The Role of Statistical Thinking in the Review and Approval of Cellular and Gene Therapies

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Trends and Innovations in Clinical Statistics and Beyond: Cell and Gene Therapy
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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

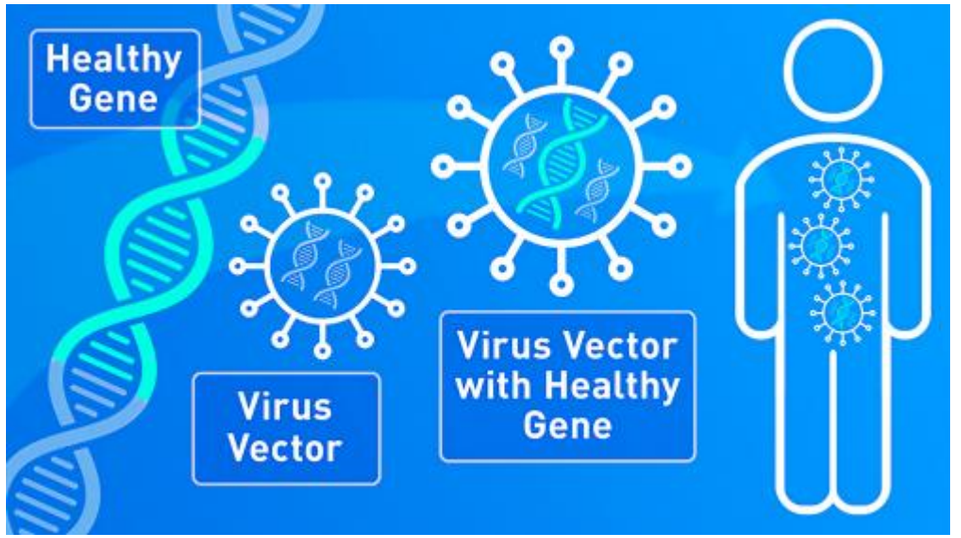
- Overview of regulated cell and gene therapies
- General statistical and trial design challenges
- Examples of approaches used in previous applications

Center for Biologics Evaluation and Research (CBER) Areas of Regulation:

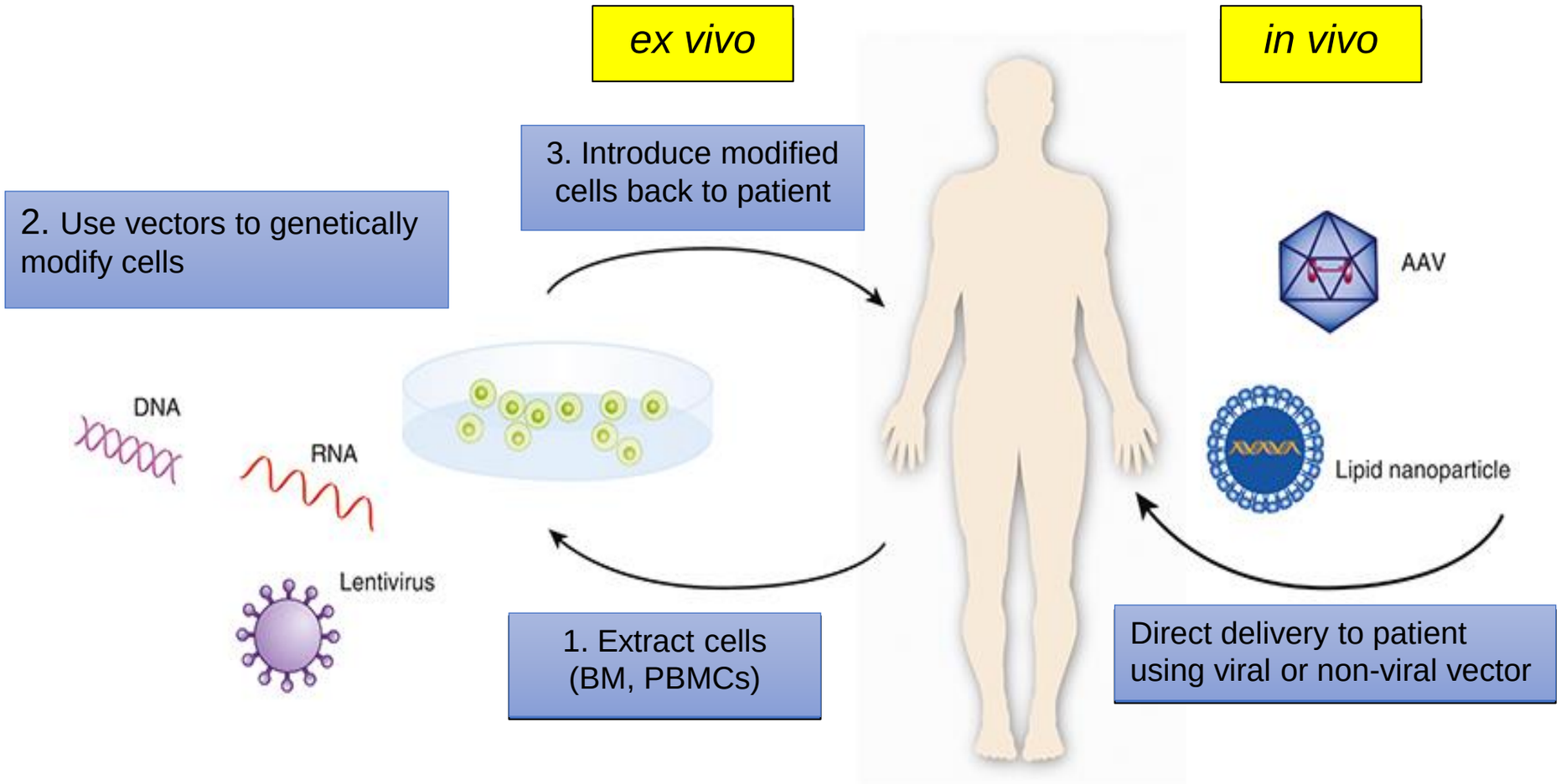
- Gene therapies
- Human tissues and cellular products
- Xenotransplantation products
- Allergenics
- Live biotherapeutic products
- Vaccines (preventative and therapeutic)
- Whole blood, plasma, and blood products
- Devices related to biologics

What is gene therapy?

