

# Exploring Novel Clinical Trial Designs for Gene Therapies

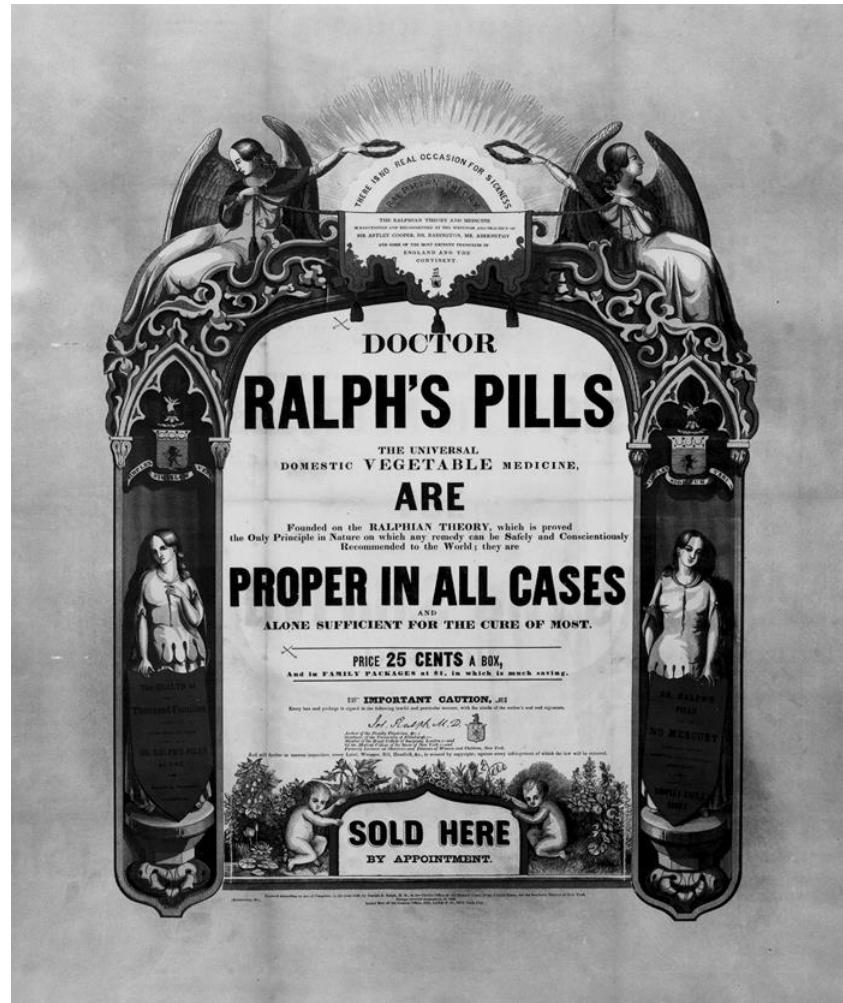
## Session III: Developing Endpoints for Clinical Trials with Gene Therapies

