

Clinical Development of Gene Therapy Products

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Learning Objectives

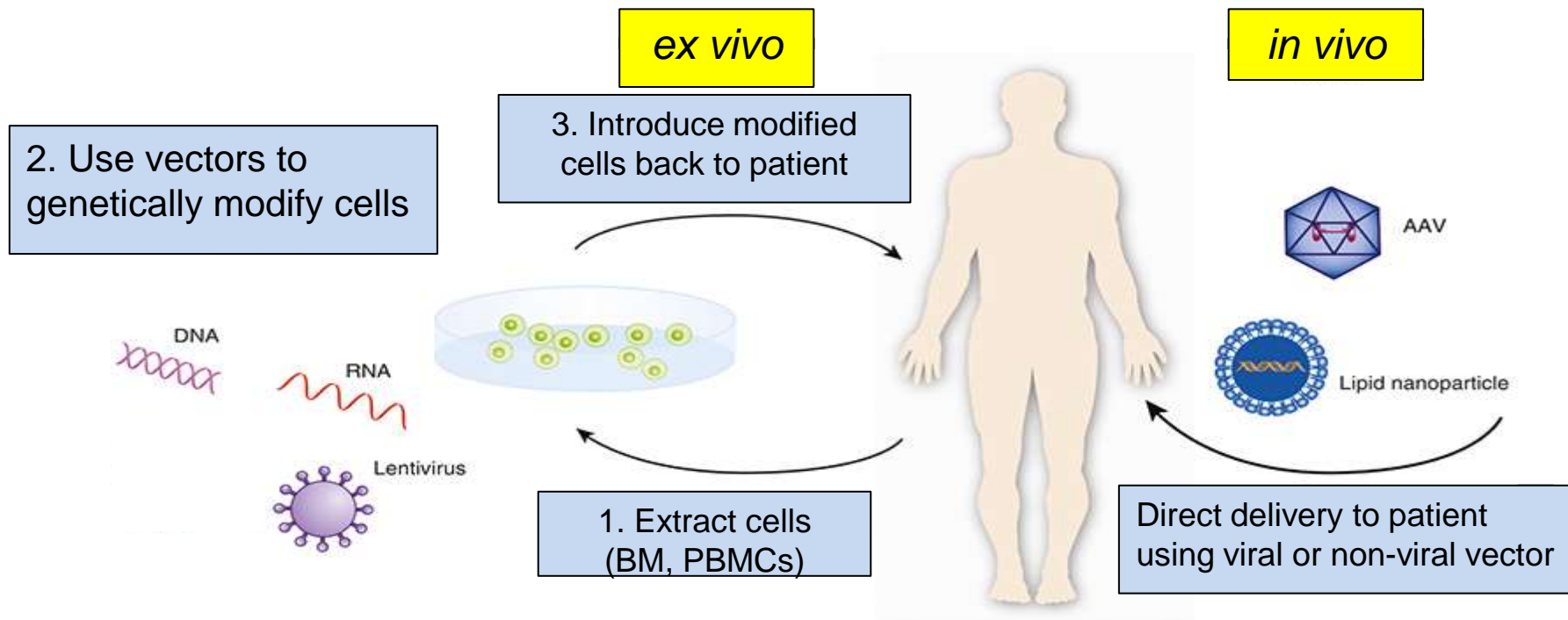
- Grasp important principles on efficient clinical development of investigational gene therapy (GT) products
- Understand regulatory requirements and flexibility

Outline

- Overview of GT
- Efficient Clinical Development of GT Products
- Regulatory Requirements and Flexibility