- Therapeutic modality based on transcription or translation of transferred genetic material or altering human genetic sequences
- Includes certain autologous cell-based therapies and viral vector-based therapies



Human Gene Therapy:
Ex vivo and in vivo Administration



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U.S. Approved Gene Therapies and Oncolytic Viruses

- Imlygic (2015)
- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
- Lyfgenia (2023)
- Casgevy (2023, 2024)
- Lenmeldy (2024)
- Beqvez (2024)
- Tecelra (2024)

Oncolytic virus Stem cell T cell Directly administered

Therapeutic areas with approved GTs

- Oncology (late line)
  - Certain leukemias, lymphomas, multiple myeloma (CAR T)
  - Bladder cancer, synovial sarcoma, melanoma
- Non-malignant hematology
  - Hemophilia A & B, sickle cell disease, ß-thalassemia
- Rare and serious pediatric / developmental disorders
  - Duchenne muscular dystrophy, metachromatic leukodystrophy, cerebral adrenoleukodystrophy, spinal muscular atrophy, RPE65 mutation-associated retinal dystrophy, epidermolysis bullosa

U.S. Approved Cellular and Tissue Therapies

- Hematopoietic progenitor cells [HPC], Cord blood (8 approvals)
- Gintuit (2012)
- Lantidra (2023)
- Laviv (2011)
- MACI (2017)
- Omisirge (2023)
- Provenge (2010)
- Rethymic (2021)
- Stratagraft (2021)

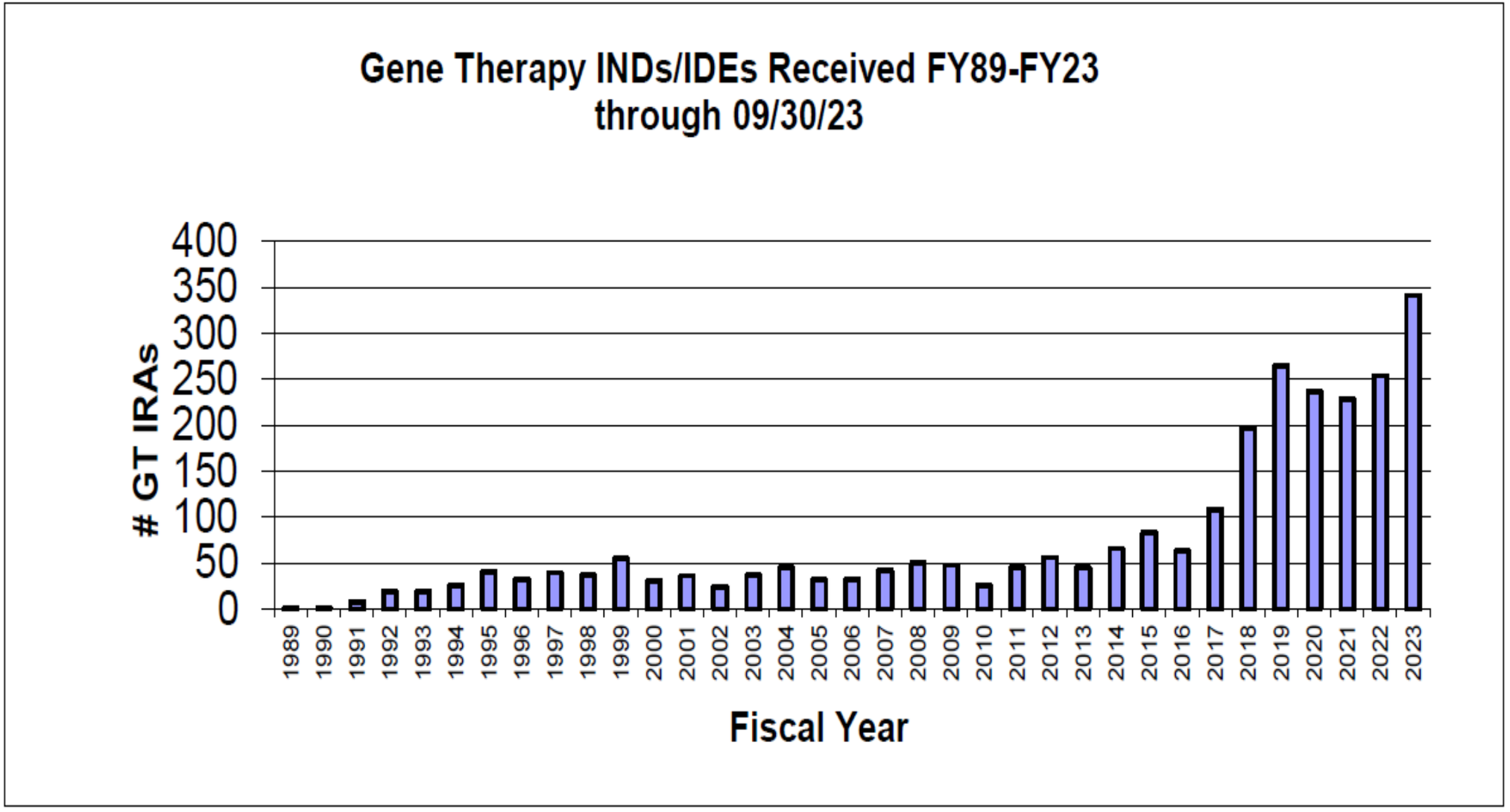
Therapeutic areas with approved cellular and tissue therapies

- Hematopoietic reconstitution
- Oncology (late line)
  - Prostate cancer
- Regenerative medicine applications
  - Periodontal graft, skin graft, chondrocytes for knee OA
- Type 1 diabetes, congenital athymia, wrinkles

Current Challenges

- Gene therapy is currently at a critical juncture due to a combination of factors
  - Manufacturing challenges
  - Clinical development timelines
  - Different global regulatory requirements

Investigational gene therapies



Source: Gene Therapy, Somatic Cell Therapy, and Xenotransplantation IND/IDE Statistical Report, CBER, FDA

Why a gene therapy talk?

