
g. Recommendation on additions or modifications to basic results data elements.
Further details regarding these recommendations and the rationale for such are included below:

a. **Adopt the ISO 14155 Definition of Serious Adverse Effect (SAE) For Use in Reporting Serious Adverse Events for Medical Devices**

Section 801 of FDAAA directs NLM to expand basic results reporting in ClinicalTrials.gov to serious and frequent adverse event (AE) information. As you are aware, the regulations on adverse event reporting for drugs and devices differ. The recently released FDA Guidance on Adverse Event Reporting to IRBs³ highlights the differences between drugs and devices in reporting requirements as well as in terminology and criteria for evaluation. For example, the Investigational New Drug (IND) regulations define “serious adverse drug experience”⁴. The Investigational Device Exemption (IDE) regulations on the other hand, refer to the term “serious” in “unanticipated adverse device effects” reporting requirements⁵, but do not provide a definition. Thus, there may be some variation in how “serious” is defined for trial-specific or protocol-driven reporting purposes.

During the April 20, 2009 public meeting on Section 801 of FDAAA, NLM and FDA asked AdvaMed whether the definition of serious adverse event contained in the March 9, 2009 Draft “Basic Results” Data Element Definitions document adequately captured medical device serious adverse events. After careful consideration, AdvaMed recommends that NLM and FDA incorporate the international standard ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects) definition for Serious Adverse Effect into the basic results data element definitions document for medical device serious adverse event.

ISO 14155 defines a Serious Adverse Effect (SAE) as an adverse event that:

- led to a death
- led to a serious deterioration in the health of the subject that
  - resulted in a life-threatening illness or injury, or
  - resulted in a permanent impairment of a body structure or a body function, or
  - required in-patient hospitalization or prolongation of existing hospitalization, or
  - resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
- led to foetal distress, foetal death or a congenital abnormality or birth defect.

⁴ See 21 CFR 312.32
⁵ See 21 CFR 812.150
Use of the ISO 14155 definition will ensure a harmonized approach to capturing SAEs in medical device trials, many of which are conducted outside of the United States. Additionally, we believe this definition will be more readily understood by medical device trial sponsors and will be consistent with the way they currently collect SAEs. Please see the Comparison Table in Appendix A that compares adverse event definitions that are used by medical device manufacturers to the AE definitions currently in ClinicalTrials.gov and to the IND regulation AE definitions.

b. Replace “Other (Not Including Serious) Adverse Events” with “All (Including Serious and Non-Serious) Frequent Adverse Events”

As stated previously, the default statutory language of FDAAA for adverse events requires two sections: SAEs (see comments in previous section 9. “a.”) and Frequent AEs. The Frequent AE section is defined by statutory requirements to exclude Serious AEs and as such, ClinicalTrials.gov has renamed the “Frequent AE” section as the “Other (Not Including Serious) Adverse Events” section.

AdvaMed recommends replacing the current “Other (Not Including Serious) Adverse Events” section with a requirement to report “All (Including Serious and Non-Serious) Frequent Adverse Events” exceeding a threshold of 5 percent. By doing so, NLM would ensure that the public is provided with accurate information regarding the most frequent AEs. An example illustrating this point is provided below.

**Example**

One cannot derive the frequency of all adverse events by adding the two adverse events sections (e.g. “Serious” + “Other (Not Including Serious)” AEs).

- 10 patients (of 100) reported a serious event X (e.g., headache).
- The same 10 patients also reported a non-serious event X (e.g., headache) at a different time.
- Current ClinicalTrials.gov requirements would reflect the AE reporting as follows:
  - 10 of 100 (or 10%) reported a serious event X (e.g., headache).
  - 10 of 100 (or 10%) reported an “Other (non-serious)” event X (e.g., headache).
  - What is the frequency of event X?
    - If the public assumed that no patient reporting a serious event X (e.g., headache) had also reported a non-serious event X (e.g., headache), they would assume a frequency of 20%. By adding the serious and non-serious event Xs together, it would appear that 20 of 100 patients experienced event X.
    - If the public assumed the same 10 patients that reported a serious event X (e.g., headache) also reported a non-serious event X (e.g.,
headache), they would assume a frequency of 10% or that 10 of 100 patients experienced event X.

- The Issue: Under the default statutory language, the public does not have enough information to determine the frequency of event X.
- The solution: AdvaMed recommends reporting "All (Including Serious and Non-Serious) Frequent Adverse Events" at a frequency above a 5% threshold.

c. Include an Additional “AE Reporting Criteria” Data Element

To ensure AE information is interpreted in the context of trial-specific reporting criteria, AdvaMed also proposes that FDA and NLM add a new text data element, “AE reporting criteria”, to the structure of AE reporting in ClinicalTrials.gov to enable sponsors to report any trial-specific AE definitions (e.g., “MAE,” “MACE,” and “MACCE”6) where it may be critical to interpreting the results information. Character limits should not exist in this field to allow sponsors to directly copy applicable portions of the study protocol. For example, the therapeutic area, study product (e.g., drug, device, drug and device [combination product]), stage or phase (e.g., phase I-IV, or feasibility, pivotal, post-market), and the trial’s scientific design (e.g., blinded) will drive the trial-specific requirements for adverse event reporting. Additionally, for many large post-market trials (both drug and device), where the adverse event profile of the products under study have been well-documented in product labeling, the trial may focus only on the collection of “serious” and unexpected adverse events. This approach is intended to minimize data collection and reporting burden where collection of all adverse events (e.g., grade I sinus infections) would not benefit the study or clinical care. In this case, a post-market study may not collect AEs, and therefore, will have no “frequent AEs” unless spontaneous study reports result in new information.

Thus for many appropriate reasons, each specific trial may have individual AE reporting criteria. This makes it challenging for someone to compare reported adverse events across studies without providing the context of the trial-specific reporting criteria, and in some cases, trial-specific definitions (e.g., “serious”). AdvaMed believes the addition of the new text data element, “AE reporting criteria,” will enable AE results information to be “useful and not misleading to patients, physicians, and scientists” as contemplated by FDAAA.