Gene Therapy

Ex vivo and *In vivo* Administration



Milestones & Setbacks



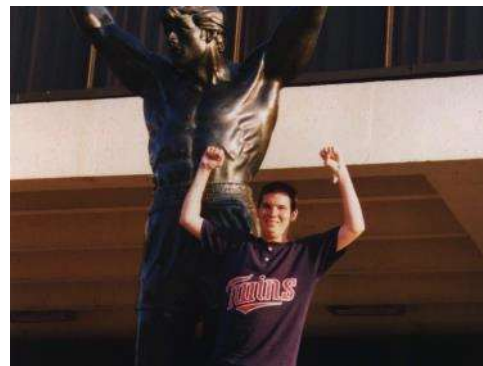
First GT Trial in U.S.: 1990

- Retroviral-mediated transfer of ADA gene into autologous T cells
- Two girls with ADA-deficient SCID received ~10 treatments for two years
- 10 years later: % of T cells carrying and expressing retroviral gene
 - 1st patient: 20%
 - 2nd patient: <0.1%

ADA: adenosine deaminase

SCID: severe combined immune deficiency

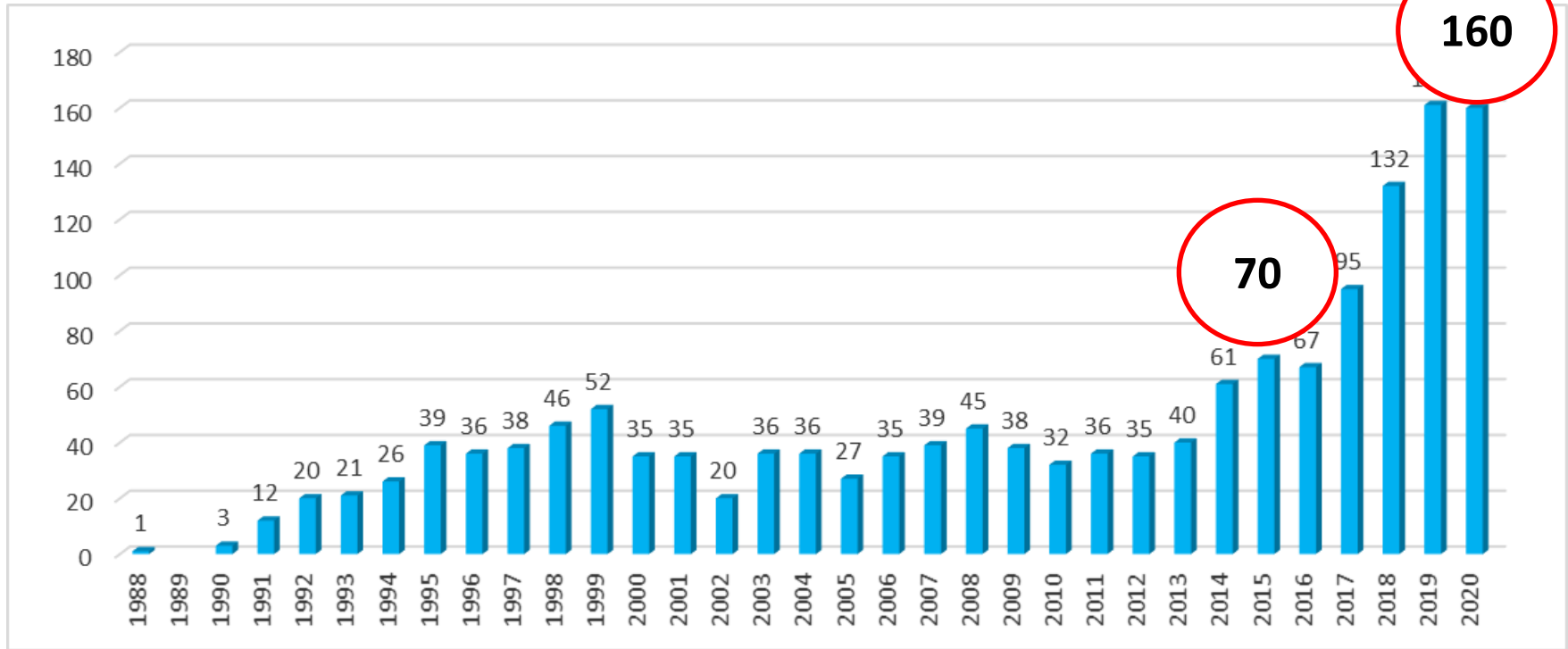
OTC: ornithine transcarbamylase



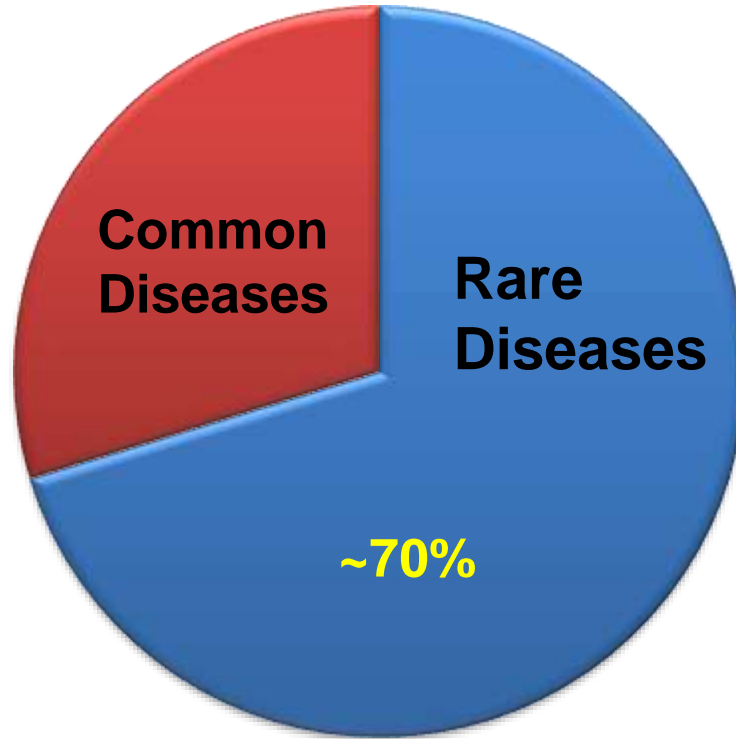
Setback: Death of Mr. Gelsinger: 1999

- 18-year-old with OTC deficiency
- Used a virus to deliver the correct gene
- Died 4 days later
- FDA investigation:
 - Should not have been treated due to high ammonia level
 - Did not disclose the death of a monkey in informed consent

Research INDs with GT Products



Gene Therapies IND Applications



FDA-Approved Cell-Based GT Products



- Tisagenlecleucel (Kymriah), 2017
 - Refractory childhood lymphoblastic B cell leukemia and large B cell lymphoma
- Axicabtagene ciloleucel (Yescarta), 2017
 - Refractory relapsed or refractory large B cell lymphoma (adult)
- Brexucabtagene autoleucel (Tecartus), 2020
 - Relapsed/refractory mantle cell lymphoma (adult)
- Lisocabtagene maraleucel (Breyanzi), 2021
