# FDA Perspectives: PFO Closure for Stroke

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# Disclosure Statement of Financial Interest

I, Ashley Boam, 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.

# PFO and stroke

- An estimated 30-40% of ischemic strokes (in patients < 55 yrs) have no identifiable cause, i.e., are “cryptogenic”
- Prevalence of a PFO is higher in individuals with cryptogenic stroke than in individuals with a stroke of known cause
- Unclear if other covariates may account for such findings (i.e., association vs. causation)
- Mechanism is plausible, but is PFO a risk factor for stroke? **Proof of concept still missing**
  - relationship between stroke and PFO remains uncertain
  - data are wide-ranging and often contradictory

# Current Therapies

- Medical therapy – ACCP and AHA/ASA guidelines
  - antiplatelet
  - anticoagulation
- Surgical therapy
  - high defect closure rates
  - debated efficacy in reducing recurrent stroke and TIA given variable recurrence rates
- Percutaneous closure
  - effectiveness not established compared to medical therapy; procedure/devices not without risk

# Clinical Trial Design

- Prospective, multi-center RCT
- “Best medical therapy” vs “device + best medical therapy”
- Composite primary effectiveness endpoint at 2 years (due to event rates):
  - Periprocedural all-cause death + late neurological death + stroke + TIA
- Recommend superiority hypothesis

# Clinical Trial Design

- Safety endpoint: device/procedure-related adverse events (bleeding, tamponade, embolization, etc)
  - judged in overall risk/benefit assessment
- Sample size calculation very sensitive to initial assumptions because endpoint event rate is small (<10%)
  - consider using adaptive trial design
  - 1:1 or other randomization (2:1) acceptable
- FDA open to US/OUS pivotal trial

# The Long Road…

- HDEs approved for patients with recurrent stroke on medical therapy
- Enrollment problems in RCTs for primary treatment indication
  - Off-label use of PMA-approved devices
  - Physicians and patients “convinced” of device effectiveness
- HDE population >> 4000 US/yr; HDEs withdrawn
- Advisory Panel meeting held February 2007
  - RCTs still appropriate trial design
- Enrollment issues not eliminated, but two trials appear to be nearing completion
- Ultimate goal – if proof of concept established, future trials may be more straightforward

# Thank you!

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