6 MAE – Major Adverse Event is defined as events related to the product and/or procedure (e.g., death, myocardial infarction, repeat revascularization, stent thrombosis, stroke) and is further defined in the protocol; MACE – Major Adverse Cardiac Event is defined as events related to the product and/or procedure (e.g., death, myocardial infarction (Q wave and non-Q wave), emergent bypass surgery, or repeat target lesion revascularization; and MACCE – Major Adverse Cardiac and Cerebrovascular Event is defined as events related to the product and/or procedure (e.g., death, myocardial infarction, cerebrovascular accident or repeat revascularization by percutaneous intervention or bypass surgery).
d. Include Additional Data Elements That Describe Whether an AE is Attributable to the Medical Device

AdvaMed also recommends the addition of data elements that enable those who use the data bank to understand the context of AEs. In the case of devices, it is important to evaluate safety information in the context of attribution to the device and/or the procedure (e.g., implant surgery) to fully evaluate the benefit-to-risk ratio. This allows for evaluation of incremental or comparative risk between devices that are implanted with the same or similar procedure. Also, the complexity of combination products (those regulated as a device would be reported per device study requirements) may require additional attribution categories to be specified (e.g., drug). While attribution may be debated, the information on attribution provided by the investigator closest to the situation and/or a committee of experts (e.g., data safety monitoring committee, AE committee) provides useful information to patients and physicians evaluating the results of the study. We propose incorporating the ability to assign attribution to each AE type in the tabular structure. Attribution categories for devices should include: device/system, procedure, other (specify: e.g., drug if applicable, patient co-morbidities or other medical conditions). See Table B below which is intended to help illustrate our recommendations.

e. Calculate Percentages Automatically

AdvaMed also proposes that percentages should be automatically calculated or requested and presented in AE tables for reporting on proportional data. The current data bank structure leads sponsors to enter the total sample size in each group, along with the number of events, or subjects in a particular event category. The public or other users of the data bank may make incorrect conclusions about a comparison if percentages are not presented in the AE tables. A person quickly looking at a study where 400 subjects were randomized to treatment A with 100 experiencing adverse events, and 200 were randomized to control with 90 experiencing adverse events might make a direct comparison of 100 to 90 and conclude that treatment A was less safe. The explicit presentation of proportions or percentages is more meaningful for interpretation (e.g., 25% in treatment A group and 45% in the control group in this example). See Table B below.

f. Require Entry of “Number of Participants at Risk” Once Per Study Arm

ClinicalTrials.gov requires the entry of “number of participants at risk” for each adverse event term reported. Since the “Number of Participants at Risk” may vary for each study arm/group but will not vary for each adverse event term, AdvaMed recommends allowing the “Number of Participants at Risk” to be entered once per study arm, rather than repeating the entry for each unique adverse event term. See Table B below.
Table B: Mock AE Table Including Relatedness Categories

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Group X # participants at risk</th>
<th>Group Z # participants at risk</th>
<th>Determined Related to: (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Device / System</td>
</tr>
<tr>
<td>Total, Serious AE</td>
<td>XXX</td>
<td>XXX</td>
<td>Y</td>
</tr>
<tr>
<td># of events</td>
<td>XX</td>
<td>XX</td>
<td></td>
</tr>
<tr>
<td># participants</td>
<td>X%</td>
<td>X%</td>
<td></td>
</tr>
<tr>
<td>affected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event A</td>
<td>XX</td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td># of events</td>
<td>XX</td>
<td>XX</td>
<td></td>
</tr>
<tr>
<td># participants</td>
<td>X%</td>
<td>X%</td>
<td></td>
</tr>
<tr>
<td>affected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event B</td>
<td>X</td>
<td>X</td>
<td>N</td>
</tr>
<tr>
<td># of events</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td># participants</td>
<td>X%</td>
<td>X%</td>
<td></td>
</tr>
<tr>
<td>affected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Note: allow multiple “other (specify:        )” columns to accommodate different study designs as currently allowed in reporting by group (e.g., only adjudicated to device or implant; adjudicated to device, implant, drug X, or patient co-morbidities/medical conditions)

g. Recommendations on Additions or Modifications to Basic Results Data Elements

With respect to additions or modifications to the manner of reporting of the data elements established under the basic results reporting provisions of FDAAA, AdvaMed recommends a new results data element (e.g., checkbox or drop-down menu option) that would enable companies to explain to data bank users the following situations:

- The trial was voluntarily registered prior to the FDAAA effective date and results posting is not legally required.
- The trial is an applicable trial and results are required to be submitted.
- The trial is not an “applicable clinical trial” and was entered into the registry on a voluntary basis and results posting is not legally required.
- The trial is completed and the device is FDA cleared or approved but results are not required to be posted at this time.
- Primary results only have been entered.
- If applicable, secondary results will be entered 18 months following study completion date (i.e., final date on which all primary and secondary data were collected on the last study subject).
- The trial was stopped for reasons unrelated to safety and will have no results to post.
• The trial is completed and the device is pending FDA clearance or approval. Therefore, results are not required to be posted at this time.

We also propose that an additional data element be added to disclose when secondary data and technical and non-technical summaries are anticipated (based on scientific study design and 18 months following “Study Completion Date”).

Finally, in actual practice, the format for the submission of clinical trial information and especially the manner of reporting results is not user-friendly and is very burdensome for those who must input data. In particular, it is awkward if the data don't fit into the standard categories that are provided. Given the wide variability in device products this is not an infrequent occurrence. The XML option is not useful for non-IT users who must input the data at many companies. AdvaMed recommends that the data bank be expanded to allow sponsors to upload Word or Excel tables, rather than manually entering data field-by-field. The current techniques are also burdensome for the ClinicalTrials.gov Quality Assurance (QA) group and lay audiences because they do not result in concise presentation of data. We believe that the ability to upload tables in Word or Excel could simplify the process for all users.

10. A statement to accompany the entry for an applicable clinical trial when the primary and secondary outcome measures for such clinical trial are submitted as a “voluntary submission” after the date specified in the FDAAA for submission of such information.

AdvaMed Response
As discussed in AdvaMed’s response to Question 9, section “g.” regarding “additions or modifications to the manner of reporting of the data elements established under the basic results reporting provisions of the FDAAA,” we believe that the addition of a new results data element (e.g., checkbox or drop-down menu option) that explains to databank users various situations would be useful. Please see our suggested additions in “g.” in Question 9 above.

11. Other issues associated with Section 801 of the FDAAA that will inform rulemaking.
AdvaMed details a number of implementation concerns and our associated recommendations below:

a. Create waiver for delayed disclosure.
b. Rely on existing FDA definitions of devices subject to Sections 510(k), 515, and 520(m).
c. Establish formal extension process.
d. Clarify in guidance factors that will be considered when applying civil or criminal penalties.
e. Clarify in guidance that results are never due sooner than 12 months after last subject seen for primary outcome.

f. Provide opportunity to comment on draft NLM guidance via Federal Register process.

g. Clarify registration requirements in guidance for observational IVD trials ensuring consistency with Section 801 of FDAAA and with existing FDA regulations and practices.

a. Create Waiver for Delayed Disclosure

As you know, AdvaMed supported the inclusion of language in FDAAA providing for “delayed disclosure” of device clinical trial registry information to ensure that such information is posted publicly in the registry data bank not earlier than the date of clearance or approval and not later than 30 days after such date (Section (j)(2)(D)(ii)(I)). We supported this provision on behalf of our companies, particularly smaller device companies, in order to protect and maintain the competitiveness of the device industry and continued innovations for patients by ensuring that sensitive, confidential commercial information would be protected from public disclosure until after FDA approval or clearance. Unlike the drug industry where entire molecules are patented (and are frequently patented even before the first clinical trial begins), patents provide little protection in the device industry because competitors can easily negate device patents with simple engineering or design changes. Disclosure of the existence of an IDE through the data bank could provide significant advantages to competitors who could potentially speed a competing device into clinical trials and obtain FDA clearance or approval in order to take advantage of the benefits associated with being first to market. Such disclosures could have the unintended consequence of eliminating many small device companies from the marketplace. Small companies account for a vast number of device innovations for patients and contribute greatly to maintaining strong price competitiveness across the industry. In many instances, small companies are willing to invest in developing technologies for niche and orphan markets – patient communities that may otherwise be overlooked.

