



Louis Jacques, MD
Director, Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Blvd.
Baltimore, MD 21244

APR 27 2012

Dear Dr. Jacques,

The Agency for Healthcare Research and Quality understands that the Centers for Medicare & Medicaid Services (CMS) will cover transcatheter aortic valve replacement (TAVR) only when these procedures are performed under Coverage with Evidence Development (CED) and when the following specific conditions are met:

- In the treatment of symptomatic aortic valve stenosis for indications approved by the FDA, enrollment of the patient and participation of the treating physician team in a prospective national registry that consecutively enrolls TAVR patients and tracks at least the following outcomes on a patient level for at least one year from the time of the TAVR procedure.
 - i. Stroke;
 - ii. All cause mortality;
 - iii. Transient Ischemic Attacks (TIAs);
 - iv. Major vascular events;
 - v. Acute kidney injury;
 - vi. Repeat aortic valve procedures;
 - vii. Quality of Life (QOL).

The registry should collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary):

- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
- How do outcomes and adverse events in subpopulations compare to patients in the pivotal clinical studies?
- What is the long term (≥ 5 year) durability of the device?
- What are the long term (≥ 5 year) outcomes and adverse events?
- How do the demographics of registry patients compare to the pivotal studies?

The registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes.

- For indications not approved by the FDA, clinical studies must fulfill criteria a-m below and as a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-TAVR (minimum of 1 year), but must also address at least one of the following questions:
 - What is the incidence of stroke?
 - What is the rate of all cause mortality?
 - What is the incidence of transient ischemic attacks (TIAs)?
 - What is the incidence of major vascular events?
 - What is the incidence of acute kidney injury?
 - What is the incidence of repeat aortic valve procedures?

We understand that CMS is requiring and will assume an oversight role to assure that covered studies meet the following standards:

- a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- c. The research study does not unjustifiably duplicate existing studies.
- d. The research study design is appropriate to answer the research question being asked in the study.
- e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR parts 50 and 56. In particular, the informed consent includes a straightforward explanation of the reported increased risks of stroke and vascular complications that have been published for TAVR.
- g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see <http://www.icmje.org>).
- h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare coverage requirements.
- i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
- k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the

International Committee of Medical Journal Editors (<http://www.icmje.org>). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

- l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Specifically, for the registry of patients that meet the indications approved by the FDA, AHRQ understands that CMS will undertake a study validating the ability to measure durability, outcomes and adverse events of the device using Medicare claims data or other data sources that will be available to CMS. Further, CMS will assess the efficiency of one-year follow up in the registry at 18 months after initiation of the registry. CMS will present the results of the validation and efficiency study to AHRQ within 21 months after initiation of the registry and based on the results, CMS will re-evaluate whether the research design is appropriate to answer the research question (standard d above).

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research areas of interest.

Sincerely,

A handwritten signature in black ink, appearing to read "J. Slutsky". The signature is fluid and cursive, with a large initial "J" and a long, sweeping underline.

Jean R. Slutsky

Director, Center for Outcomes and Evidence