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International Committee of Medical Journal Editors (ICMJE)

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Dear Sir/Madam:

On behalf of AdvaMed, we are pleased to submit comments on the International Committee of Medical Journal Editors (ICMJE) proposal to share clinical trial data. AdvaMed is the world's largest trade association, representing manufacturers of medical devices, in vitro diagnostic ("IVD"), and health information systems. AdvaMed's member companies develop and produce the medical innovations that are transforming health care through earlier disease detection, less invasive medical procedures, and more effective treatments for diseases and conditions. AdvaMed has more than 400



member companies, ranging from the smallest to the largest medical technology innovators and companies. 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.

Description of ICMJE Proposal

The January 20, 2016 ICMJE editorial states that as a condition of consideration for publication of a clinical trial in a member journal, no later than six months after publication in a journal, authors would be required to share de-identified individual patient data (IPD) underlying clinical trial results and to make public plans for data sharing in registries that have a data-sharing plan element or another mechanism to do so. Data sharing would apply to those data needed to reproduce the article's findings, including metadata. Authors must provide de-identified IPD in a public repository or if not in a public repository, provide another mechanism by which data may be accessed. ICMJE proposes that this requirement will go into effect within one year after ICMJE considers feedback on its proposal and adopts data-sharing requirements.

ICMJE further states that the rights of investigators and trial sponsors must be protected by stating that sharing IPD trial data will not constitute prior publication, that authors of secondary analyses must attest that use of the shared data was in accordance with any terms required by the owner of the data, that appropriate credit must be given to those who generated the data, and that secondary analyses authors must explain how their analysis differs from previous analyses.

While we agree with and support the sponsor protections ICMJE describes, we are nonetheless, concerned the ICMJE proposal fails to fully consider the negative impact associated with the proposal and fails to consider current regulatory requirements for initial product approval and maintenance of registration and other likely unintended consequences associated with the proposal, as outlined below.

Device Industry 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 negative impact to medical device innovation. Small device companies account for the vast number of device innovations.¹ 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 R&D and clinical trial strategies, and may have a corresponding deleterious impact on patient access to innovative technologies.

Medical device manufacturers must submit clinical trial data to independent health authorities such as the Food and Drug Administration (FDA), the China Food and Drug Administration (CFDA), 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.

¹ 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.

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, patents² 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 or niche populations receive each generation of the device. Sometimes the first generation device is never marketed at all. As a result, device companies may have a small market and a relatively short time from which to recoup the resources spent on the 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.³ 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.

For these reasons, AdvaMed believes that sponsors may decide to share individual patient level clinical trial data on a study-by-study, product-by-product basis, 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. Further, 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.

We are concerned the ICMJE proposal will undercut device innovation. 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.

The ICMJE Proposals Fails to Consider Impacts on Patient Privacy and Human Subject Protection

The ICMJE proposal will also jeopardize privacy and patient protection of human subjects participating in medical device trials. Clinical trials for medical device studies (including feasibility studies) frequently have a small number of human subjects (feasibility studies may include fewer

² 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.

³ As noted by Dr. Josh Makower, “The medical device innovation ecosystem 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, DC: The National Academies Press.

than 10 or 15 subjects) and rely on data collection methods that are specific to the device under study. Devices also frequently treat niche or very small patient populations. As a result, it may be very difficult, if not impossible, to appropriately de-identify patients. The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome.⁴ This definition does not exclude feasibility or other trials conducted on small populations.

We would also note that in the context in which clinical trial data is intended to be shared beyond government regulators such as FDA, current anonymization or de-identification methodologies may be insufficient. The Institute of Medicine's (IoM) *Discussion Framework for Clinical Trial Data Sharing* noted that "questions have been raised about the sufficiency of commonly used de-identification methodologies; consequently, additional protections may be needed."⁵ We believe regulators and other stakeholders, including ICMJE, have a duty to 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, efforts should be made to ensure strong requirements and methods for *maintaining* de-identification and patient privacy protection are in place before any trial data sharing is initiated. Given the many questions surrounding the strength of current de-identification methodologies, we believe it may be premature for ICMJE to mandate this requirement.