FDA and NLM have implemented the delayed disclosure language by requiring device companies to first indicate whether the trial is an “applicable” device trial, then whether delayed posting applies. This approach is appropriate for companies that desire protection from disclosure of their clinical trial information until after the device is cleared or approved, per FDAAA. However, some device

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7 A 2008 study found that overall prices of medical technology grew more slowly than either the Medical Consumer Price Index (MCPI) or the Consumer Price Index (CPI) in the 15-year period ending in 2004. Over the same period, medical technology has accounted for a relatively low and constant percentage of total national health expenditures. Roland King & Gerald F. Donohue, *Estimates of Medical Device Spending in the United States*, 3-4 (Advanced Medical Technology Association, 2008).
companies are willing to disclose clinical trial information prior to FDA clearance or approval in order to ensure publication in peer review journals that follow ICMJE guidelines. In this latter case, companies have been advised by NLM and FDA to either provide inaccurate information that the device trial is not subject to delayed disclosure or to leave the question blank. In the first instance, the government is advising companies to provide inaccurate information to ClinicalTrials.gov. Similarly, in the second, the government advises companies to provide incomplete information to ClinicalTrials.gov.

AdvaMed recommends that FDA and NLM create an additional option in the data bank that indicates the trial is an applicable device trial for which the manufacturer seeks no delays on public disclosure of the registry data in order to meet ICMJE requirements. FDA and NLM should make clear in accompanying instructions the differences in the options.

AdvaMed retained outside counsel to provide a legal assessment of whether NLM can register and list clinical trial information for a device that has not been previously marketed prior to the approval or clearance of the device if waived by the device submitter. AdvaMed’s legal assessment is attached in Appendix B.

We understand that some journals who are members of ICMJE have – paradoxically – indicated they will penalize device companies who comply with the law. As a result, device manufacturers seeking to meet the non-statutory requirements of some ICMJE member journals are forced to choose between two options: leave the checkbox blank or declare that the trial is not an applicable device trial.

It should be noted that AdvaMed communicated with Dr. Harold Sox, Editor of the Annals of Internal Medicine, in advance of the June 2008 ICMJE meeting to propose a potential solution on the delayed disclosure issue. We made the assumption that some ICMJE representatives believed that device industry compliance with the delayed disclosure provision Section (a)(2)(D)(ii)(I) would affect a journal’s ability to assess whether a device sponsor had appropriately registered a device trial. We proposed that the unique National Clinical Trial (NCT) number assigned by ClinicalTrials.gov provides evidence that a sponsor has indeed registered the trial as required. The NCT number could be included in the cover letter of a manuscript submission, thereby demonstrating trial registration. We continue to believe this approach represents a resolution to this issue.

b. Rely on Existing FDA Definitions of Devices Subject to Sections 510(k), 515, and 520(m)

In a December 8, 2008 draft guidance, NLM elaborates on the statutory definition of “applicable device clinical trial.” In this draft, NLM further describes what is intended by the element “a device subject to 510(k), 515, or 520(m) of the Federal
Food Drug and Cosmetic Act.” In doing so, the draft guidance proposes that the criteria for determining whether or not a device is subject to 510(k), 515, or 520(m) is “where the device being used in the clinical study is manufactured.” This new criteria changes the current statutory requirements defined in sections 510(k), 515, or 520(m) of the FDC Act. To define device 510(k), 515, and 520(m) requirements in this manner has implications well beyond clinical trial registration, extending to areas such as product application/submission and manufacturing requirements.

It is not uncommon for U.S. companies to manufacture devices in the U.S. that are intended for export only with no intent to market the device in the U.S. The NLM guidance implementing clinical trial registration and results posting should not alter the statutory requirements for these devices through statements that such devices are subject to 510(k), 515, and 520(m).

Sections 510(k), 515, and 520(m) of the FDC Act clearly define when a device is subject to one of these provisions. That is, when one proposes to begin the introduction or delivery for introduction of the device into interstate commerce for commercial distribution. Because the statutory provisions 510(k), 515, and 520(m) clearly define when a device is subject to one of these sections it is unnecessary to redefine these provisions in the context of clinical trial registration and results posting. By redefining these provisions in a manner contrary to long-standing understanding and interpretation, new requirements are established where they did not exist before.

To redefine these sections whenever they are referenced in a statutory provision has the potential to result in multiple definitions and confusion.

Consistent with long-standing understanding and interpretation, AdvaMed recommends continued reliance on the existing definitions of devices subject to sections 510(k), 515, and 520(m) in the context of Section 801 of FDAAA.

c. Establish Formal Extension Process

FDAAA allows for delayed submission of results information with certification where the sponsor is seeking initial approval or clearance of a product or approval or clearance of a new use for an existing product. Additionally, FDAAA allows the Director of NIH to provide an extension of the deadline for submission of results information where the responsible party demonstrates good cause for the extension in a written request and provides an estimate of the date on which the information will be submitted. NLM has provided “Temporary Instructions for Certification or Request for Extension” directing the responsible party to provide specific information in an e-mail to register@clinicaltrials.gov with “Certification or Extension Request” in the subject line. AdvaMed appreciates that NLM provided these temporary instructions and understands there is an ongoing effort
to establish and implement a formal process. We would like to request NLM replace these Temporary Instructions with the following process:

- Certifications or requests for extensions should be made through the ClinicalTrials.gov data bank. To implement this automated process, NLM should add new data elements to input the certification or request and connect it to the specific trial registration information (i.e., under or prior to the Results Information tab).
- NLM responses to certifications or requests for extension should be sent to the submitter through the automated response system that is currently in use on the ClinicalTrials.gov database that notifies a submitter when NLM has made an edit to one of the submitter’s records.
- NLM responses to certifications or requests for extensions should be posted on the ClinicalTrials.gov data bank so that the information is made public to ensure transparency and to minimize any perception of non-compliance in the timing of results information submission where delays or extensions have been approved.

In addition, we suggest that NLM develop guidance to provide information on the process used to review certifications or requests for extensions, the criteria used to approve or deny a request for extension, and identify operational groups responsible for making these decisions.

