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RE: Proposed Decision Memo for Transcatheter Aortic Valve Replacement (TAVR) (CAG-00430N)

Dear Dr. Jacques and Dr. Menikoff:

These comments from Public Citizen's Health Research Group are being submitted in response to the Centers for Medicare & Medicaid Services' (CMS) February 2, 2012 proposed decision memo referenced above:

(1) While we support the collection of data on the safety and effectiveness of TAVR for the treatment of severe symptomatic aortic valve stenosis, we object to the proposed requirement for Medicare beneficiaries to participate in a research registry as one of the conditions of coverage for TAVR because such a policy would fail to comply with the requirements for obtaining informed consent for research under the Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 C.F.R. § 46.116. In particular, we note the following:

(a) The decision memo fails to stipulate that the informed consent of the subjects for participation in the registry research will be obtained in accordance with these HHS regulations;
(b) By allowing coverage for TAVR only for Medicare beneficiaries who agree to enroll in the research registry, the informed consent of the subjects would not be obtained under circumstances that minimize the possibility of coercion or undue influence; and

(c) Medicare beneficiaries who refuse to participate in the research registry will be penalized (i.e., they will be denied coverage for TAVR treatment of severe symptomatic aortic valve stenosis with a device approved by the Food and Drug Administration (FDA) for that use), in direct violation of the requirements of HHS regulations at 45 C.F.R. § 46.116(a)(8).

(2) We urge CMS and the Office for Human Research Protections (OHRP) to work together to develop an alternative approach for implementing the research registry for TAVR under which:

(a) The voluntary informed consent of the subjects of the proposed research registry is obtained in accordance with all requirements of the HHS regulations at 45 C.F.R. § 46.116; and
(b) The few Medicare beneficiaries who may decline to consent to such research are not penalized by being denied coverage by CMS for their TAVR procedures.

I. FDA status of TAVR medical devices

On November 2, 2011, the FDA approved the premarket approval application for the Edwards SAPIEN Transcatheter Heart Valve. This FDA-approved device is indicated "for transfemoral [via the femoral artery in the leg] delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of aortic stenosis."[1]

II. CMS's proposed national coverage decision for TAVR

In response to a request from the Society of Thoracic Surgeons and the American College of Cardiology, CMS initiated a national coverage analysis for TAVR.[2] CMS proposes that TAVR would be covered only for the treatment of severe symptomatic aortic valve stenosis and only when five conditions are all satisfied. The first condition is that the procedure is furnished for an FDA-approved indication, with a complete valve and implantation system that has received FDA premarket approval. TAVR treatment with the Edwards SAPIEN Transcatheter Heart Valve would satisfy this condition. The second through fourth conditions, which specify criteria for (a) the pre-procedure clinical evaluation of the patients, (b) the qualifications for the treating medical facility, and (c) the qualifications and experience of the treating physicians performing the procedure, appear to be appropriate.

The fifth condition, which we find objectionable, is as follows:

> The patient is enrolled in, and the treating physician team is participating in a prospective national registry that consecutively enrolls TAVR patients and tracks at least the following outcomes at the patient data level for a period of at least five years from the time of the TAVR procedure.

i. Major stroke;
ii. All cause mortality;
iii. Minor stroke/[transient ischemic attack (TIA)];
iv. Major vascular events;
v. Acute kidney injury;
vi. Repeat aortic valve procedures;
vii. Quality of Life measures.

The registry must be designed to permit identification and analysis of patient, practitioner and facility level factors that predict patient risk for these outcomes. The patient must have, after being informed of the reported risks of TAVR and reasonable alternative management strategies, given informed consent.

III. The proposed national registry involves research with human subjects and does not qualify for any exemption

HHS regulations at 45 C.F.R. § 46.102(d) define *research* as follows:

> A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

The proposed prospective national registry for Medicare beneficiaries undergoing TAVR clearly meets this definition. Under the CMS coverage with evidence development policy, this registry is primarily intended to develop generalizable knowledge about the risks, benefits, and quality of life impact of TAVR in the Medicare beneficiary population. Such a registry also falls within the scope of what would be considered research as described in the handbook issued by the HHS Agency for Healthcare Quality and Research (AHRQ) entitled, "Registries for Evaluating Patient Outcomes: A User's Guide."[3]

HHS regulations at 45 C.F.R. § 46.102(f) define a *human subject* as follows:

> A living individual about whom an investigator (whether professional or student) conducting research obtains
>
> (1) Data through intervention or interaction with the individual, or
> (2) Identifiable private information.
>
> … *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may be readily ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Again, the research registry proposed under the CMS coverage decision will involve human subjects as defined by the HHS regulations because the information is private (medical information) and will have to be recorded in a manner that allows the identity of the subjects to be readily ascertained by the investigators (i.e., the registry data will have to be recorded in a manner that allows subjects to be identified so that serially collected medical data for each patient undergoing TAVR can be linked in the registry).

Finally, this human subjects research does not qualify for any exemption under HHS regulations at 45 C.F.R. § 46.101(i). In particular, the registry does not qualify for the exemption at 45 C.F.R. § 46.101(i)(4) – research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subject – because the data and records for the proposed research registry would not be existing at the time the research is proposed.

