



**AdvaMed**

Advanced Medical Technology Association

# AdvaMed Guiding Principles on Clinical Trial Data Transparency

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There is growing interest in clinical trial transparency and data sharing on the grounds that it “could lead to improved clinical care and greater public trust in clinical research and health care”<sup>1</sup> AdvaMed describes unique concerns for medical device development and innovation associated with clinical trial transparency in Part I and approaches to achieve these objectives in Part II below.

## PART I: CONSIDERATIONS FOR CLINICAL TRIAL DATA SHARING

To ensure continued medical device innovation, careful approaches to clinical trial data sharing will be necessary. Clinical trial data sharing for medical device trials that are company sponsored must be balanced against the potential impact to medical device innovation. Small device companies account for the vast number of device innovations.<sup>2</sup> According to U.S. Census data, 68 percent of the approximately 5,000 U.S. medical device manufacturers have fewer than 20 employees and 86 percent have fewer than 100 employees. Disclosure of proprietary, confidential clinical trial data may, in particular, disadvantage small device companies or have the unintended consequence of eliminating many small device companies from the marketplace by allowing competitors to shortcut research and development (R&D) and clinical trial strategies and may have a corresponding deleterious impact on patient access to innovative technologies.

Medical device manufacturers’ clinical trial data are already fully accessible to independent health authorities such as the Food and Drug Administration (FDA), the China Food and Drug Administration, and Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) for review –independent government agencies with the proper expertise to evaluate those data and resulting conclusions. FDA’s review and summary of data, which is made public by FDA in Summaries of Safety and Effectiveness Data (SSEDs) and in 510(k) Summaries, already provides significant data transparency for medical device clinical trials. In addition, medical device sponsors also provide considerable information about their applicable clinical trials and trial results (both positive and negative) in ClinicalTrials.gov and in associated product labeling.

Medical device companies devote significant resources to design and conduct clinical trials and to ensure the validity and quality of clinical data that are submitted to FDA. This includes proprietary information such as trial designs, data collection tools (e.g., case report forms (CRFs)), and data

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<sup>1</sup> *Discussion Framework for Clinical Trial Data Sharing*, National Academy of Sciences, 2014, p. ix.

<sup>2</sup> FDA Impact on U.S. Medical Technology Innovation, A Survey of over 200 Medical Technology Companies: Prepared by Josh Makower, M.D., Aabed Meer, M.D. November 2010. p. 12.

analysis tools and methods. Protection from disclosure of these proprietary data would fall within the definition of a trade secret or confidential commercial information that is not available for disclosure under 21 C.F.R. Parts 20 and 814, as well as the Federal Food, Drug and Cosmetic Act, Section 520.

In company-sponsored medical device trials, the clinical trial data as well as the protocols and test methodologies that produced them and the associated metadata, are typically owned by the companies that support the medical device research and represent confidential, commercial, trade secret information which is also subject to copyright protections. Disclosure of trial data could violate copyright protections and could effectively serve as a nonexclusive royalty-free license to any third-party user, including sponsor competitors.

The protocol may include details regarding prototype devices, formulations or designs of pre-commercial products, and iterations or alterations of devices that may serve as blueprints for designs that may not be captured in patent filings.<sup>3</sup> Making transparent or sharing protocols could jeopardize patent protections as it can be cost prohibitive to file on every potential indication, iteration, or alteration of a device in every country and disclosure of such information may prevent companies from obtaining patent protection for prototype device designs and/or procedures in key markets.<sup>4</sup>

In addition, disclosure of such data has the potential to provide competitors unfair advantage by divulging sponsor strategy and methods. Where devices may be similar, especially for 510(k) devices, it is not clear how clinical trial data generated by one sponsor would be protected from being used by a competitor to gain FDA clearance of their similar device. 510(k) clearance is based on a demonstration of substantial equivalence of safety and effectiveness to a predicate device, thus the more information that is publicly available, the easier it will be to demonstrate substantial equivalence.<sup>5</sup>

Sharing of proprietary and confidential clinical trial data could chill interest in developing new and innovative devices. Companies and venture capital firms are likely to be reluctant to fund projects if sharing of clinical trial data enables competitors to shortcut R&D for competing products. Unlike the drug industry where entire molecules are patented, patents<sup>6</sup> provide relatively little protection in the device industry. Competitors can easily negate device patents with engineering or design changes. This lack of strong patent protection explains the rationale for the statutory ban in the U.S. on the disclosure by FDA of any information related to an investigational device exemption (IDE) including even the existence of the IDE until the device has been cleared or 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. Sometimes the first-generation device is never marketed at all. As a result,

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<sup>3</sup> Protocol for these purposes is defined as elements above and beyond those that are required to comply with ClinicalTrials.gov requirements.