We also urge NLM to include a process for “reconsideration” in the event that a request for extension is not approved to ensure the responsible party has the opportunity to provide additional information or resolve any potential misinterpretation of information.

d. Clarify in Guidance Factors That Will Be Considered When Applying Civil or Criminal Penalties

FDAAA placed new strict liability prohibited acts that relate to conduct under the registry and results data bank requirements in Section 301 of the FDC Act. This could subject device companies to significant penalties for minor omissions or inadvertent errors in data entry.

Strict liability is a very exacting standard that we do not believe was intended to apply to data entry of multiple layers of highly technical clinical trial information. In determining whether to apply a penalty under this subsection for a violation of Section 301(jj), AdvaMed requests that FDA and NLM clarify in guidance that they will consider “intent” such as:

- whether the responsible party promptly corrects the noncompliance when provided notice;
- whether the responsible party has engaged in a pattern or practice of noncompliance; or
• the extent to which the noncompliance involved may have significantly misled health care providers or patients concerning the safety and effectiveness of the device involved.

e. **Clarify in Guidance That Results Are Never Due Sooner than 12 Months After Last Subject Seen for Primary Outcome**
Based on interactions with NLM and FDA, we understand that clinical trial results are never due sooner than 12 months after the final subject was seen for the primary outcome even though the device may have been cleared earlier. In response to Question 6, AdvaMed supports expanding the 12 month timeframe to 18 months. In either case (i.e., a 12 month or 18 month timeframe), AdvaMed concurs with NLM that one timeframe should be consistently used to ensure that posted results reflect the complete analysis and to minimize the number of requests for good cause extensions. AdvaMed recommends that NLM clarify these points in guidance using examples.

f. **Provide Opportunity to Comment on Draft NLM Guidance Via Federal Register Process**
AdvaMed recognizes and appreciates that NLM has developed draft guidance to assist sponsors and others in complying with and understanding the FDAAA clinical trial data bank requirements and that this draft guidance is available for informal comment on the ClinicalTrials.gov website. We recognize that this informal process is helpful to share early drafts of NLM’s thinking on how to proceed with aspects of a challenging and complex system, to “work out the kinks.” We appreciate having this opportunity and would like it to continue. However, to ensure transparency, we believe that before finalizing such guidance, it is important that the broadest possible audience is made aware of the draft guidance documents and of the process for submitting comments on them. For these reasons, AdvaMed recommends that NLM follow a guidance process that utilizes traditional mechanisms for public distribution and comment i.e., a Federal Register Notice and a minimum 60-day comment period process prior to finalizing draft guidance documents. Such a comment process would also be consistent with FDA’s Good Guidance Practices (GGP).

g. **Clarify Registration Requirements in Guidance for Observational IVD Trials Ensuring Consistency with Section 801 of FDAAA and with Existing FDA Regulations and Practices**
AdvaMed recommends that NLM clarify clinical registration requirements and guidance regarding observational device studies, such as most in vitro diagnostic (IVD) device studies, to ensure consistency with Section 801 of FDAAA as well as FDA’s existing regulations and practices. AdvaMed supports providing full and complete clinical trials registry information of applicable device trials under Section 801. Information issued to date on observational trials, such as in vitro diagnostic studies, however, has been confusing. Most IVD studies merely compare the performance of a device to another existing device and are non-
interventional with no direct impact on patients. FDA has historically treated most IVD studies as observational and has distinguished them from interventional trials.

FDAAA is clear that there must be an intervention with a device to be an applicable device trial. Further, FDAAA recognizes that some types of trials are not applicable device trials, such as feasibility studies. Similarly, IVD non-interventional studies do not constitute applicable device trials. Based on the well-established FDA regulatory framework for IVD devices and other device studies where the devices do not have direct impact on patients, such studies are observational studies. Consistent with the definition under FDAAA, these types of non-interventional studies are not applicable device clinical trials.

For IVD and other observational studies, it is also important to distinguish the intervention at issue from ancillary procedures. For example, for IVD device studies, the blood draw is done merely to obtain specimens for use in the device study—the blood draw is not the intervention that the clinical study is designed to evaluate (i.e., the purpose of the study is not to evaluate whether the blood draw is safe and effective). The blood draw is merely a procedure done to collect a routine sample with the purpose of evaluating the diagnostic device.

FDA’s treatment of such observational studies is well-established, including recognition of the non-interventional characteristics of most IVD studies. For example, the FDA’s Investigational Device Exemption (IDE) regulations under 21 CFR § 812.2 (c)(3) and CFR § 812.3 (k) specifically exempt certain IVD studies from IDE regulation on the basis of minimal risk to the subject from whom samples are collected and the fundamental characteristics of such studies, in particular the impact on the subject. Most IVD studies are exempt because the studies are noninvasive (i.e., blood sampling involves simple venipuncture); the study sampling procedure does not present significant risk (e.g., provision of urine, stool, swab, or blood samples) and does not introduce energy into a human subject, and the results are generally not used to diagnose a patient or, in the rare event that the result is used by a physician, it cannot be used without confirmation by other, medically established diagnostic products or procedures.

As mentioned, most IVD studies simply compare the performance of a device to another existing device. IVD device study results are often not even provided to health care providers or used in patient management. Even in instances when results are available to health care providers, in most cases the results of the investigational diagnostic device are prohibited from being used to treat or diagnose a patient. Furthermore, the health care provider is often using a similar, FDA-cleared IVD device within the accepted standard of care.

Consistent with Section 801 and FDA’s regulatory framework, interventional trials (which includes certain IVD trials) where results directly impact patient care
are subject to registration. In the case of studies with IVD devices where results (per study protocol) are provided to the health care professional or to the patient to assign treatment options or are used as a sole determinate to assign subjects to treatment or control groups, AdvaMed agrees these trials are interventional in nature and constitute “applicable clinical trials” under Section 801.

During the April 20, 2009 public meeting, FDA asked AdvaMed to provide examples to better understand the types of IVD clinical trials that meet the definition of applicable device clinical trial and that require registration. To illustrate our points, below we provide the following examples of both interventional and observational IVD studies:

\textbf{a) Examples of Interventional IVD Clinical Trials (That Require Registration)}

\begin{itemize}
\item[i)] Subjects enrolled in a study to provide blood specimens for assessing clinical specificity of an IVD device (also referred to as an IVD “test”) and determining the assay cutoff are provided study results and asked to consent for a follow-up blood draw. The specimens are prospectively collected. If specimen results fall into a particular range of values, the subjects are called back and given feedback on their study results and asked to consent for a follow-up blood draw. Here there is an intervention with a device because the subject is provided information about the test result and because there is direct impact on the patient (follow-up testing) as a consequence of the device’s result. Therefore, we believe this study is an applicable device clinical trial. (Note: This study would be conducted with FDA oversight under an IDE or Investigational New Drug Application (IND)).