The ICMJE proposal also does not account for privacy laws and informed consent requirements. Given the lengthy timelines associated with the conduct of clinical trials and clearance or approval of devices, it is not unlikely that informed consents associated with clinical trials for which sponsors may seek publication in an ICMJE-affiliated journal, would fail to allow for disclosure of patient level data to third parties or fail to allow for its inclusion in a publicly accessible database. Additionally, privacy laws from the jurisdiction from which the data were obtained or the participating institution will be applicable and may prevent the disclosure of patient level data. Privacy laws (at the country, state or institutional level) may prevent the disclosure of individual patient level data or may limit its release only for regulatory purposes. Elimination of large amounts of individual patient level data for these reasons may invalidate the data sets.

The ICMJE Proposal Fails to Consider Costs Associated with the New Requirement

We believe the ICMJE proposal fails to acknowledge or take into consideration the significant costs that will be associated with making de-identified patient level data available and being accessible to answer questions from investigators conducting secondary analyses. The proposal does not detail how the costs of preparing the data supporting the secondary investigators will be borne and suggests data could be housed in a public repository. With respect to the latter, this implies that sponsors and investigators of the original trial will bear the full costs associated with housing the data in a public repository as we are unaware of any mechanisms that would allow cost-sharing with government-run databanks.

⁴ *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*, p. 12.

⁵ 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.

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 didn't 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 available in a public database 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 IPD to meet the approved secondary analysis research proposal.
6. Costs with sponsor monitoring of the worldwide web, lay and professional media publications, social media sites, and peer-reviewed and non-peer reviewed publications for invalid research relying on IPD housed in public repositories.
7. Costs associated with assuring adherence to IPD sharing obligations.

We would note with respect to item four, if the number of subjects who do not provide consent for their data to be included in a public database grows, research relying on publicly available data sets may not result in valid conclusions.⁶ With respect to item five, we would also note that it appears that ICMJE expects that research data housed in public repositories will be available for anyone's use rather than limited to research use by qualified scientific or medical researchers. Invalid research conducted by potentially unqualified researchers could be made public and result in public confusion or panic, and further mistrust of the research enterprise and product approval processes.

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 would significantly increase study costs. The costs associated with data sharing requirements may prevent or inhibit sponsors and investigators from publishing important research and/or reduce submissions for publication in ICMJE affiliated journals, inhibiting the free-flow of important health care information. Importantly, the ICMJE proposal will significantly increase the costs associated with the conduct of clinical trials which will have negative effects on sponsors' ability to innovate.

The ICMJE Proposal Violates Confidential, Commercial, Trade Secret Device Information

The ICMJE proposal may also violate confidential, commercial, trade secret device information. The study protocol and related clinical trial data and metadata are considered confidential, commercial trade secret information which is also subject to copyright protections. Studies are often performed to evaluate new product designs or to make changes to designs. The results of these studies contribute to patent filings.

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

⁶ As noted in 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."

that may not be captured in patent filings.⁷ Making the protocols available for third party use would be a public disclosure that could jeopardize patent protections. 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 markets⁸.

Clinical trial data also potentially qualifies as copyrighted material. If so, mandatory disclosure for the purposes outlined in the editorial could violate copyright protections and would effectively serve as a nonexclusive royalty-free license to any third party user, including sponsor competitors.

In company-sponsored medical device trials, the clinical trial data, including metadata, as well as the protocols and test methodologies that produced them, are typically owned by the companies that support the medical device research. 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 analysis tools and methods. Protection from disclosure of these proprietary data falls 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.

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.⁹

Disclosure of de-identified patient level data and related protocol and metadata would divulge commercial product strategies and detailed results to competitors and provide them with an unfair advantage to develop and market products. In this arrangement, competitors benefit from the time and money spent by the first party to run a clinical trial on a new device/technology at the first party's loss.