National Academies of Sciences, Engineering, and Medicine  
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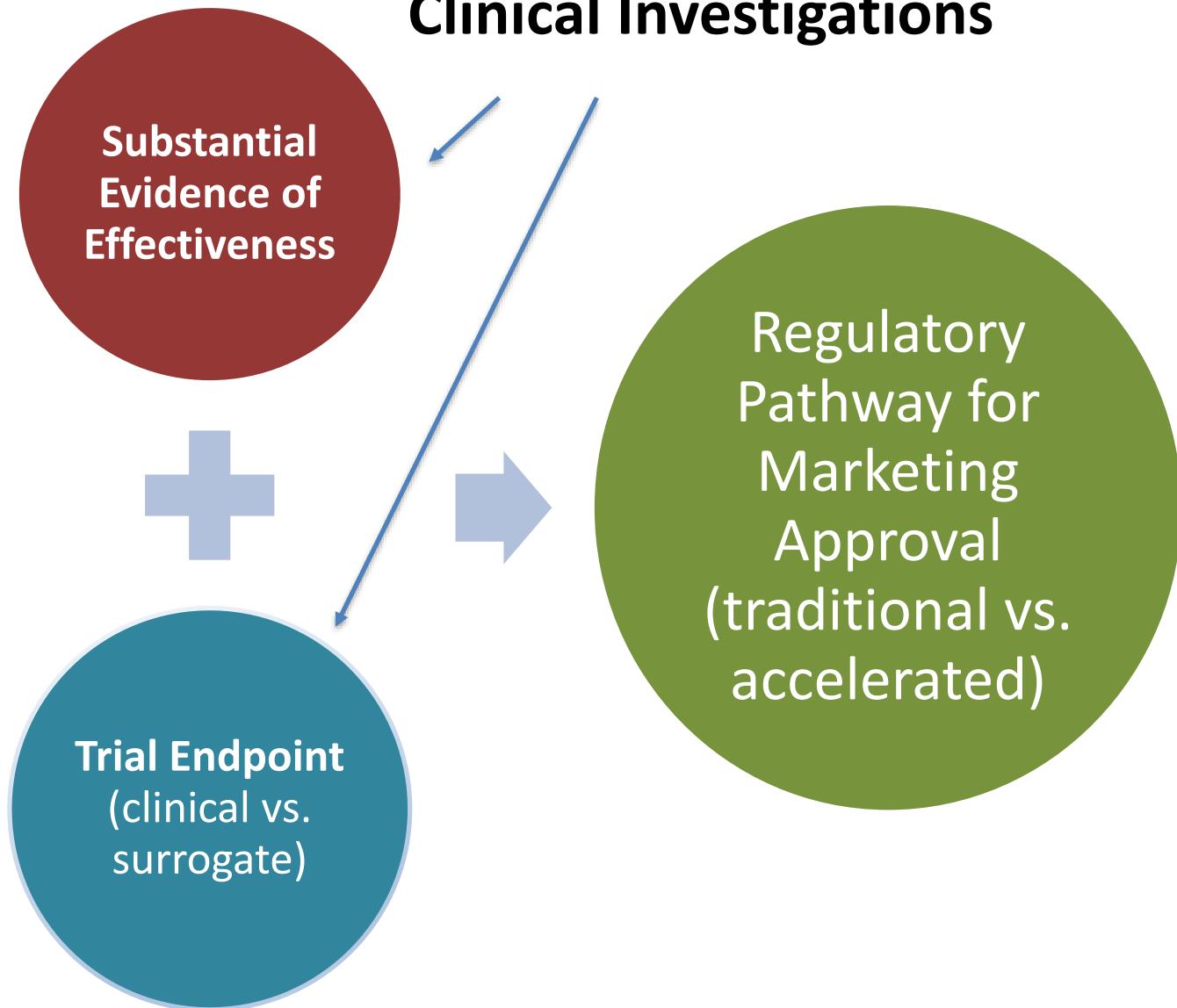
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# Medical Product Label circa 1890

## FDA's Slide Collection



# Clinical Investigations



# Trial Endpoints

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- Clinical outcomes as trial endpoints directly measure clinical benefit (i.e., how a person feels, functions, or survives)
- Surrogate endpoints:
  - Validated
  - Reasonably likely
  - Candidate

**BEST (Biomarkers, EndpointS, and other Tools) FDA-NIH Biomarker Working Group** <https://www.ncbi.nlm.nih.gov/books/NBK326791/>

# Surrogate Endpoints

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**validated** surrogate endpoint is supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit

**reasonably likely** surrogate endpoint is supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint

# Approval Pathways and Trial Endpoints

## Traditional Approval

- **Clinical** endpoints that directly measure clinical benefit (i.e. how a person feels, functions, or survives)
- **Validated** surrogate endpoints that are known to predict clinical benefit

## Accelerated Approval\*

- **Surrogate** endpoints that **reasonably likely** predict clinical benefit
- **Intermediate** (early time) clinical endpoints that reasonably likely predict clinical benefit as effect on irreversible morbidity and mortality

**\*Subject to post-marketing requirements to verify and describe the clinical benefit**

Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

<https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf>

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Dec 2018

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf>

# Clinical and Surrogate Endpoints in Regulatory Practice

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- **Surrogate Endpoints** used in traditional and accelerated drug approval or biologic licensure  
<https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure>
- Pilot Compendium of **Clinical Outcome Assessments** used as trial endpoints in development programs of approved products  
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm459231.htm>

# Choosing Endpoints for Clinical Trials with Gene Therapies (GT): Points to Consider

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- Long-term or potentially irreversible effects of GT treatment
  - Leave little room for uncertainty about endpoint performance
  - Require increased vigilance in validity and accuracy of endpoint measurement
- Mechanistically agnostic endpoints reflective of common pathogenetic pathways may not be sufficiently sensitive in GT trials
  - Increased availability of genetic screening, early diagnosis, advanced laboratory testing shifted the demand toward surrogate and clinical endpoints reflective of early disease manifestations
  - Identification of genetic defects associated with not well-characterized phenotypes increased the need for novel clinical endpoints
- Opportunity to identify and validate surrogate endpoints along the pathway of gene transcription, transgene protein synthesis & levels, functional activity, and clearance

# Session III: Developing Endpoints for Clinical Trials with Gene Therapies

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## Speakers

- Dwight Koeberl, M.D., Ph.D.
- Albert Maguire, M.D.
- Julie Kanter, M.D.

## Moderator

- Larissa Lapteva, M.D., M.H.S., M.B.A

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