<sup>4</sup> Disclosure before a patent application is filed is immediately fatal to patent protection in some countries including the European Patent Office.

<sup>5</sup> A 510(k) requires demonstration of substantial equivalence to another legally U.S. marketed device. Substantial equivalence means that the new device is at least as safe and effective as the predicate.

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketnotification510k/default.htm#se>

<sup>6</sup> 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 patents, patents do not play the same strong role of protecting intellectual property that they play in the development of drugs, for example.

device companies may have a small market and a relatively short time from which to recoup the resources spent on product development including the conduct of a clinical trial(s). 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 such projects will diminish.<sup>7</sup> For both PMA and 510(k) products, sharing clinical trial data is likely to reduce the time and investment it will take for competitors to develop and market a similar device and will likely negatively impact medical device innovation. In this arrangement, competitors benefit from the time and money spent by the innovator to run a clinical trial on a new device at the innovator's loss. The required disclosure of clinical trial data and metadata will change the device industry ecosystem to focus on "fast followers" to the detriment of investment in innovative technology, reducing incentives for industry to aggressively invest in product innovations to meet the unmet needs of patients.

A sponsor's de-identified data set also has tremendous monetary value as these may be aggregated for meta-analysis for new product concepts and claims, used to satisfy post-market regulatory requirements, and provide other competitive advantages. Making this data public so competitors and others may freely use it to serve their purposes (after the sponsor of the clinical studies have invested tremendously in the product development and in the trial design and implementation) does not seem commercially fair or reasonable. It is also almost certain to have a strong and negative impact on companies' willingness to invest in new products and innovate on behalf of patients.

## OTHER CHALLENGES TO SHARING OF CLINICAL TRIAL DATA

### Informed Consent Issues

With respect to sharing of clinical trial data, privacy laws in the country in which the trial was conducted and the jurisdiction (including the state or institution) from which the data were obtained will be relevant to the ability to disclose patient level data or may limit release of data only to health authorities. It is possible that informed consents for previous or ongoing clinical trials would not allow sharing of patient level data (whether de-identified or identifiable) with entities other than those specified in the informed consent document. Elimination of individual patient level data can change data analysis results. Sponsors may have to revise their informed consent forms to allow for future disclosure of patient level data to third party requestors.

### Ensure Current De-Identification Methodologies Are Sufficient

In the context in which clinical trial data will be shared beyond government regulators such as FDA, current anonymization or de-identification methodologies may be insufficient.<sup>8</sup> In addition, clinical trials for medical devices (including feasibility studies) frequently have a small number of human subjects (feasibility studies may include fewer than 10 or 15 subjects), may contain data collection methods that are specific to the device under study and often evaluate and provide therapies to very

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<sup>7</sup> As noted by Dr. Josh Makower, "The medical device innovation system is fragile and extremely sensitive to changes in the cost of innovation which is substantial." See IOM (Institute of Medicine) 2010. Public Health Effectiveness of the FDA 510(k) Clearance Process: Balancing Patient Safety and Innovation: Workshop Report. Washington, D.C.: The National Academies Press.

<sup>8</sup> The IoM has noted that "questions have been raised about the sufficiency of commonly used de-identification methodologies; consequently, additional protections may be needed." IOM (Institute of Medicine). 2014. *Discussion framework for clinical trial data sharing: Guiding principles, elements, and activities*. Washington, D.C.: The National Academies Press. p.10.

small or niche patient populations. As a result, it may be very difficult, if not impossible, to appropriately de-identify patients. Regulators should ensure that current de-identification methodologies are sufficient before significant efforts to share clinical trial data proceed. In addition, given the ever-increasing challenges related to cyber-security, regulators should ensure strong requirements and methods for maintaining de-identification and patient privacy protection are in place before any trial data sharing is initiated.