 - Relapsed/refractory large B cell lymphoma
- Idecabtagene vicleucel (Abecma), 2021
 - Refractory Multiple Myeloma



FDA-Approved AAV-Based GT Products



- Voretigene neparvovec (Luxturna), 2017
 - 1st FDA-approved directly administered gene therapy targeting a genetic disease due to single gene mutation
 - AAV2-based GT expressing the *RPE65* gene, encoding human retinal pigment epithelium 65 kDa protein
 - Bi-allelic RPE65 mutation-associated retinal dystrophy
- Onasemnogene abeparvovec (Zolgensma), 2019
 - 1st FDA-approved systemically administered gene therapy
 - AAV9-based GT expressing the gene encoding the survival motor neuron (SMN) protein
 - Spinal muscular atrophy with bi-allelic mutations in the SMN1 gene (< 2 years of age)



CLINICAL DEVELOPMENT OF GENE THERAPY PRODUCTS

Clinical Development for GT Products



- Similar fundamental considerations: GT products and other biological products
- Clinical development programs for different diseases may vary substantially
- Discuss with FDA early in their product development

Early-Phase Trials: Objectives

- Safety
- Activity and preliminary clinical efficacy
- Try to hit a home run!
 - Design first-in-human (FIH) clinical trial to provide **evidence of effectiveness**
 - Resolve **manufacturing** issues, as much as possible, before FIH clinical trial