\item[ii)] \textbf{Subjects are enrolled in a study for a new blood donor screening test for a parasitic or infectious disease with no previously licensed comparator assay. The clinical trial protocol is conducted under an IND and requires informed consent from the donor for collection and testing of the blood sample. Testing performed on the blood donor sample with the investigational assay is positive. Confirmatory testing is performed on the same blood sample using a licensed confirmatory test or unlicensed reference test. The blood donor is deferred from future blood donations based on the results of the investigational assay and confirmatory result and the current blood donation is not released into blood inventory. In this example, the donor receives the study results and is referred to a private physician for consultation and possible treatment. Because the subject is provided information about the test result and there is direct impact on the patient (the patient is referred for medical consult), we believe such study is an applicable device clinical trial.}
\end{itemize}
iii) Subjects are enrolled in a study to determine safety and potential for improved efficacy of lowering the diagnostics cutoff for a tumor marker assay. The current standard of care requires ultrasound and biopsy for antigen detection with results greater than 4.0 ng/ml. The study requires follow-up ultrasound and biopsy for subjects with results showing greater than 3.0 ng/ml. In this example, there is an intervention (ultrasound and biopsy) for patients with results between 3.0 and 4.0 ng/ml. Because the tests results have an impact on this subset of patients, the study should be classified as an applicable device clinical trial. (Note: This study would be conducted with FDA oversight under an IDE).

b) Examples of IVD Observational Studies (Would Not Require Registration)

i) Subjects are enrolled in a study to provide blood specimens. The specimens are prospectively collected, but no investigational test results are given to the subjects or to the subjects’ physicians. The medical history and test results will be used in assessing clinical sensitivity and clinical specificity of the IVD device and determination of the assay cutoff. In this example, there is not an intervention with a device because the device does not have an impact on patient care. This study would not be an applicable device clinical trial.

ii) Subjects are enrolled in a study evaluating a licensed or approved test that is modified. The objective of the study is to confirm the already approved performance characteristics of the device as they appear in the labeling. (Note: These studies most often use direct comparison with a previously approved or cleared IVD device.) Patient intervention based upon the use of the test result from the IVD device is not possible or is specifically prohibited as test results are not linked to the actual donor. The objective of the protocol is to conduct a statistical comparison to the licensed/approved test. This study would not be an applicable device clinical trial.

iii) Subjects are enrolled in a study to evaluate a new investigational tumor marker assay. Subjects are enrolled prospectively and their medical history and test results will be evaluated to ensure the investigational assay meets FDA expectations for safety and effectiveness. Test data for a previously cleared IVD device will also be obtained and the investigational device results will be compared with those from the cleared device. Subjects will receive standard care and no investigational data will be used in the care of the subject, although results from the previously cleared device will be used as current standard of care. Here again, there is no intervention with the device and no impact on patient care as a result of the device. This study would not be an applicable device clinical trial.
iv) Subjects are enrolled in a study to determine the safety and effectiveness of raising the diagnostic cutoff for a tumor marker assay. The current standard of care requires ultrasound and biopsy for antigen detection with results greater than 3.0 ng/ml. The study requires that the follow-up ultrasound and biopsy information, which would be otherwise conducted for the patient, be collected for patients with results between 3.0 and 4.0 ng/ml. The ultrasound and biopsy information will be compared to the entire population to determine if ultrasound or biopsy for patients with results between 3.0 and 4.0 ng/ml should be indicated. There is no intervention with the device because there is no additional activity with the patients that affect care. Because there is no intervention with the subject, the device does not have an impact on patient care. This study would not be an applicable device clinical trial.

v) Subjects are enrolled in a study to determine the usability of a new IVD device that has not been cleared in order to support validation of a design change for human factors improvement. There is no control group. Each subject enrolled in the study is using the device, which is similar to a previously cleared device. There is no comparison of different interventions. This study would not be an applicable device clinical trial.

In sum, as illustrated by the above examples, most IVD studies merely compare the performance of one IVD device to another existing IVD device and do not have a direct impact on patients. In most cases, IVD device study results are never provided to the health care provider or used in patient management. Under FDA’s longstanding regulatory framework for IVD devices, such studies are observational, not interventional. Consistent with FDAAA and FDA regulatory requirements pertaining to IVD studies, IVD interventional device trials where there is an impact on the patient as a consequence of the device results (e.g., protocol calls for additional treatment intervention or referral for follow-up testing or physician consult for a patient subset) are applicable clinical trials and should be registered.

AdvaMed recommends that NLM guidance recognize that observational IVD clinical studies, which are non-interventional studies, are not applicable device clinical trials under Section 801 and that NLM provide examples of both observational IVD studies that do not require registration and interventional IVD trials that do require registration. AdvaMed retained outside counsel to provide a legal assessment in this area. AdvaMed’s legal assessment is attached in Appendix C.
In conclusion, thank you for your consideration of AdvaMed’s comments on issues the Agency will consider as it develops regulations to expand the clinical trial registry and results data bank as well as additional areas of concern to device manufacturers associated with implementation of Section 801. Please don’t hesitate to contact me if you have any questions.

Sincerely,

Tara Federici
Vice President
Technology and Regulatory Affairs
## Appendix A

### Comparison Table on “SERIOUS” Adverse Event or Effect Definitions: Events that lead to or result in . . .

<table>
<thead>
<tr>
<th>ClinicalTrials.gov: Serious Adverse Event</th>
<th>21 CFR Part 312 (IND Regulations): Serious Adverse Drug Experience</th>
<th>21 CFR Part 812 (IDE Regulations): Unanticipated Adverse Device Effect — The following events when caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence . . .</th>
<th>21 CFR Part 803 (Medical Device Reporting for Marketed Devices): MDR Reportable Event and Serious Injury</th>
<th>ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects): Serious Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Death</td>
<td>Death or serious injury</td>
<td>Death or serious injury</td>
<td>Death or serious injury</td>
</tr>
<tr>
<td>Inpatient hospitalization or the prolongation of hospitalization</td>
<td>Inpatient hospitalization or prolongation of existing hospitalization</td>
<td>Inpatient hospitalization or prolongation of existing hospitalization</td>
<td>Inpatient hospitalization or prolongation of existing hospitalization</td>
<td>Inpatient hospitalization or prolongation of existing hospitalization</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>Life-threatening</td>
<td>Life-threatening</td>
<td>Life-threatening</td>
<td>Life-threatening illness or injury</td>
</tr>
<tr>
<td>Persistent or significant disability/incapacity</td>
<td>Persistent or significant disability/incapacity</td>
<td>Permanent impairment of a body function or permanent damage to a body structure</td>
<td>Permanent impairment of a body structure or a body function</td>
<td></td>
</tr>
<tr>
<td>Congenital anomaly/birth defect</td>
<td>Congenital anomaly/birth defect</td>
<td>Foetal distress, foetal death or a congenital abnormality or birth defect</td>
<td>Foetal distress, foetal death or a congenital abnormality or birth defect</td>
<td></td>
</tr>
<tr>
<td>Other important medical events, based upon appropriate medical judgment . . . if a trial participant’s health is at risk and intervention is required to prevent an outcome as mentioned</td>
<td>Important medical events . . . based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition</td>
<td>Serious Adverse effect on health or safety NOTE: Does not define “serious”</td>
<td>Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure</td>
<td>Medical or surgical intervention to prevent permanent impairment to body structure or a body function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Device) has malfunctioned and . . . would be likely to cause or contribute to a death or serious injury if the malfunction were to recur</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix B
Outside Counsel Legal Assessment
Waiver of Delayed Posting of Device Clinical Trial Information