### **Device Regulatory Requirements Drive Sponsor Studies**

Proponents of data sharing have stated that sharing of patient level data will “enable independent confirmation of results” and will “make progress more efficient by making the most of what may be learned from each trial and by avoiding unwarranted repetition.”<sup>9</sup> These are commendable goals but they fail to recognize that independent confirmation of results by global health authorities already exists for regulated device product submissions. Global health authorities insist upon “repetition” by each company to demonstrate safety and effectiveness of their devices. In addition, few independent researchers are in a position to capitalize on the research findings they may discover in sponsor data via submission of product applications to regulators. To do so efficiently and effectively requires incorporation, and substantial funding and expertise associated with product filings.

### **Sharing De-Identified Patient Level Data Will Be Costly**

Significant costs will be associated with making de-identified patient level data available and for sponsors to be accessible to answer questions from qualified researchers that wish to conduct secondary analyses. The added costs (both financial and personnel-related) associated with sharing clinical trial data include, among others, the following:

1. Costs associated with de-identifying patient level data.
2. Costs associated with formatting the data so it is understandable to individuals who did not participate in the trial.
3. Costs associated with making personnel available to respond to questions from those seeking to use the data
4. Costs associated with removing human subjects' data from the data set that do not provide consent for their de-identified data to be shared beyond the original trial<sup>10</sup> and assessing whether the data sets are still valid after removal of this human subject data.
5. Costs associated with engaging a third party to accept and vet data request proposals, and to provide de-identified patient level data to meet the approved secondary analysis research proposal.
6. Costs associated with assuring researcher adherence to data sharing obligations.

Clinical trial costs are already expensive, with device trials typically costing millions of dollars per study. Requiring ongoing data sharing and the related maintenance costs described above would significantly increase study costs. The costs associated with a data sharing requirement will significantly increase the costs associated with the conduct of clinical trials which will have negative effects on sponsors' ability to innovate.

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<sup>9</sup> International Committee of Medical Journal Editors Editorial, 20 January 2016.

<sup>10</sup> As noted in the International Committee of Medical Journal Editor's (ICMJE's) *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*, “Patients have a right to privacy that should not be violated without informed consent.”

## PART II: CLINICAL TRIAL RESULTS COMMUNICATION AND DATA TRANSPARENCY PRINCIPLES

### 1. Make Existing FDA Summaries of Medical Device Clinical Trials More Readily Available

The Federal Food, Drug, and Cosmetic Act<sup>11</sup> and the Code of Federal Regulations<sup>12</sup> require medical device manufacturers to develop a Summary of Safety and Effectiveness Data (SSED) for all devices which receive premarket approval. Similarly, devices which receive 510(k) clearance are required to develop a 510(k) summary. The SSED includes a description of the clinical trial protocols, the inclusion/exclusion criteria, study population demographics, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation and complaints, data tabulations, and statistical analysis results. Although relatively few 510(k) devices require clinical trials, for those that do, the 510(k) summary must include a discussion of the clinical tests that were relied upon, describe how the results support a determination of substantial equivalence of safety and effectiveness, a description of the human subjects upon whom the device was tested, and a description of any adverse events or other complications or any other relevant information. The SSEDs and 510(k) summaries are currently posted on FDA's website. FDA should better publicize the existence of this information and make the summaries more prominent on FDA's website so they can be more easily accessed by the public.

### 2. Better Publicize ClinicalTrials.gov to Lay Audience

ClinicalTrials.gov was expressly developed to provide more transparency about clinical trials and to provide public access to information (both positive and negative) about publicly and privately supported clinical trials. The ClinicalTrials.gov results database includes information about the numbers of participants who started, completed, and dropped out of each period of a clinical study; demographic information such as age and gender, and study-specific measures; information for pre-specified primary and secondary outcomes, post hoc outcomes, and any appropriate statistical analyses; and information on all anticipated and unanticipated serious adverse events and anticipated and unanticipated other adverse events exceeding a specific frequency threshold. For each serious or other adverse event, it includes the adverse event term, affected organ system, number of participants at risk, and number of participants affected. Given patient needs for clinical trial information, we encourage NIH to better publicize ClinicalTrials.gov.

