FDA perspective: the use of imaging in clinical trials

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Focus on phase 3 trials of therapeutic products

- **Why use imaging in a clinical trial**
- **Image acquisition considerations**
- **Image interpretation considerations**
- **Regulatory aspects**
- **Summary: key points**

Guidance for Industry

Standards for Clinical Trial Imaging Endpoints

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.
For questions regarding this draft document contact (CDER) Dr. Rafel Rieves at 301-796-2050 or (CBER) Office of Communication, Outreach, and Development at 301-827-1800 or 800-835-4709.

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AMERICAN SOCIETY OF ECHOCARDIOGRAPHY REPORT

American Society of Echocardiography Recommendations for Use of Echocardiography in Clinical Trials

A Report from the American Society of Echocardiography's Guidelines and Standards Committee and The Task Force on Echocardiography in Clinical Trials

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ASE EXPERT CONSENSUS STATEMENT

Echocardiographic Imaging in Clinical Trials: American Society of Echocardiography Standards for Echocardiography Core Laboratories

Endorsed by the American College of Cardiology Foundation

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Why use imaging in phase 3 clinical trials?

- **Eligibility**
  - ***e.g. identify patients with defined lesions***
- **Safety**
  - ***assess cardiac toxicity using LV function, valvulopathy***

Why use imaging in phase 3 clinical trials?

- **Primary efficacy endpoint**
  - ***Composite including echo assessments***
- **Secondary efficacy endpoints**
  - ***Functional and anatomic measurements e.g. LVEF, LV mass, vascular intima-media thickness***

Considerations for drug approval

- **"Substantial evidence"**
- **Adequate and well-controlled clinical trials**
- **Risk:benefit considerations**

Image acquisition

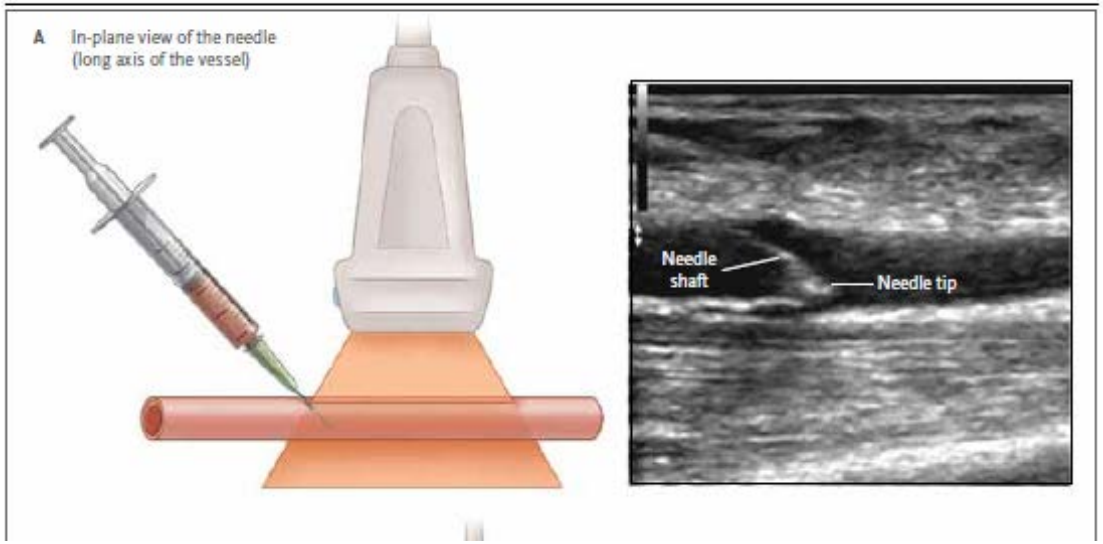
Standardization!

Imaging standards in phase 3 trials

- **Medical practice imaging standard**
  - ***Acquisition/interpretation methods do not exceed those used in medical practice***
    - ***eligibility, safety***
- **Clinical trial imaging standard**
  - ***Acquisition/interpretation methods address items listed in guidance***
    - ***efficacy endpoints, sometimes safety***

If imaging is used as an efficacy endpoint:

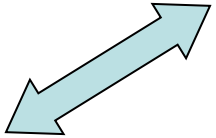
- Consult FDA review division
- Consider endpoint meaningfulness



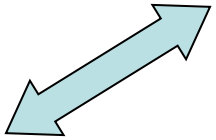
N Engl J Med 2011;364:749-57

Endpoint meaningfulness continuum

Self-evident, established benefit



Reasonably likely to predict benefit



Bioactivity, pharmacodynamics

Regulatory standard

- **Applications for new drugs must contain:**

  full reports of investigations to show whether such drug is safe and effective in use

- **Effectiveness must be based on:**

  substantial evidence from adequate and well-controlled investigations

Key points

- **Adequate and well-controlled investigations**
- **Methods of assessment of response well-defined and reliable**
- **Imaging standardization essential**
- **In choosing an imaging endpoint, consider meaningfulness continuum**

bioactivity  ***established benefit***