- Statistics is (are?) statistics
  - Usual clinical trial methodologies apply to cell and gene therapies
- **But**, there are distinctive themes for GT studies:
  - Small sample sizes
  - Single administration / long-term effect
  - Manufacturing complexities
  - Qualitatively different patient experiences – benefit / risk
  - Long term safety risks and follow-up

Indication-related limitations

- Gene therapies to date are for rare diseases
  - Sometimes very rare
  - Usually serious and life threatening, often unmet needs
- Limited applicability of statistical inference
  - Small sample sizes
  - Single arm studies in many cases
- Increased reliance on:
  - Descriptive and graphical methods
  - Very large effect sizes

Example: Spinal muscular atrophy

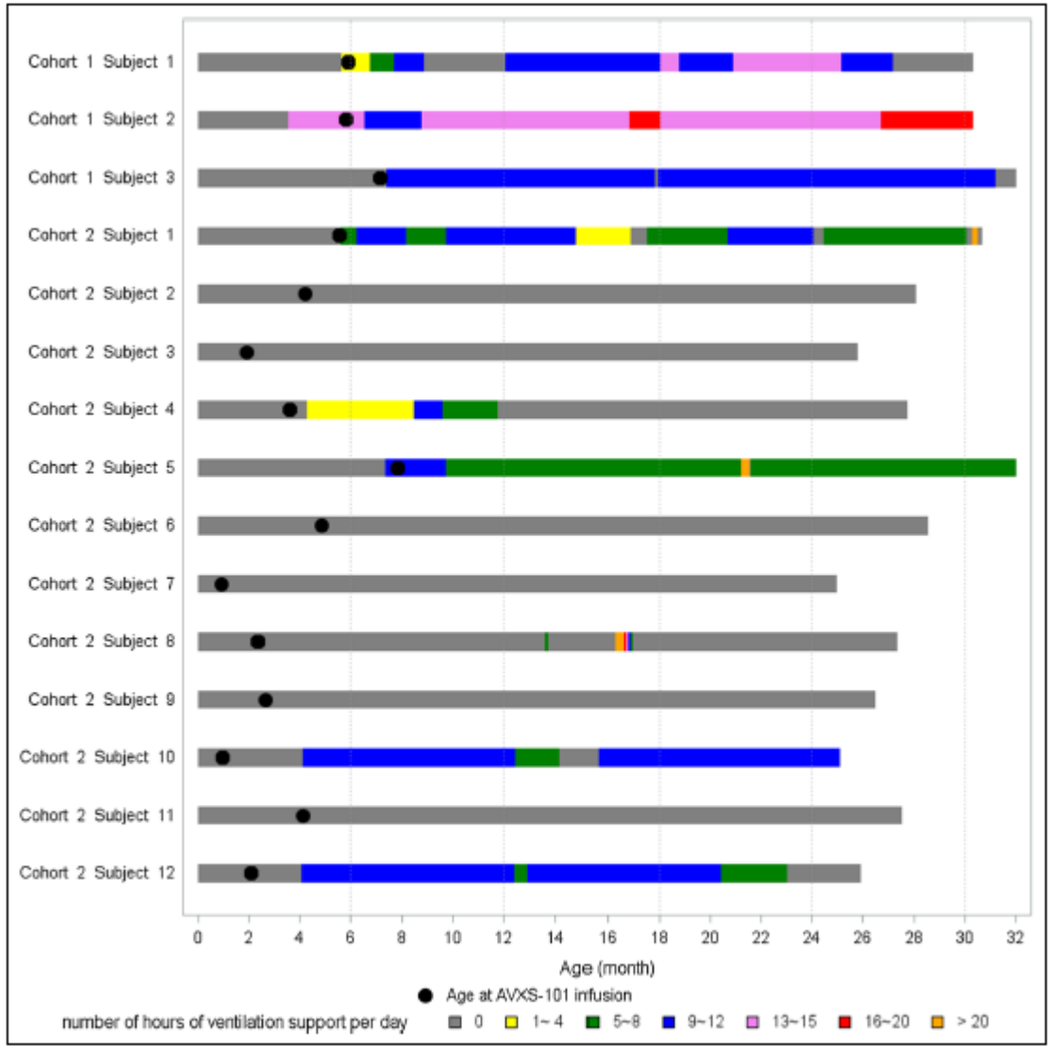
- Infantile-onset SMA is a devastating neuromuscular disorder
  - Most infants never reach developmental milestones such as sitting up unassisted
  - Average life expectancy is less than 2 years
- Evidence of effectiveness of Zolgensma came from a single arm study (n=21) with a natural history control

Table 2. Survival and Motor Milestone Achievement in the Ongoing Phase 3 Trial

Endpoints	Phase 3 trial (N=21) n (%)	Natural history control (N=23) %
Survival at 14 months of age*	13 (67%)	25%
Sitting without support for ≥ 30 seconds	10 (47%)	0

* Only 13 patients had reached 14 months of age by the data cutoff.

Example: Spinal muscular atrophy



- Figures like this swimmer plot of ventilation support facilitate full understanding of study data
- Each patient's experience is summarized

