Lessons learned from the ethical challenges posed by a first-in-human gene transfer trial for a neurodegenerative disease

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Early-Phase Gene Transfer (GT) Trials for Neurodegenerative Diseases: Ethically Complex

Severe conditions

Progressive conditions

Limited existing treatment options

Perceived therapeutic promise of GT

Unresolved Research Ethics Challenges

Selecting participants in ‘high-demand’ GT trials

Selecting among patients with different stages of disease

Methods

- Case study: phase 1 GT trial for giant axonal neuropathy (GAN)
  - Ultra-rare, childhood-onset neurodegenerative disorder
  - Progressive problems with walking, strength, coordination
  - Eventual respiratory failure (second or third decade)

- Literature review & conceptual analysis

- Extrapolation from GAN GT trial to other pediatric early-phase GT trials for severe, rare diseases

HOW MAY INVESTIGATORS SELECT PARTICIPANTS IN 'HIGH-DEMAND' GT TRIALS?

High-Demand Trials

- High-demand trials = trials where there are more eligible and interested patients than available slots
  - By definition, a trial can only become high-demand after eligibility criteria have been designed and implemented

- What made the GAN GT trial high-demand?
  - A combination of limited trial slots, and strong perceived health incentives that caused many families to seek enrollment for their child
    - Severe, progressive disease
    - Lack of targeted treatments
    - Perceived therapeutic promise of GT

Developing a Strategy for Selecting Among Eligible Patients

- Defining a clear participant-selection strategy in high-demand trials is important to avoid ad hoc and potentially biased decisions

- Any such strategy can affect four ethical dimensions of a trial
  - Social value
  - Risk-benefit profile for participants
  - Justice
  - Time and effort of enrollment

Operationalizing Ethical Trial Dimensions into Participant-Selection Strategies

Ethical Trial Dimension	Example Strategy/Strategies
Social value	• Prioritize eligible patients whose inclusion would increase the sample's representativeness
Risk-benefit profile for participants	• Prioritize eligible patients who would face the lowest risks (or have the the highest prospect of benefit) if enrolled
Justice	• Give all eligible patients an equal chance to enroll • Prioritize most disadvantaged eligible patients
Enrollment time/effort	• Select among eligible patients via first-come, first-served to reduce enrollment time

*Any strategy may optimize one or more ethical trial dimensions, but likely not all trial dimensions. Investigators should carefully consider which ethical dimensions to prioritize.

Points to Consider for Selecting Participants in High-Demand GT Trials

1. Defining a clear participant-selection strategy is important to avoid ad hoc and potentially biased decision-making.

2. Any strategy can affect four ethical dimensions of a trial: social value, the risk-benefit profile for participants, justice, and the effort of enrollment.

3. Investigators should carefully consider which ethical dimensions to prioritize. The preferred strategy will depend on the trial.

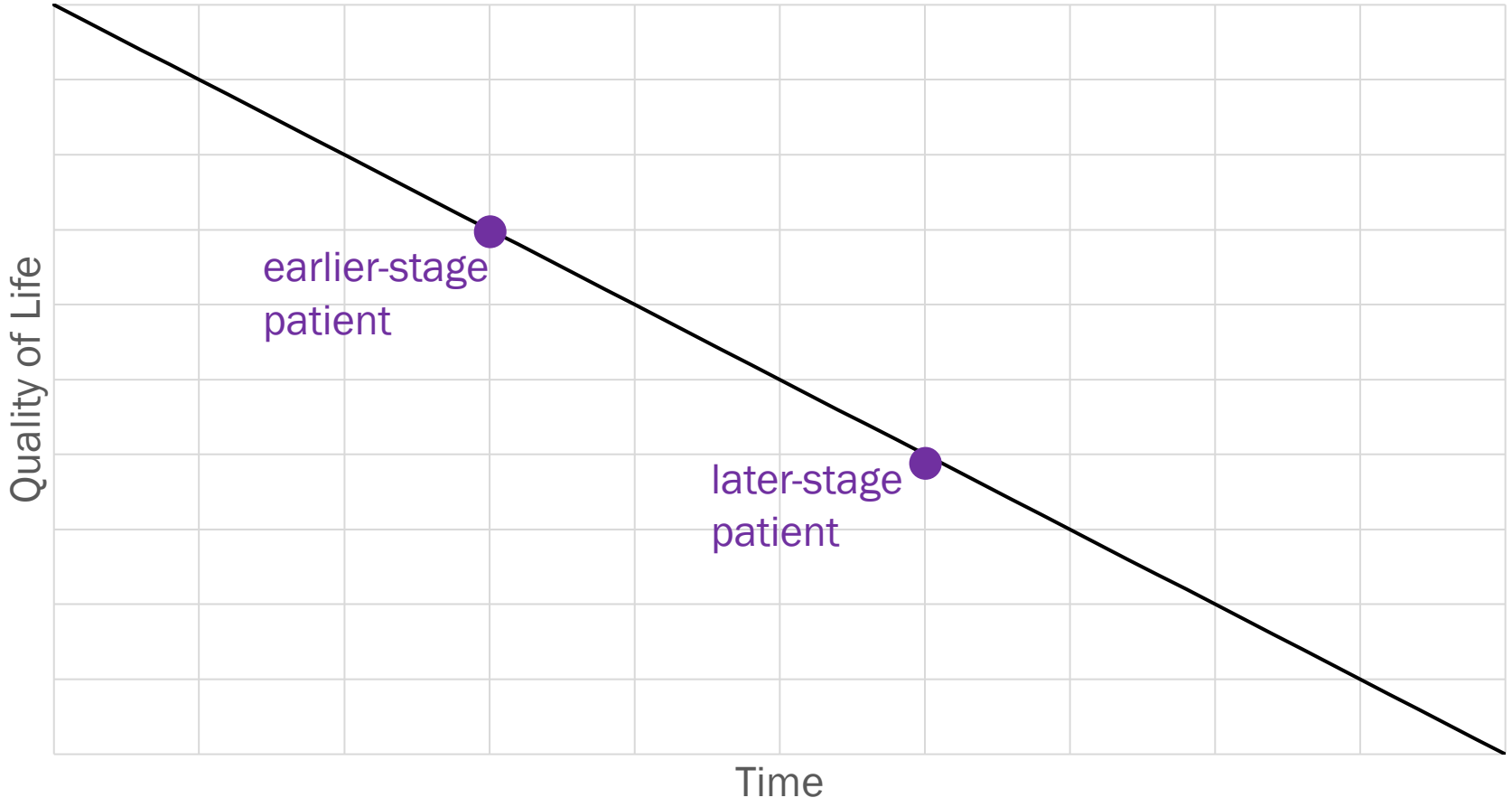
HOW MIGHT INVESTIGATORS CONSIDER WHETHER TO ENROLL PATIENTS WITH EARLIER- OR LATER-STAGE DISEASE IN GT TRIALS FOR DEGENERATIVE DISEASES?