FDA Guidance: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015),
<https://www.fda.gov/media/106369/download>



Study Design



- Randomized, placebo-controlled clinical trials
 - May be the most efficient means
 - Obtain persuasive evidence of effectiveness
- Many diseases
 - poorly understood etiology and/or pathophysiology
 - poorly characterized or highly variable natural history
- Consider randomized, concurrent-controlled (e.g., placebo, sham-procedure), double-blind clinical trials, even for first-in-human studies
 - Facilitate data interpretation
 - Especially important for rare diseases
 - Maximize the use of valuable resources
 - May provide sufficient evidence of effectiveness to support a marketing application.

Study Design

- Standard of care (SOC) for all subjects
- No subject should be denied effective therapies in order to be randomized to a placebo-only arm
- Add-on designs: All subjects receive SOC, then be randomized to the added GT product or placebo

External / Historical Controls

- External, historical controls may be appropriate:
 - An unmet medical need
 - A concurrent control: not practical or ethical
 - Disease course: well-documented, highly predictable
 - Study population and historical controls: suitably comparable;
 - Expected effect: large, self-evident, and temporal to the intervention
- Historical controls may be inadequate
- Generally, use of external, historical controls in place of a concurrent comparator group is NOT encouraged

Study Population

- Confirm the genetic mutation prior to enrollment
- Enroll patients with disease severities that offer a favorable benefit-risk profile
- Initiate in adults who can provide informed consent
- Must offer the prospect of direct benefit to individual pediatric subjects (21CFR50.52) - Clinical investigations involving greater than minimal risk

Dose Selection and Product Delivery



- Early Phase studies: dose ranging
 - Substantial dose exploration
 - Initial dose: Supported by preclinical studies and/or available clinical information
 - Initial dose: Reasonably safe and have therapeutic potential
 - In pediatric population
 - Invasive administration procedure
- Invasive surgical procedure
 - Staged approach
 - Unilateral first, then bilateral
 - Detailed description of delivery procedure and devices used

Safety Considerations

- Monitor risks associated with GT product and the administration procedure:
 - Standard safety monitoring
 - Immune response: immunoassays measuring cellular and humoral immune responses to both the vector and the transgene-encoded protein

Use of immunosuppressants

- Justification for use of immunosuppressants is needed.
- Risks due to use of immunosuppressants is expected to be monitored.

Safety Monitoring Duration



- Duration of monitoring
 - Sufficient to cover expected duration of effect
 - Depends on information from preclinical studies, and experience with related products
- Required long term follow-up for certain GT products
 - e.g., 15 years of follow-up for integrating viral vector-based products
 - Clinical development can move on while long term follow-up ongoing

FDA Guidance: Long Term Follow-Up After Administration of Human Gene Therapy Products (2020), <https://www.fda.gov/media/113768/download>

Study Endpoints



- Early Phase studies: Encouraged to explore a wide spectrum of endpoints
 - Clinical endpoints - Assessment of potential clinical benefit;
 - Biomarkers - may indicate activity of the GT product;
 - Guide further clinical development, e.g., changes in the amount of transgene product expressed in the targeted tissue may provide early evidence of GT product activity and thus inform subsequent dose selection.

Endpoints in Trials Supporting the BLA



- Primary efficacy endpoints
 - Clinically meaningful endpoints - directly measure how patients feel, function or survive, or
 - Surrogate endpoints - reasonably likely to predict a clinical benefit.
- FDA Guidance: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998), <https://www.fda.gov/files/drugs/published/Providing-Clinical-Evidence-of-Effectiveness-for-Human-Drug-and-Biological-Products..pdf>
- FDA draft Guidance: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019), <https://www.fda.gov/media/133660/download>

REGULATORY REQUIREMENTS AND FLEXIBILITY

Regulatory Requirements

- Approval of drugs and biologics must be based on **substantial evidence of effectiveness** and evidence of safety.
- Evidence of effectiveness should be obtained from **adequate and well-controlled studies**.
- Certain aspects of product development that are feasible for common diseases may not be feasible for rare diseases. FDA regulations provide **flexibility** in applying regulatory standards (21 CFR 314.105).