https://doi.org/10.1007/s43441-020-00219-y

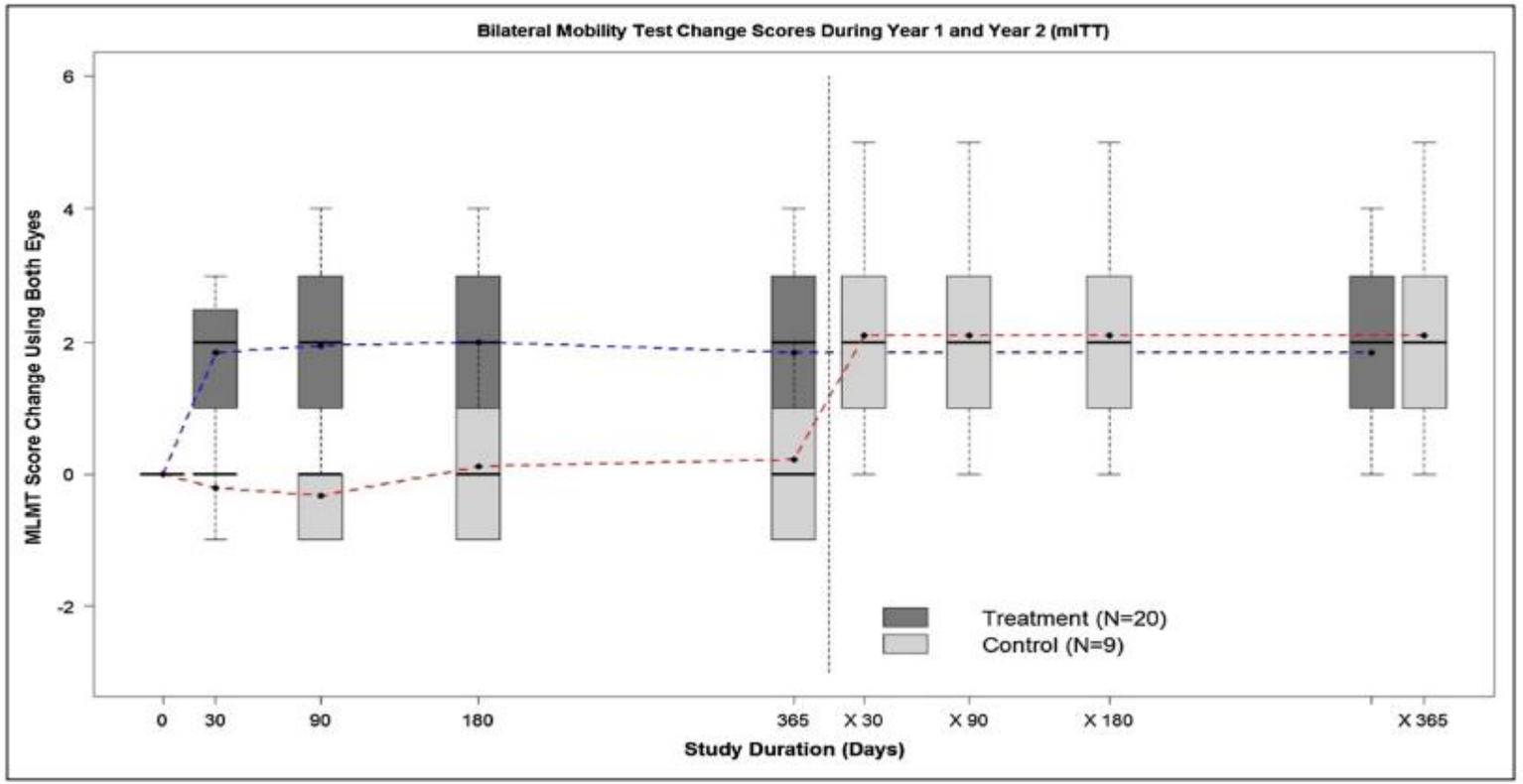
Example: Retinal dystrophy

- Biallelic RPE65 mutation-associated retinal dystrophy leads to progressive deterioration of vision, often in childhood or adolescence
  - Ultimately progresses to complete blindness
- Luxturna efficacy was based on a randomized cross-over P3 study (n = 31)
  - Novel endpoint: change in multi-luminance mobility testing (MLMT)

Table 5. Efficacy Results of the Phase 3 Study at Year 1, Compared to Baseline

Efficacy Outcomes	LUXTURNA n=21	Control n=10	Difference (LUXTURNA minus Control)	p-value
MLMT score change using both eyes, median (min, max)	2 (0, 4)	0 (-1, 2)	2	0.001
MLMT score change using the first-treated eye, median (min, max)	2 (0, 4)	0 (-1, 1)	2	0.003

Example: Retinal dystrophy



- Creative boxplots clearly show group difference and improvement after crossover

https://doi.org/10.1007/s43441-020-00219-y

Administration of GT

- Unlike most other biologics or small molecule drugs, gene therapies are usually intended for single administration
  - Patients can't typically be effectively exposed to the same viral vector twice
  - Benefit-risk assessment for a GT may include opportunity cost of other GT interventions
- GT is also intended to have a long-term effect
  - In some cases, potentially curative
  - May require longer-term follow-up for efficacy than non-GT products to get full picture of benefit-risk