Question Presented
Can NIH post information from an applicable device clinical trial prior to the approval or clearance of a device that has not been previously cleared or approved by FDA under Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), when the device sponsor requests that the clinical trial information be posted in NIH’s Clinical Trial Registry Data Bank?

Short Answer
Yes, the device sponsor should be able to waive the statutory requirement that delays the posting of clinical trial information until after a device is cleared or approved by FDA.

Discussion
The law governing the clinical trial registry states that

[the Director of NIH shall ensure that clinical trial information for an applicable device clinical trial submitted in accordance with this paragraph is posted publicly in the registry data bank –

(I) not earlier than the date of clearance under section 510(k) of the Federal Food, Drug, and Cosmetic Act, or approval under section 515 or 520(m) of such Act, as applicable, for a device that was not previously cleared or approved, and not later than 30 days after such date….

42 U.S.C. § 282(j)(2)(D)(ii)(I) (emphasis added). This delayed posting requirement was created to protect device submitters of 510(k)s and PMAs from premature disclosure of confidential commercial information that is protected from disclosure under FDA’s regulations. Specifically, FDA will not disclose the existence of a pending premarket submission under most circumstances. See, e.g., 21 C.F.R. § 807.95(b) (stating FDA “will not disclose publicly the existence of a premarket notification submission for a device that is not on the market and where the intent to market the device has not been disclosed for 90 days from the date of receipt of the submission…”); 21 C.F.R. § 814.9(b) (“The existence of a PMA file may not be disclosed by FDA before an approval order is issued to the applicant unless it previously has been publicly disclosed or acknowledged.”). Maintaining this protection was particularly important for devices that had not been previously cleared or approved by FDA, and the delayed posting was limited to these devices.

Creating the delayed posting provision balanced the desire for public awareness of clinical trials with the need to protect device innovators’ confidential commercial information related to the development of new devices. The delayed posting provision ensures that the
confidentiality of a company’s product development is maintained by restricting the posting of clinical trial information until after approval or clearance when the existence of the new device becomes public.

Because this delayed posting provision is intended to protect the confidential information and interests of the potential marketer, i.e., the person potentially submitting a 510(k) or PMA, the 510(k) or PMA submitter should be in a position to waive the delayed posting if that is the submitter’s preference, assuming the waiver would not interfere with the purpose of the registry data bank legislation. For example, if the device sponsor would need to register its trial with NIH as a condition to publication of its clinical trial results,8 delayed posting would be a detriment not a benefit to the sponsor. Indeed, inflexibly refusing to publicly acknowledge the registration of a clinical trial, thus precluding its publication in the medical literature when registration with the data bank is a publication prerequisite, would frustrate the intent of Section 801, i.e., to make clinical trial information publicly available for patients and physicians.

A sponsor’s interest in posting its clinical trial in the registry data bank earlier than after the device’s approval or clearance is entirely consistent with the intent behind the clinical trial registry, namely to share clinical trial information with the public.9 Thus, if a device sponsor wishes to waive the right to delayed posting, the statutory language prohibiting the earlier posting should not be understood as a bar to a consensual disclosure of a clinical trial. Indeed, not only would the waiver of delayed posting make available the statutorily required data bank information, but it could result in the publication of trial results in the medical literature, thus providing another means of distributing information about new devices. Under circumstances where a party wishes to waive a statutory right, and that waiver would not frustrate the public purpose of the statute, courts have acknowledged that statutory rights intended to protect individual rights may be waived by the persons for whom the statute provides protection.10

Additionally, the Supreme Court explained in the context of construing a statute that broad statutory language should not be read to result in an outcome at odds with the spirit of the law. The Court stated:

8 See http://prsinfo.clinicaltrials.gov/ (“ClinicalTrials.gov facilitates registration of trials in accordance with the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical trials in a public registry as a condition for publication.”).
9 See, e.g., 153 Cong. Rec. S11831 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy) (“A second major element of our legislation is a public registry of clinical trials and their results. A complete central clearinghouse for this information will help patients, providers and researchers learn more and make better health care decisions. Now, the public will know about each trial underway, and will be able to review its results.”); 153 Cong. Rec. H10551, H10596-97 (daily ed. Sept. 19, 2007) (statement of Rep. Markey) (“[A] mandatory clinical trial registry and results database… will ensure that the public has accurate and complete information about drugs and devices. This bill will create that mandatory clinical trials database.”).
10 See, e.g., Canal Electric Co. v. Westinghouse Electric Co., 406 Mass. 369, 378 (1990) (“A statutory right or remedy may be waived when the waiver would not frustrate the public policies of the statute.”).
[F]requently words of general meaning are used in a statute, words broad enough to include an act in question, and yet a consideration of the whole legislation, or of the circumstances surrounding its enactment, or of the absurd results which follow from giving such broad meaning to the words, makes it unreasonable to believe that the legislator intended to include the particular act.

Public Citizen v. United States Department of Justice, 491 U.S. 440, 454 (1989) (quoting Church of the Holy Trinity v. United States, 143 U.S. 457, 459 (1892)). In Public Citizen, the Supreme Court found the Federal Advisory Committee Act (FACA) did not apply to the American Bar Association’s Standing Committee on Federal Judiciary (ABA Committee), when the President, through the Justice Department, requested the ABA Committee’s advice in nominating federal judges. Although FACA defines an advisory committee to be a committee “utilized” by the President or an agency, the Court found if it “[r]ead [the word “utilized”] unqualifiedly, it would extend FACA’s requirements to any group of two or more persons, or at least any formal organization, from which the President or an Executive agency seeks advice.” 491 U.S. at 452. The Court concluded Congress never intended such a result.

In the current situation, the intent behind the delayed posting provision was to benefit the person submitting the 510(k) or PMA for a new device; an inflexible reading of that provision would punish the submitter and frustrate the purpose of the registry data bank law, which was to make clinical trial information available to the public at the earliest reasonable time. Under these circumstances, a waiver of the delayed posting provision “would not frustrate the public policies of the statute” see Canal Electric Co., 406 Mass. at 378. Moreover, permitting early posting is consistent with FDA’s own disclosure regulations, which permit FDA to disclose the existence of a 510(k) or PMA if the sponsor has already publicly acknowledged its existence. See 21 C.F.R. § 807.95(a)(2); 21 C.F.R. § 814.9(b).