### 3. Expand Public Access to Journal Information

Medical journals should be encouraged to make their articles free and accessible to the general public, potentially after a period of exclusivity or within a defined timeframe after publication. Currently, accessing individual medical journal articles is prohibitively expensive for many members of the general public.

### 4. Development of Lay-Person Summaries for Clinical Trial Participants

In addition to clinical trial data that are made available via SSEDs, 510(k) summaries, ClinicalTrials.gov, and through peer-reviewed journals, sponsors of medical device clinical trials

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<sup>11</sup> See Section 520(h)(1) of the Federal Food, Drug and Cosmetic Act which requires a "detailed summary of information respecting the safety and effectiveness of a device ... shall be made available to the public...."

<sup>12</sup> See 21 CFR 814.44(d)(1) which requires "that a detailed summary of information respecting the safety and effectiveness of the devices, which was the basis for . . . approving the PMA. . . "be made available on the Internet...."

should develop lay-person summaries of clinical trial results. The lay-person summary for applicable trials as defined in ClinicalTrials.gov may be developed by sponsors and shared with clinical trial investigators who can make them available to the patients who participated in a clinical trial. In order to make ClinicalTrials.gov as helpful as possible for the lay audience – for which the database was largely created – we recommend that ClinicalTrials.gov include lay- person summaries of results of applicable clinical trials. Since such summaries may not be able to capture every detail about the trial important to a particular patient, patients should thoroughly review the ClinicalTrials.gov database information and the Summary of Safety and Effectiveness Data (SSED) and/or 510(k) summary and discuss any questions they have with their health care practitioner.

#### **5. Clinical Trials that are Wholly Financed by the National Institutes of Health Should Be Transparent and Share Clinical Trial Data**

AdvaMed strongly supports clinical trial transparency and data sharing for clinical trials that are wholly financed by U.S. taxpayers (consistent with human subject’s informed consents) such as those sponsored and fully funded by the National Institutes of Health (NIH).

#### **6. Determinations by Companies to Share Clinical Trial Patient Level Data**

Medical device clinical trial sponsors may at their discretion, on a study-by-study, product-by- product basis share clinical trial data with qualified scientific or medical researchers as determined by the sponsor or by an independent review board established by or working with the company. Sponsor determinations about whether particular clinical trial data can be shared must be consistent with the informed consent associated with a particular trial. Sponsors should give consideration to transparency at the outset of future trials balanced by the need to protect trade secret, confidential commercial information and the ability to continue to innovate on behalf of patients.

**For the reasons described above, sponsors may consider the following issues when determining whether to share their clinical trial data:**

- To ensure protection of confidential or proprietary data, discretionary determinations to share clinical trial data will generally only be made after sufficient time has elapsed for product clearance or approval and related publication(s).
- Requests for clinical trial data may require identification of the actual requestor as well as all individuals or organizations that will be involved in the research conducted using the requested clinical trial data to ensure they are qualified scientific or medical researchers or to provide financial support for the analysis.
- The scope of analysis performed on the released clinical trial data may be required to be limited to the analysis described in the initial request for release of the data.
- To ensure that the requested clinical trial data are appropriate to answer the particular research questions, the proposed study protocol and methodology may be required to be shared with the sponsor or with the independent review board.
- Similarly, the research analysis and final conclusions may be required to be shared with the sponsor or independent review board prior to its use, especially if the intent is to make the information public, in order to ensure that findings and analysis of the research proposal are not misleading or inaccurate. In addition, the sponsor may require full access to the data analysis and/or the raw data (including raw data from studies not conducted by the sponsor).
- Given the high costs associated with de-identifying data and preparing data for further analysis which was not planned, the qualified scientific or medical researchers that receive

- the sponsor's data may be required to contribute to the sponsors' costs associated with sharing the clinical trial data.
- Sponsors may require that no clinical trial data made available in response to a transparency request can be used in a competitor's 510(k) or PMA submission.