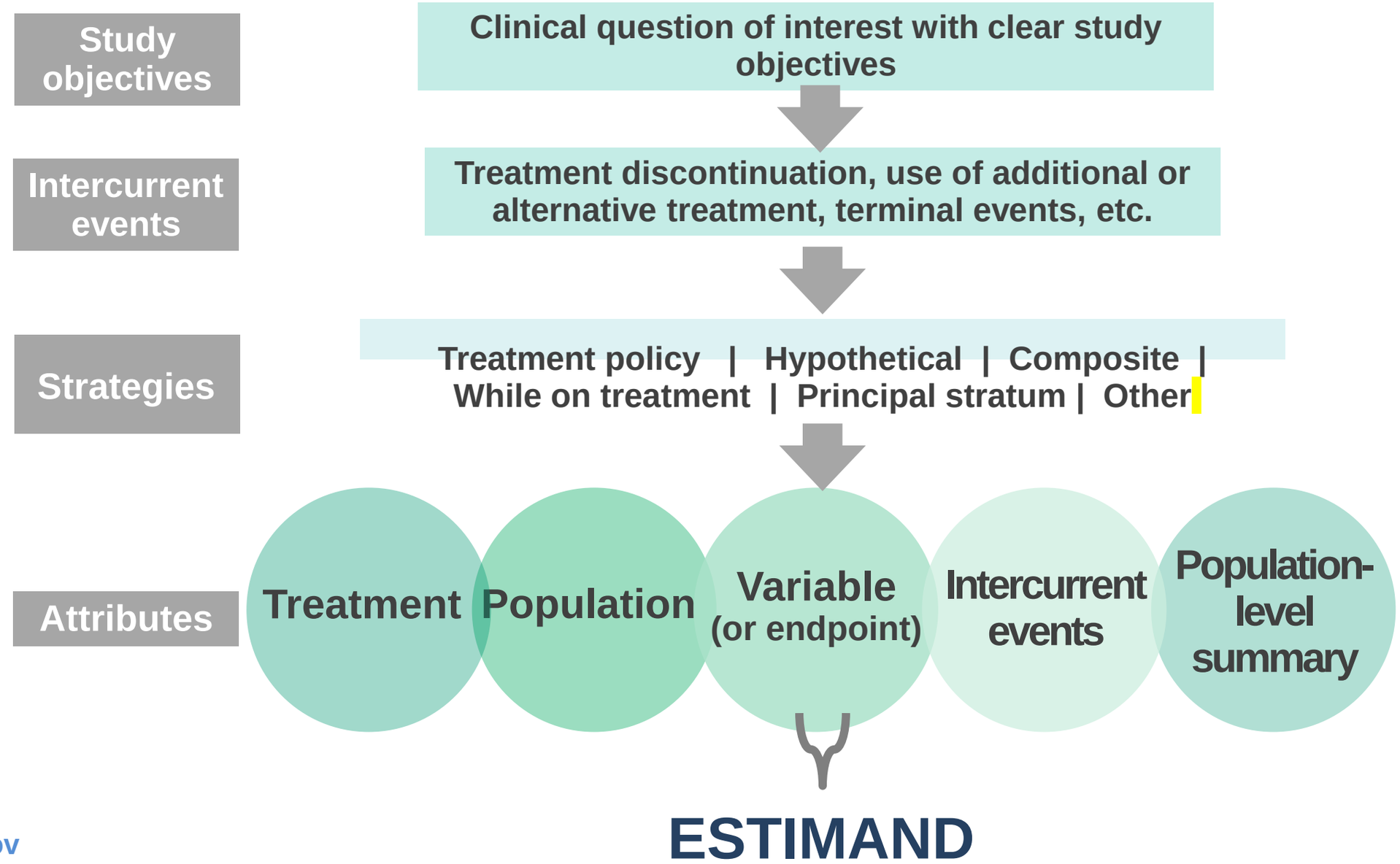
Qualitative differences for GT vs. SOC

- For lifelong chronic illnesses, comparison may be between:
  - Chronic therapy with some efficacy and predictable side effects
  - One-time GT with some efficacy, curative potential, different side effect profile
- When comparing against active control, we use non-inferiority comparisons
  - Can the extreme advantage in dosing and potential advantage in safety be taken into account in a non-inferiority margin?
  - Complicated benefit-risk considerations

Examples

- Hemophilia A & B
  - Standard therapy is routine prophylaxis with replacement factor or bispecific monoclonal antibody
  - Factor replacement requires frequent infusion, carries risk of neoantigenicity
  - GT provides non-inferior effectiveness, single dose, unknown how long it lasts
- Sickle cell disease

Estimand framework



Return to replacement treatment as an intercurrent event

- In hemophilia GT trials, bleeds are sometimes treated with Factor replacement
- Some patients return to Factor replacement for longer periods
  - Unclear on individual basis whether this represents a delay in engraftment, a failure of GT, or something else
- Substantial discussion on how to address in analyses

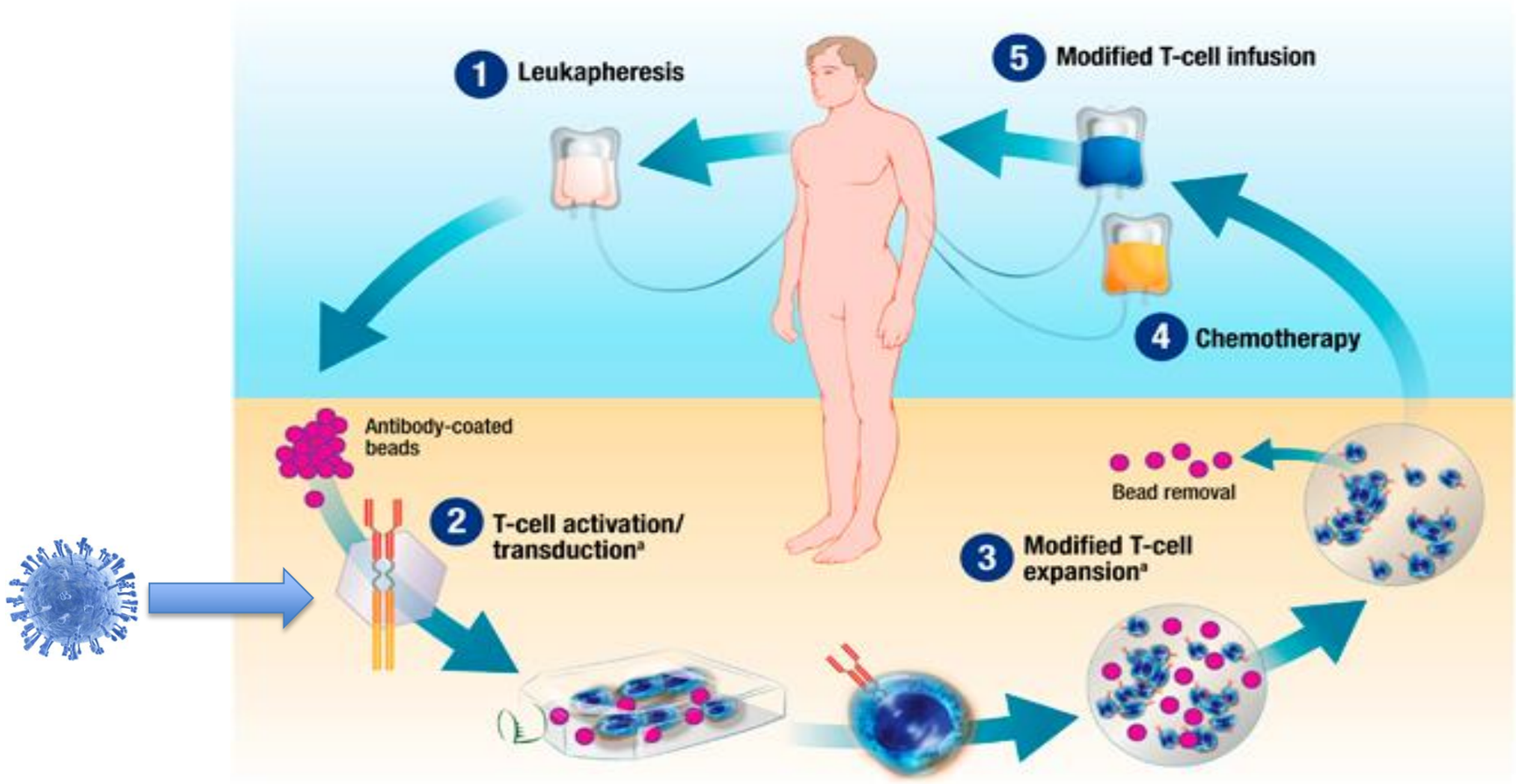
Possible strategies for return to treatment