NIH recognizes that registrants of device trials often want their clinical trial information promptly posted and not delayed until after receipt of clearance or approval. To accommodate such requests NIH in the past instructed registrants to check the box on the registration form indicating that the device was previously approved or cleared by FDA. See ClinicalTrials.gov Protocol Data Element Definitions (DRAFT) (Aug. 20, 2008), http://prsinfo.clinicaltrials.gov/definitions.html. By doing so, the delayed posting of clinical trial information would not be applicable to the device trial. However, NIH’s advice would result in incorrect statements to the government. NIH understands its form and past recommendation created a conundrum for itself and device sponsor registrants, and now recommends that registrants not answer the question as the means to avoid delayed posting. This approach creates some of the same concerns as counseling registrants to make incorrect statements.

In sum, we believe that the Director of NIH could fairly interpret the statute to permit waivers of the delayed posting of device clinical trials. Interpreting the statute this way would avoid placing NIH in a position where it is counseling registrants to submit incomplete forms or to make incorrect statements. A far preferable approach for the government and device sponsors would be for NIH to release a new form that permits a waiver election.
Appendix C

Outside Counsel Legal Assessment

Applicability of FDAAA Clinical Trial Registry Requirements to Non-Interventional IVD Studies

Question Presented

Are non-interventional studies on *in vitro* diagnostic (“IVD”) devices “applicable device clinical trials” under section 801 of the Food and Drug Administration Amendments Act of 2007 (“FDAAA”)?

Short Answer

No. IVD studies that are non-interventional do not meet Section 801’s definition of applicable device clinical trials and do not need to be registered. Because such non-interventional studies do not impact patient care, their registration would not serve the purpose of Section 801 to enhance patient access to, and information on, experimental therapies.

Analysis

FDAAA subjects “applicable device clinical trials” to the enhanced clinical trials registry requirements. Among other things, to be an applicable device clinical trial, the trial must compare an “intervention with a device” against a control. The statute does not define the phrase “intervention with a device”, so in interpreting this language, we look to statutory intent and purpose, other relevant sources of law, and commonly accepted definitions of such terms. These authorities persuade us that an “intervention with a device” requires that the IVD device being studied impact the subject’s care, diagnosis, or treatment.

IVD device studies often do not have such an impact on human subject participants. For example, such studies often focus on assessing the performance characteristics of the IVD and do not inform any patient diagnosis or treatment. As a result, IVD studies will often not meet the statutory definition of an “applicable device clinical trial” because they do not involve an “intervention with a device,” which is a key element under the statute.

12 Importantly, the converse — that interventional IVD studies are required to be registered — is not necessarily true. Interventional IVD studies and other device studies may also not meet the definition of applicable device clinical trials for other reasons, such as not having a control. This could be the case, for example, in a study of an IVD device that is focused on the usability features of the IVD. The subjects or their caregivers may even use the results, but because the focus is on the user features of the IVD device, there may be no control. In this case, the study would not be an applicable device clinical trial even though there was an invention (i.e., patient impact) with the device.
At the outset, understanding the patient-focused objectives of the clinical trial registry requirements enacted by FDAAA is important. Specifically, the central objectives of Section 801 include (a) providing patients and healthcare providers with information on and access to enrollment in clinical trials for experimental therapies and (b) providing safety and efficacy information to the public. As discussed below, requiring registration of non-interventional studies that by definition do not impact patient care would not fulfill those purposes of the FDAAA requirements.

1. To be subject to FDAAA’s enhanced registration requirements, a device clinical trial must compare an “intervention with a device” to a control.

Section 801 of FDAAA sets forth enhanced registration requirements for “applicable device clinical trials.” The statute defines an “applicable device clinical trial” as “a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects.” The statute also sets forth certain exceptions to this definition, such as feasibility studies. While there are several important elements to this definition, this memorandum is largely focused on the phrase “intervention with a device.” To state that phrase another way, device trials requiring registration must be “interventional,” in addition to meeting the other statutory requirements.

Before discussing the meaning of “intervention,” we first want to be very clear on the phrase as a whole.

a. The intervention at issue for purposes of registering the clinical trial is an intervention “with the device.”

At the outset, it’s important to recognize that the “intervention” at issue for registering the clinical trial is an “intervention with a device” – not an intervention with ancillary procedures that may be used in the research. For example, in IVD studies, if a blood draw is done merely to obtain specimens for use in research, the blood draw is not the intervention that the clinical study is designed to evaluate -- i.e., the purpose of the study is not to evaluate whether the blood draw is safe and effective. The blood draw is merely a procedure done to evaluate the diagnostic test. The question is whether there is an intervention with the diagnostic test. The statutory language is clear on this point.

13 See H.R. Rep. No. 110-225, at 12, 49 (2007); See also FDA, Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff: Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007 (Jan. 2009).

14 We can conceive of a situation (though admittedly far-fetched) in which the blood draw itself might be the “intervention.” Consider a clinical trial designed to compare a blood draw with some alternative procedure for collecting specimens from a person (e.g., as a mouth swab). The subjects are divided into two groups. The intervention group would have their blood drawn; the control group would give a swab of tissues from their mouths. The purpose of the study would be to decide whether it is safer and more effective to do a blood draw
The NIH recognized this distinction in its draft protocol data element definitions document issued in August 2008. Specifically, in considering whether a trial is an “applicable clinical trial”, the document first poses the question of whether the trial concerns an “FDA regulated intervention” (i.e., a drug or medical device). Thus, the question is whether there is an intervention with the studied device – not ancillary procedures such as blood draws. Further, additional questions about whether a trial is an “applicable clinical trial” only come into play if the answer is “yes” to an FDA-regulated intervention.

In another context, ClinicalTrials.gov has defined interventions as follows:

“INTERVENTION NAME: The generic name of the precise intervention being studied.

INTERVENTIONS: Primary interventions being studied: types of interventions are Drug, Gene Transfer, Vaccine, Behavior, Device, or Procedure.”

Thus, the statutory language and the agency interpretations are clear that, in order for a study to potentially qualify as an applicable device clinical trial, there must be an intervention with the device that’s being studied. Next we turn to what, in fact, is an “intervention” – i.e., what impact must the device have?

b. To have an “intervention with a device”, there must be some impact on patient care.