IV. Informed consent for subjects enrolled in the research registry must be obtained in accordance with the requirements of 45 C.F.R. § 46.116

For non-exempt human subjects research, HHS regulations at 45 C.F.R. § 46.116 require the following:

> Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and **that minimize the possibility of coercion or undue influence**… [Emphasis added]

Furthermore, HHS regulations at 45 C.F.R. § 46.116(a)(8) requires that the following information be provided to each subject when consent is being sought:

> A statement that participation is voluntary, **refusal to participate will involve no penalty** or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subjects is otherwise entitled. [Emphasis added]

As noted above, in describing the proposed requirement for Medicare beneficiaries to enroll in a research registry as a condition for obtain coverage for TAVR, CMS stated that the "patient must have, after being informed of the reported risks of TAVR and reasonable alternative management strategies, given informed consent."[4] We presume this statement is referring to clinical informed consent for undergoing the TAVR procedure itself, and not for participation in the mandated research registry. The need to obtain informed consent for the research registry in accordance with the requirements

HHS regulations at 45 C.F.R. § 46.116 is not specifically mentioned in this part of the proposed coverage decision.

More importantly, the proposed coverage decision would be incompatible with the requirements of 45 C.F.R. § 116 noted above for two reasons. First, by allowing coverage for TAVR only for Medicare beneficiaries who agree to enroll in the research registry, the informed consent of the subjects would not be obtained under circumstances that minimize the possibility of coercion or undue influence. Second, Medicare beneficiaries who refuse to participate in the research registry will be penalized (i.e., they will be denied coverage for TAVR treatment of severe symptomatic aortic valve stenosis with a device approved by the FDA for that use), in direct violation of the requirements of HHS regulations at 45 C.F.R. § 46.116(a)(8).

The importance of obtaining the informed consent of subjects enrolled in research registries was highlighted by AHRQ in its handbook on registries.[5] It is important that CMS follows HHS's own guidance on research registries.

Although the HHS regulations at 45 C.F.R. § 46.116(d) provide an avenue for institutional review boards (IRB) to waive the requirements for obtaining informed consent, the third criteria for such a waiver – the research could not practicably be carried out without the waiver – would not be satisfied for the proposed research registry. The informed consent of the prospective subjects for enrollment in the registry could be easily obtained at the time they present for their TAVR procedure. Furthermore, it is highly likely that nearly all Medicare beneficiaries eligible for treatment with TAVR with the Edwards SAPIEN Transcatheter Heart Valve (or any future TAVR devices approved under a PMA by the FDA) would agree to participate in the research registry; thus, loss of results from the few patients who decline to volunteer to participate in the research registry is unlikely to lead to significant bias that would adversely affect the study. Therefore, a waiver of the informed consent requirements by an IRB would not be appropriate for the proposed research registry.

V. Proposed solution

We urge CMS and OHRP to work together to develop an alternative approach for implementing the research registry for TAVR under which (a) the voluntary informed consent of the subjects of the proposed research registry for TAVR is obtained in accordance with all requirements of the HHS regulations at 45 C.F.R. § 46.116; and (b) the few Medicare beneficiaries who may decline to consent to such research are not penalized by being denied coverage by CMS for their TAVR procedures.

This could be accomplished by revising the fifth condition for coverage of TAVR as follows (see new language in bold):

> The patient **is asked to voluntarily enroll** in, and the treating physician team is participating in a prospective national registry that consecutively enrolls TAVR

patients and tracks at least the following outcomes at the patient data level for a period of at least five years from the time of the TAVR procedure.

i. Major stroke;
ii. All cause mortality;
iii. Minor stroke/TIA;
iv. Major vascular events;
v. Acute kidney injury;
vi. Repeat aortic valve procedures;
vii. Quality of Life measures.

The registry must be designed to permit identification and analysis of patient, practitioner and facility level factors that predict patient risk for these outcomes. The patient must have, after being informed of the reported risks of TAVR and reasonable alternative management strategies, given informed consent for the clinical procedure. **The registry must be conducted in accordance with the requirement of the HHS regulations for the protection of human subjects at 45 C.F.R. part 46, including the requirements for obtaining informed consent of the subjects at 45 C.F.R. § 46.116**.

Thank you for the opportunity to comment on the proposed national coverage decision memo.

Sincerely,

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Public Citizen's Health Research Group

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Director
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[1] Foreman C. Letter from the Food and Drug Administration's Center for Devices and Radiological Health to Edwards Science LLC approving the premarket approval application for the Edwards SAPIEN Transcatheter Heart Valve. November 2, 2011. Available at http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100041a.pdf. Accessed February 23, 2012.
[2] Centers for Medicare & Medicaid Services. Proposed decision memo for Transcatheter aortic valve replacement (TAVR) (CAG-00430N). Available at http://www.cms.gov/medicare-coverage-

database/details/nca-proposed-decision-memo.aspx?NCAId=257&ver=5&NcaName=Transcatheter+Aortic+Valve+Replacement+(TAVR)&bc=AAAAAAAIAAA&. Accessed February 23, 2012.

[3] Agency for Healthcare Research and Quality. Registries for Evaluating Patient Outcomes: A User's Guide (2nd Edition). Available at http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf. Accessed February 23, 2012.

[4] Centers for Medicare & Medicaid Services. Proposed decision memo for Transcatheter aortic valve replacement (TAVR) (CAG-00430N). Available at http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=257&ver=5&NcaName=Transcatheter+Aortic+Valve+Replacement+(TAVR)&bc=AAAAAAAIAAA&. Accessed February 23, 2012.

[5] Agency for Healthcare Research and Quality. Registries for Evaluating Patient Outcomes: A User's Guide (2nd Edition). Available at http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf. Accessed February 23, 2012.