- Treatment policy strategy:
  - Patient outcomes are analyzed regardless of return to prophylaxis
  - Unsatisfactory because guarantees non-inferiority even for a completely ineffective GT
- Composite strategy:
  - Patients are considered to have failed if they return to prophylaxis
  - Unsatisfactory because may not reflect long-term outcomes
- Hypothetical strategy:
  - Patients are given imputed bleed rates as if Factor weren't available
  - Unsatisfactory because reflects a scenario that wouldn't occur in practice

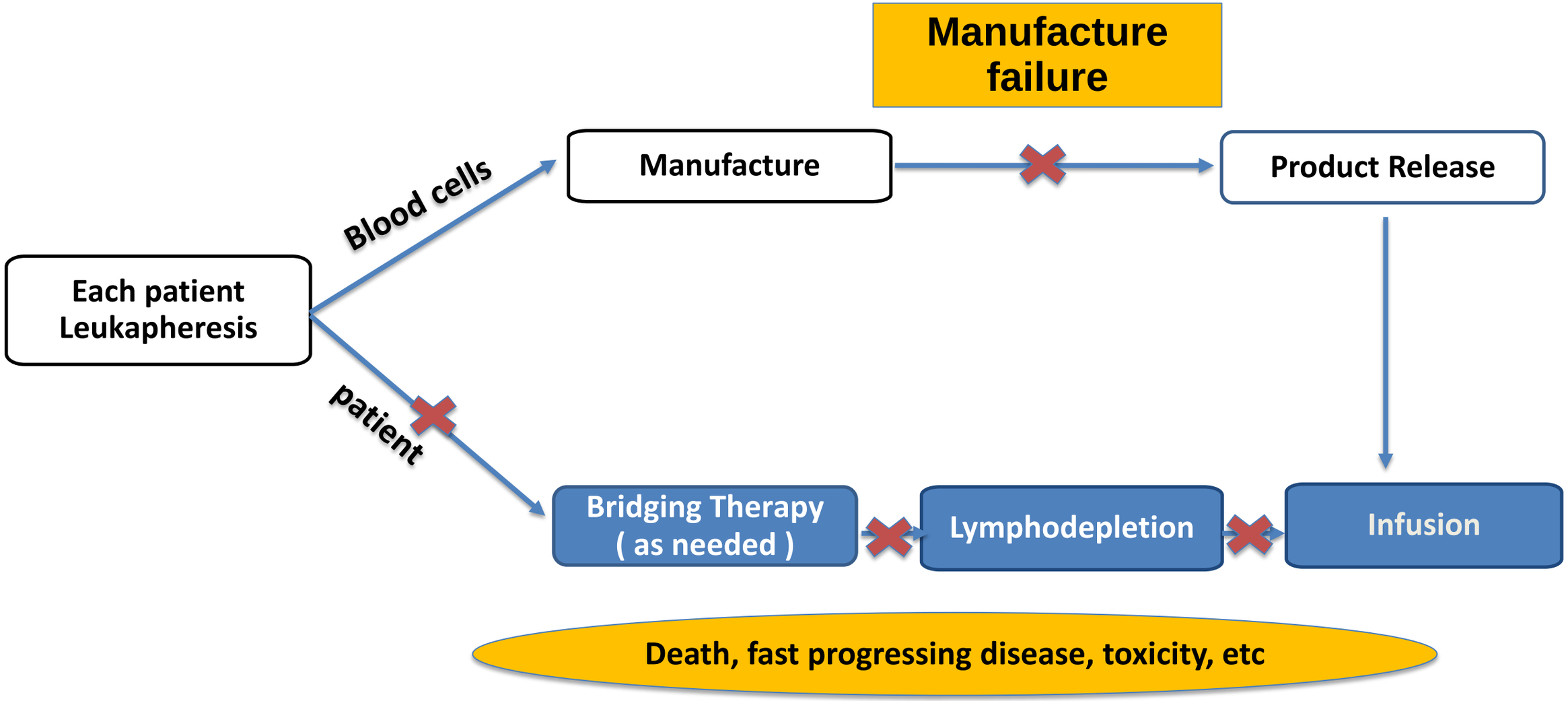
Manufacturing complexities

- Chimeric antigen receptor T cell (CAR T) therapies and other autologous cellular therapies are personalized for each patient
- Cells go through a multi-step process:
  - Apheresis
  - Cell activation / transduction
  - Culture / expansion
  - Infusion
- This process takes some time
  - And can sometimes fail to produce an adequate (or any) dose

CAR T manufacturing



CAR T Process Schema



Manufacturing failure as intercurrent event

- Consider a randomized clinical trial of CAR T (autologous cellular therapy) vs. standard of care in an oncology indication
- After randomization, control patients begin SOC therapy, CAR T patients undergo leukapheresis followed by product manufacture
- Manufacture of autologous cell therapy may take several weeks
- Manufacturing failure is a potential intercurrent event that should be addressed in the estimand description

Possible strategies for manufacturing failure

- Treatment policy strategy:
  - Patient outcomes are analyzed as randomized regardless of treatment failure
  - Addresses question: What is the effect of intending to treat someone with CAR T relative to SOC, regardless of successful manufacturing?
- Composite strategy:
  - Manufacturing failure is considered treatment failure
  - May not realistically reflect prognosis