Lastly, a sponsor's de-identified data set has tremendous monetary value as these may be aggregated for meta-analysis for new product claims, used to satisfy post market regulatory requirements, and provide other competitive advantages. Making this data public so competitors and others may freely

⁷ Protocol for these purposes is defined as elements above and beyond those that are required to comply with ClinicalTrials.gov requirements.

⁸ Disclosure before a patent application is filed is immediately fatal to patent protection in some countries including the European Patent Office.

⁹ 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/premarketnotifications/premarketnotification510k/default.htm#se>

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.

The Necessary Infrastructure Is Not in Place to Accommodate ICMJE's Proposal

The ICMJE editorial references the data-sharing plan elements outlined in the Institute of Medicine's (IoM) 2015 report implying that the IoM has endorsed sharing of clinical trial data immediately. In fact, the IOM Report Recommendation 4 discusses the need to "convene a multi-stakeholder body with global research and broad representation to address, in an ongoing process, the key infrastructure, technological, sustainability and workforce challenges associated with the sharing of clinical trial data." The IoM recommendation recognizes the current challenges associated with IPD sharing, acknowledging that there is a cost and an infrastructure required to create a sustainable system to accommodate a significant number of study sponsors to share IPD. However, this necessary infrastructure is not in place. If ICMJE requires IPD sharing prior to the creation of an appropriate infrastructure to support it, it could lead to unintended consequences including preventing publication of medical research and disclosure of confidential, private patient information. Without first establishing an infrastructure, such as independent review boards designed to recognize and manage proprietary elements and patient privacy and confidentiality, as well as to determine whether data requests are made by qualified researchers, the ICMJE proposal will have a deleterious effect on innovation.

ICMJE has also failed to describe how it will enforce data sharing policies. Interpretation of data in device studies is often challenging, particularly when the data is focused on the detailed aspects of the procedure or the device function. This is a key differentiator between device studies and pharmacologic studies. Misinterpretation of the data without direct involvement of the original study sponsor and/or investigators is likely to be common. As this would be highly damaging to the accurate interpretation of therapy outcomes among the journals' readership, infrastructure must first be in place to assist and support secondary researchers and review their work.

Related infrastructure issues that should be addressed prior to requiring sharing of IPD include: ensuring that there are strong methodologies to guarantee de-identification of patient level data, protection measures against misuse of de-identified patient level data, measures to protect against secondary analyses that were conducted without appropriate due diligence with the data owner, protection against manipulation of data for fraudulent or illicit purposes, and measures to protect against usurping device manufacturer's intellectual property by criminals or other nefarious elements.

The ICMJE Proposal Does Not Consider Existing Regulatory Requirements

ICMJE states "authors of secondary analyses must explain completely how theirs differs from previous analysis." However, ICMJE does not acknowledge what this means for regulated agencies, such as FDA where such studies may have been used to assess the safety and effectiveness of a medical device. For example, what if secondary analyses raise questions about the safety and effectiveness of an already approved product? ICMJE also states that sharing de-identified individual patient data will "enable independent confirmation of results, an essential tenet of the scientific process." This fails to recognize that independent confirmation of results already exists for

regulated device product submissions. ICMJE also maintains that “done well, sharing clinical trial data should also make progress more efficient by making the most of what may be learned from each trial and by avoiding unwarranted repetition.” While this is a commendable goal, it fails to recognize that global health authorities insist upon “repetition” to demonstrate safety and effectiveness of medical products and few independent researchers are in a position to capitalize on their research findings via submission of product applications to regulators. To do so efficiently and effectively requires incorporation, and substantial funding and expertise associated with product filings.

ICMJE Journals Should Contribute More to the Research Enterprise

We understand that the ICMJE proposal is motivated in part by a desire for greater transparency and a desire to better communicate and understand trial results and related data. ICMJE has called for greater disclosure of trial results and data, however, ICMJE could itself greatly assist the research enterprise by making journal articles free and accessible to the general public, clinicians and researchers, potentially after a short period of exclusivity or within a short, defined timeframe after publication.

In closing, thank you for this opportunity to share our concerns about the ICMJE proposal to require clinical trial data sharing.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs