FDA perspective on first ICVR prospective project: Rupture AAA Treatment Outcome by EVAR vs Open Repair

-Potential for labeling modification?

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Disclosure Statement

I, Jose Pablo Morales, do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

Objectives

- Outline current indications for use of devices approved for the treatment of aortic abdominal aneurysm (AAA) in the United States (US)
- Describe labeling modifications
  - Removal of warning/precautions
  - Expansion (refinement) of indications for use
    - General and Specific Indications
- Outline potential clinical study design and sample size calculations
- Group discussion

Current indications for use of AAA endovascular grafts in the US

- There are currently 5 device manufactures with AAA devices approved in the US.
  - Total of 12 different devices

- Indication for use statement example:

"The (device name) is indicated for the endovascular treatment of infrarenal abdominal aortic (or aorto-iliac) aneurysms in patients with the following characteristics:

- Adequate iliac/femoral access that is compatible with vascular access techniques, devices and/or accessories
- Proximal neck length of ……
- Infrarenal neck angulation of ……
- Distal fixation length of ……
- Aortic neck diameters with a range of XX to YY mm
- Iliac diameters with a range of XX to YY mm
- Morphology suitable for aneurysm repair"

As per the approved indication for use language

-There is no differentiation about the presentation of the AAA

-symptomatic vs asymptomatic

-rupture vs intact

-elective vs urgent/emergent

- Therefore, treatment of rupture AAA could be considered included in the indication for use ("on-label").

- Caveat: Cook AUI device has "ruptured AAA" in the indications for use statement.

However, labeling of all bifurcated AAA devices includes

Warnings and Precautions

"The safety and effectiveness of the (device name) has not been evaluated in some patient populations"

Examples of language included in some IFUs:

- Patients presenting with **ruptured aneurysms**, aneurysms pending rupture or require other emergent aorta or aneurysm treatment
- leaking: pending rupture or **ruptured aneurysms**
- require emergent aneurysm treatment, eg, trauma **or rupture**
- Have traumatic aortic injury, **ruptured** aneurysms, aneurysms pending rupture or require other emergent aorta/ aneurysm treatment;

Previous Regulatory Experience Removing these type of Warnings/Precautions

- Medtronic had removed/modified the precautions in the instructions for use of the Medtronic CoreValve system in patients with end stage renal disease (ESRD) and low gradient low output (LGLO) aortic stenosis.
- Based on registry data embedded in the pivotal trial

Device	MEDTRONIC COREVALVE AND COREVALVE EVOLUT R SYSTEMS
Classification Name	Aortic Valve, Prosthesis, Percutaneously Delivered
Generic Name	Aortic Valve, Prosthesis, Percutaneously Delivered
Applicant	MEDTRONIC COREVALVE LLC 3576 Unocal Place Santa Rosa, CA 95403
PMA Number	P130021
Supplement Number	S016
Date Received	07/08/2015
Decision Date	11/10/2015
Product Code	NPT [Registered Establishments With NPT]
Advisory Committee	Cardiovascular
Clinical Trials	NCT01240902
Supplement Type	Normal 180 Day Track
Supplement Reason	Labeling Change - Indications/Instructions/Shelf Life/Tradename
Expedited Review Granted?	No
Combination Product	No

Approval Order Statement

APPROVAL FOR MODIFYING THE LABELING TO REMOVE THE PRECAUTIONS REGARDING PATIENTS WITH LOW FLOW/LOW GRADIENT AND END-STAGE RENAL DISEASE.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P130021S016

With these considerations in mind

- There appears to be value for manufacturers to remove warnings/precautions
  - Adequate promotion
  - Proper physician training
  - Mitigate potential litigation

- There appears to be value for FDA
  - update the label with clinical data so that physicians are well informed of outcomes when choosing a treatment strategy for their patients

Potential Study Design under ICVR

- Prospective, multicenter, international, single-arm, clinical study with performance goal (PG) derived from open surgical literature on ruptured AAA.
- Primary Endpoint
  - In hospital/30 day mortality
- Assuming Power= 80%, type I error rate = 5% one-sided Exact test

Hypothesis and sample size

- H_0: $p \geq PG$ vs. H_A: $p < PG$

PG (failure rate)	Estimated rate	N
0.40	0.30	142
	0.25	61

Caveats

- These estimations are just an example for discussion and have not been agreed upon by FDA for obtaining a labeling change.

- For example, due to the technological differences between devices among manufacturers, it is not clear at this time if it would be acceptable to pool the data from different devices, so a minimum dataset per individual device may need to be incorporated.

Caveats

- If a manufacturer wanted to come to FDA independently and request removal of the warnings/precautions and/or add a specific rupture AAA indication, the manufacturer could also propose to use their own study design, sample size calculations and the respective justifications.

Thank You