Evidence of Effectiveness – Rare Disease

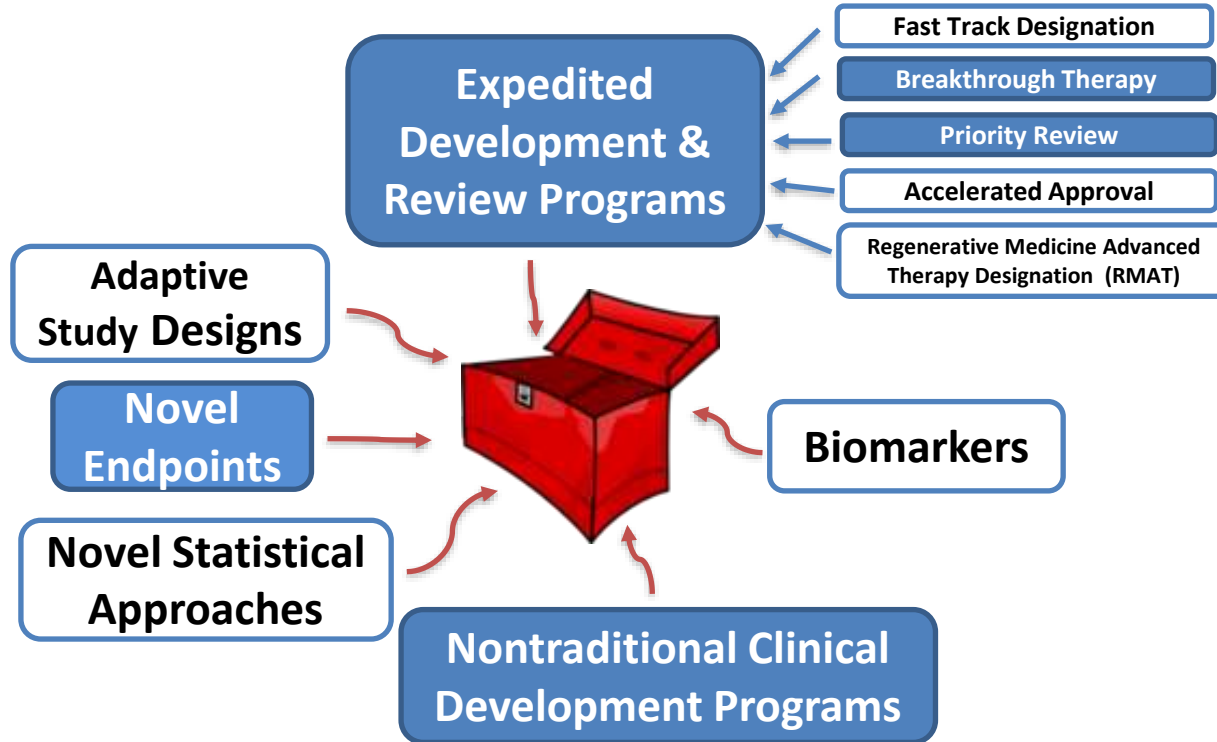


- No specific minimum number of patients to be studied to establish effectiveness and safety of a treatment for any rare disease.
- The number of patients to establish effectiveness and safety is determined on a case-by-case basis, taking into consideration
 - the persuasiveness of the data (e.g., comprehensiveness and quality)
 - the nature of the benefit provided (or expected in the case of surrogate endpoints)
 - the patient population that would be treated after marketing approval
 - the concern for potential of harm from the treatment

Voretigene Neparvovec (Luxturna)

- First-in-class AAV vector-based gene therapy via subretinal injection
- Approved by OTAT/CBER in December 2017
- Indication: Treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy

Flexible and Feasible Approaches



Biallelic *RPE65* Mutation-Associated Retinal Dystrophy



- A rare disease, 1000-2000 patients in US
- Various clinical manifestations:
 - Night-blindness and progressive visual field loss
 - Complete blindness in all patients
 - Impaired activity of daily living
- No approved pharmacological treatment