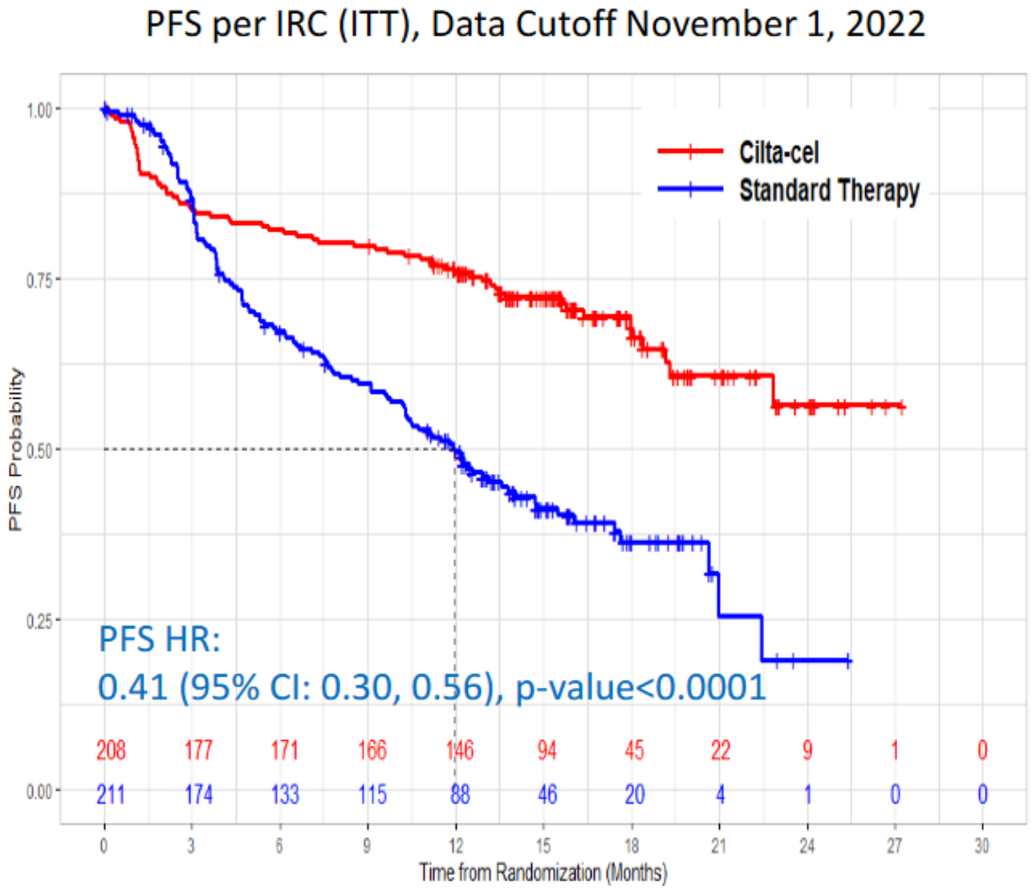
Less satisfactory strategies

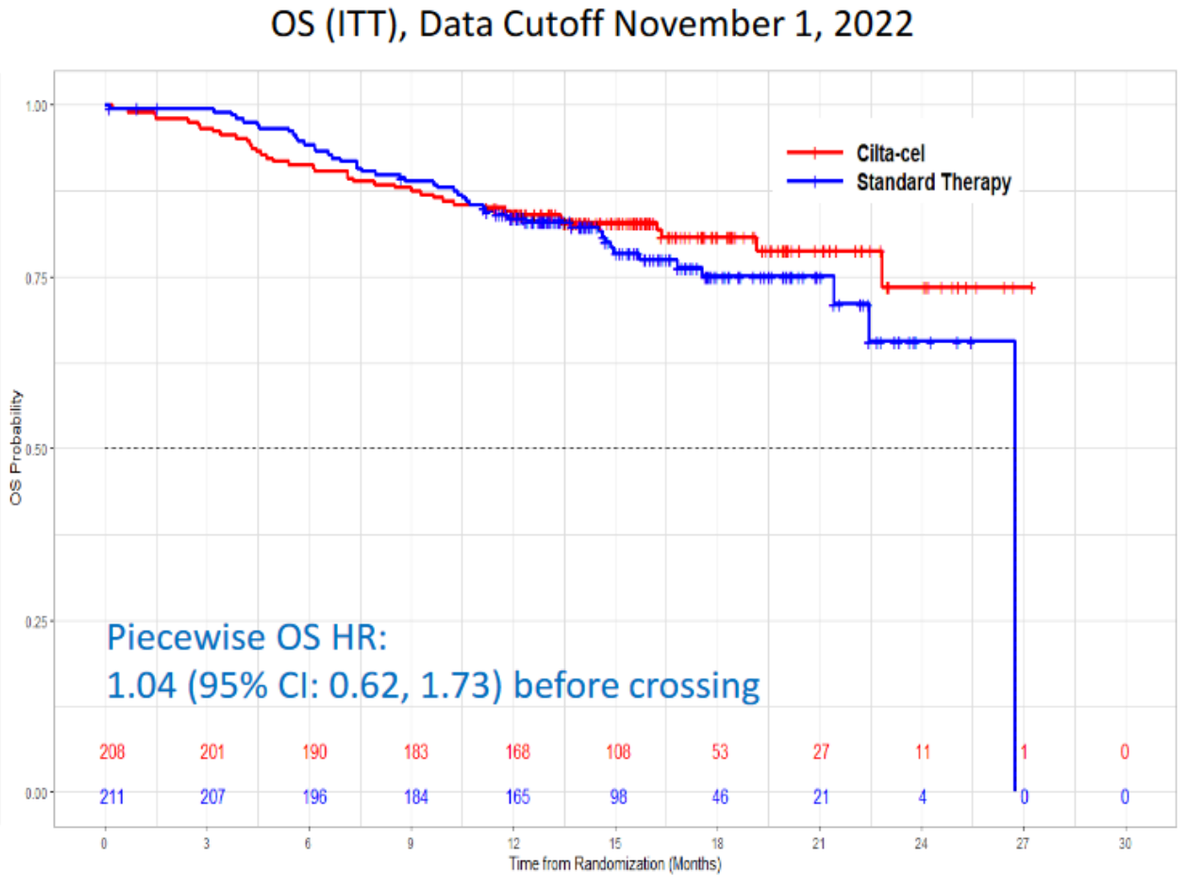
- Hypothetical strategy:
  - Statistical modeling is used to address question: What would have been the treatment effect if there hadn't been any manufacturing failures?
  - Is it relevant to ask what would happen if no failures in a world where failures occur?
  - Strong assumptions required to predict patient course under counterfactual of successful manufacture
- Principal stratum strategy:
  - Statistical modeling used to address: What is the treatment effect comparing only CAR T and SOC subjects who would have had successful CAR T product manufactured?
  - Is it worth knowing the effect in patients who would have successful manufacture if they can't be identified prospectively in clinical practice?
  - Very strong assumptions required to model stratum

Non-proportional hazards

- Cellular and gene therapies often have a delayed effect
  - Time to engraftment
  - Manufacturing time (autologous products)
- In survival analyses, this can lead to difficulties in interpretation
  - Especially when combined with potential crossover