The statute does not define “an intervention with a device”. As a result, we must be informed by other sources of authority. In this regard, well-accepted definitions of a clinical trial illustrate that in order to have an “intervention,” there must be some impact on the patient. For example:

“A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings…. A clinical trial must employ one or more intervention techniques. These may be ‘prophylactic, diagnostic or therapeutic agents, devices, regimens, procedures, etc.’ Intervention techniques should be applied to participants in a standard fashion in an effort to change some aspect of the participants.”

as opposed to taking a swab. In this hypothetical, the blood draw itself would be the “intervention” that is being evaluated.

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Another example is found in the International Committee of Medical Journal Editors’ ("ICMJE") definition of clinical trial:

“All research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes).”

And another example from a registry focused on a particular condition:

“In an interventional trial, the investigators give the participants a particular investigational drug or other intervention, which may include a gene transfer, vaccine, device, or procedure, such as surgery. The intervention may or may not be assigned randomly, and sometimes treated individuals might be compared with those who receive no treatment. The researchers then measure how the health of the participant changes. Interventional trials determine whether experimental treatments or new ways of using known therapies are safe and effective.”

All of these definitions have in common a focus on the intervention changing or modifying a health outcome. Applied here, to be considered under the statutory test, the device being studied would need to be applied in such a way to “change” the research subjects.

Most IVD studies do not meet this definition because the device being studied has no effect on the patients – the device is not used to impact or influence any patient treatment, diagnosis, or outcome. Results of studied IVDs often are not even provided to a healthcare professional or the patient because most IVD studies simply compare performance results produced by the investigational device to existing devices – not on an individual basis. As a result, IVD study results are generally not used to diagnosis or treat a patient. Further, as discussed above, this can be true even if the study happens to make use of blood or tissue specimens that were taken for prospective use in the study via ancillary procedures, such as a blood draw or other form of clinical intervention with a patient.

This interpretation of the non-interventional nature of most IVD studies is consistent with the FDA regulatory framework for IVD studies. For example, the FDA’s investigational device exemption regulation specifically exempts certain IVD studies from IDE regulations, on the

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18 PDtrials, available at http://www.pdtrials.org/en/browse/type/10/1 (last accessed June 5, 2009). PDtrials is a collaborative initiative of Parkinson’s organizations dedicated to increasing education and awareness about clinical research. (Emphasis added.)
basis of risk and the fundamental characteristics of such studies. Under the regulations, in order to be exempt from IDE requirements, the study must meet the following criteria: (i) Is noninvasive, (ii) Does not require an invasive sampling procedure that presents significant risk, (iii) Does not by design or intention introduce energy into a subject, and (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. Thus, FDA regulations recognize that IVD studies that do not impact patient care (or indeed, even have a risk-managed impact on patient care) are different from other studies.

In sum, when IVD study results are not used in patient management, there simply is no intervention with the device. Moreover, this interpretation is consistent with the underlying intent and purpose of the FDAAA requirements in enhancing patient access to, and information on, experimental therapies. Registration of IVD studies that do not involve the use of test results in patient treatment or diagnosis is not needed to serve the purpose of the FDAAA requirements.

2. Current drafts of interpretive documents do not address this fundamental consideration of impact on patient care in defining applicable device clinical trials.

As we all know, the implementation of the enhanced clinical trials registry requirements has resulted in a greatly increased workload for NIH and FDA, and they have been under pressure to interpret and implement the requirements in a short timeframe. Unfortunately, this time crunch seems to have resulted in some inconsistent or incomplete guidance.

One such example is in the draft elaborations document issued on March 9, 2009. In discussing applicable device clinical trials, this document recognized the unique considerations involving research on banked samples, as described in the FDA’s guidance on studies involving the use of de-identified banked samples. We agree that this is an important distinction.

On the other hand, the document also seems to infer that research on samples that are not de-identified necessarily constitutes applicable device clinical trials. However, the use of de-identified versus identified samples is not the determinative factor for deciding whether a

19 21 CFR § 812.2(c).
20 The IDE regulations provide that blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive. 21 CFR § 812.3(k).
21 21 CFR § 812.2(c)(3). (Emphasis added.) Of course such studies can impact a patient if the test result is communicated to the caregiver with the confirmatory test. We are not suggesting that all tests that meet this definition are excluded from the registry, rather simply that FDA acknowledges the uniqueness of IVD studies.
trial is interventional. In other words, a study can be subject to human subject protections yet not subject to registry requirements. A visual depiction may help illustrate this point.

<table>
<thead>
<tr>
<th>IVD STUDY DESCRIPTION</th>
<th>Do human subject protections, such as informed consent, apply?</th>
<th>Is there an intervention with the IVD device under FDAAA registry requirements?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Study of IVD device using de-identified samples</td>
<td>No&lt;sup&gt;24&lt;/sup&gt;</td>
<td>No, by definition the IVD study does not involve an intervention with a device</td>
</tr>
<tr>
<td>2 Study of IVD device using identifiable samples; results do not impact care of subject</td>
<td>Yes</td>
<td>No, the IVD study does not involve an intervention with an investigational device (i.e. the test, not the venipuncture) that impacts care</td>
</tr>
<tr>
<td>3 Study of IVD device using identifiable samples; results impact care of subject</td>
<td>Yes</td>
<td>Yes, there is an intervention (i.e., impact on the subject) with the device being studied</td>
</tr>
</tbody>
</table>

In effect, the current draft of the elaborations document does not address study 2 in the table, in which informed consent and other requirements apply, yet registry requirements do not apply to the IVD study because there is no intervention with the IVD device.

As another example of problematic guidance, the ClinicalTrials.gov resource page currently provides as follows:

“Although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol. ClinicalTrials.gov includes both interventional and observational types of studies. **Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. Observational studies are those in which individuals are observed and their outcomes are measured by the investigators.**”<sup>25</sup>

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<sup>24</sup> See id.

This definition is overly simplistic and fails to fully define interventional trials. It is also problematic because it fails to recognize that, in order to potentially be subject to registration requirements, a device clinical trial must be interventional, in addition to meeting other statutory requirements.26

In all, to be consistent with the statutory language of FDAAA, documents implementing and interpreting the FDAAA registry requirements should clarify the definition of applicable device clinical trials and recognize the important distinction between intervention and non-interventional device studies, particularly in the context of studies on IVD devices.

**Conclusion**

In summary, when considering whether an IVD clinical study has an “intervention with a device,” two points are important. One, the invention at issue is an intervention with the IVD device that’s being studied. Two, an intervention means there must be some impact to patient care with the IVD device. If the use of the IVD device being studied does not impact patient care, there’s not an intervention with the IVD device under FDAAA.

In the context of IVD studies, the device being studied is often not being used in a manner that impacts patient care. Much of IVD research – and not just research using de-identified samples – does not involve an intervention with the IVD device. This interpretation is consistent with the purpose of the FDAAA requirements, other definitions of clinical trials, as well as FDA requirements for IVD research.

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26 Of course, responsible parties may choose to register studies that do not meet the definition of applicable device clinical trial.