Normal Vision



Decreased Light Sensitivity



Source: Spark Therapeutics

MLMT: Evaluate Mobility at Different Light Levels



Light Levels	Examples
1 lux	Indoor nightlight; Moonless summer night
4 lux	Cloudless night with half moon; Parking lot at night
10 lux	1 hour after sunset in city; Bus stop at night
50 lux	Outdoor train station at night; Inside of lighted stairwell
125 lux	30 minutes before sunrise; Interior of train / bus at night
250 lux	Interior of elevator or office hallway
400 lux	Office environment or food court



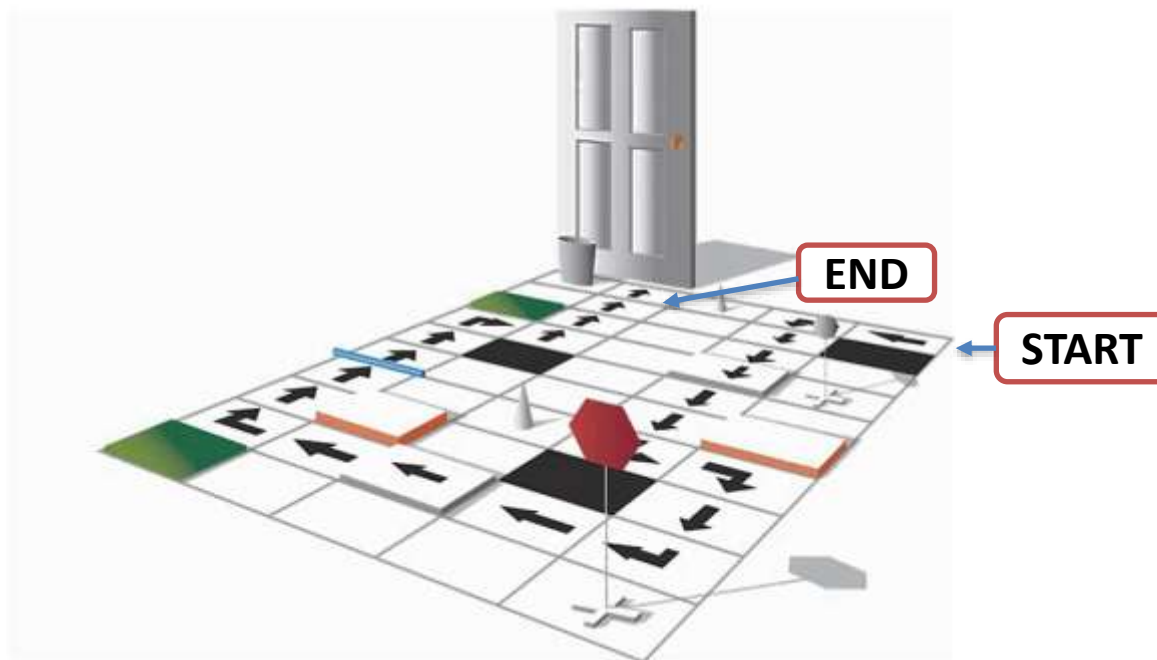
Images presented for illustrative purposes only

Light meter: National Institute of Standards and Technology-calibrated,

Extach model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing

MLMT: multi-luminance mobility test

MLMT: 12 Different Course Layouts



MLMT: multi-luminance mobility test

Recommendations

- Collaborate: scientists, clinicians, patients, advocacy groups, industry, regulatory bodies
- Plan ahead
 - An early phase trial of rare disorders may provide evidence of effectiveness and safety
- Concurrent controlled, randomized early phase trial
- Early communications with FDA

Challenge Question #1

A concurrently controlled, randomized First-in-human early phase study is not necessary or recommended because the objective of such a study is to assess safety.

- A. True
- B. False

Challenge Question #2

Which of the following gene therapy product is administered *ex vivo*:

- A. Plasmids
- B. Adeno associated virus vector
- C. Bacterial vector
- D. Genetically modified human cells

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