Non-proportional PFS





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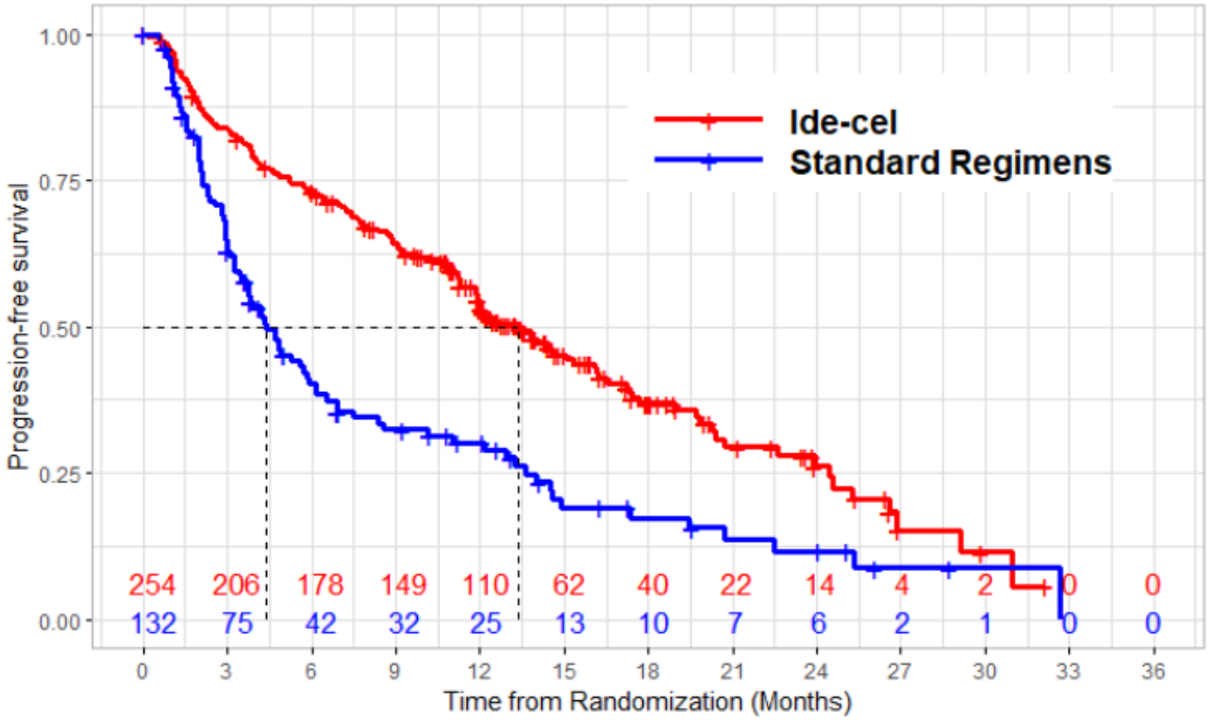
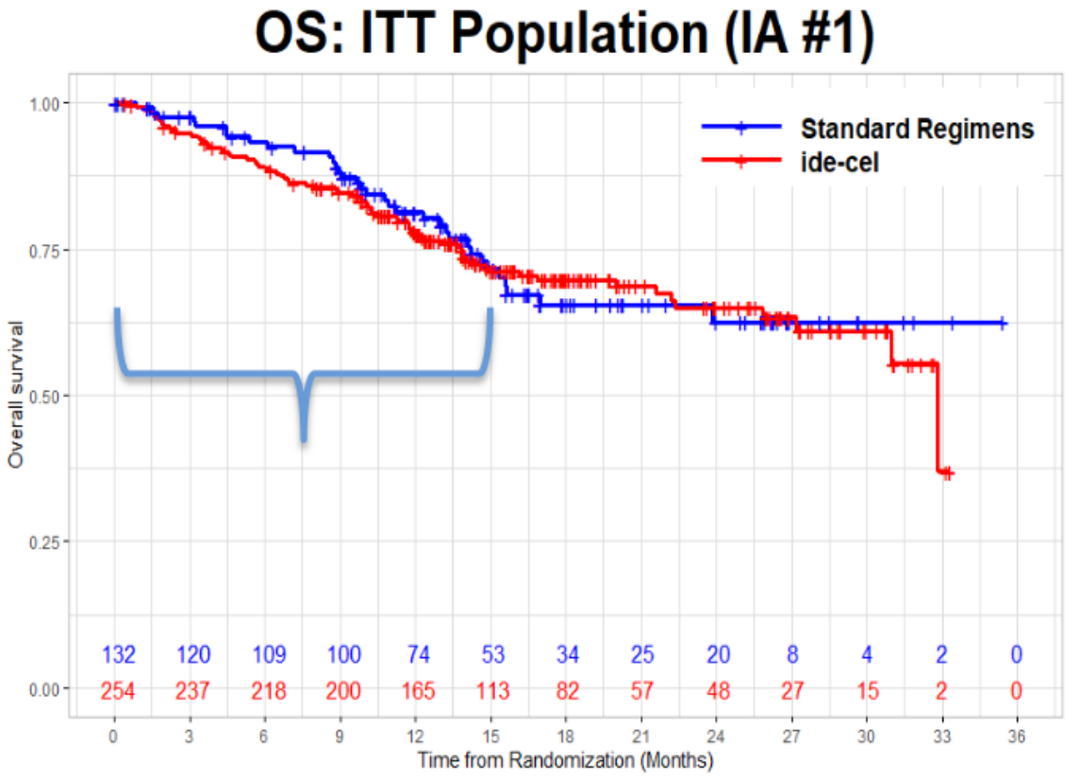
OS crossover





Source: https://www.fda.gov/media/177060/download

Long term safety and follow-up

- Historical development of gene therapy punctuated by safety-related slow downs
  - Jesse Gelsinger
  - Leukemia and clonal cell proliferation in the early trials with retroviral-vectored products
- Categories of risk:
  - Immunogenic
  - Oncogenic
  - Off-target genetic / germ line

Safety considerations

- Valid assays for immunogenicity
- Staggered enrollment in early human studies
- Long-term safety follow-up in certain cases
  - FDA has asked for 15-year follow-up with some vectors
- Viral shedding assessment
- Active monitoring of each patient as part of pharmacovigilance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