Selecting Among Patients with Different Stages of Disease

- For progressive diseases, the risks and potential benefits of trial participation may depend on a patient's stage of disease

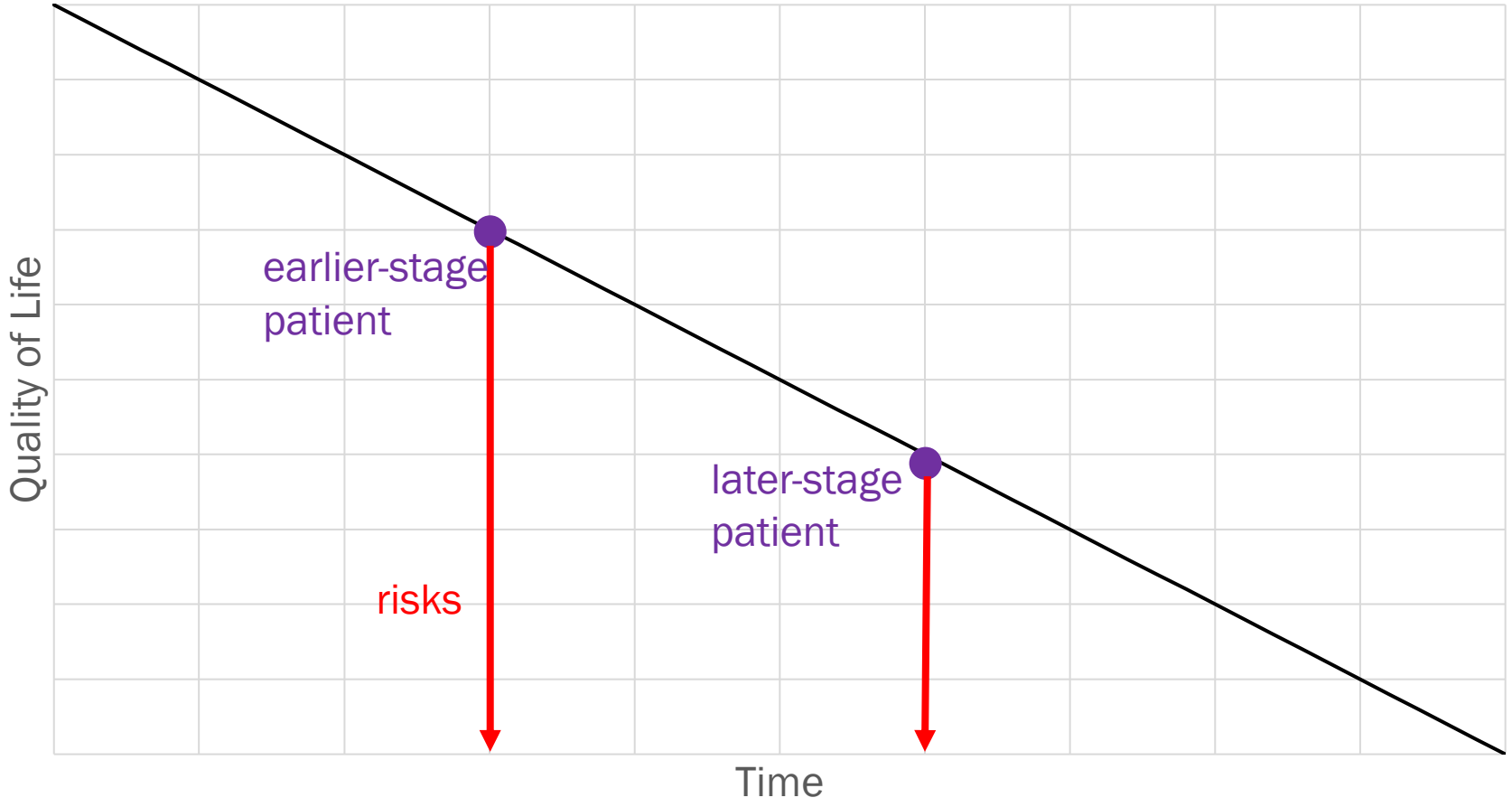
- GT may halt disease progress rather than restore tissues to health
  - Can make risk-benefit analyses more complex

Consider a GT that may halt disease progression but not restore tissues



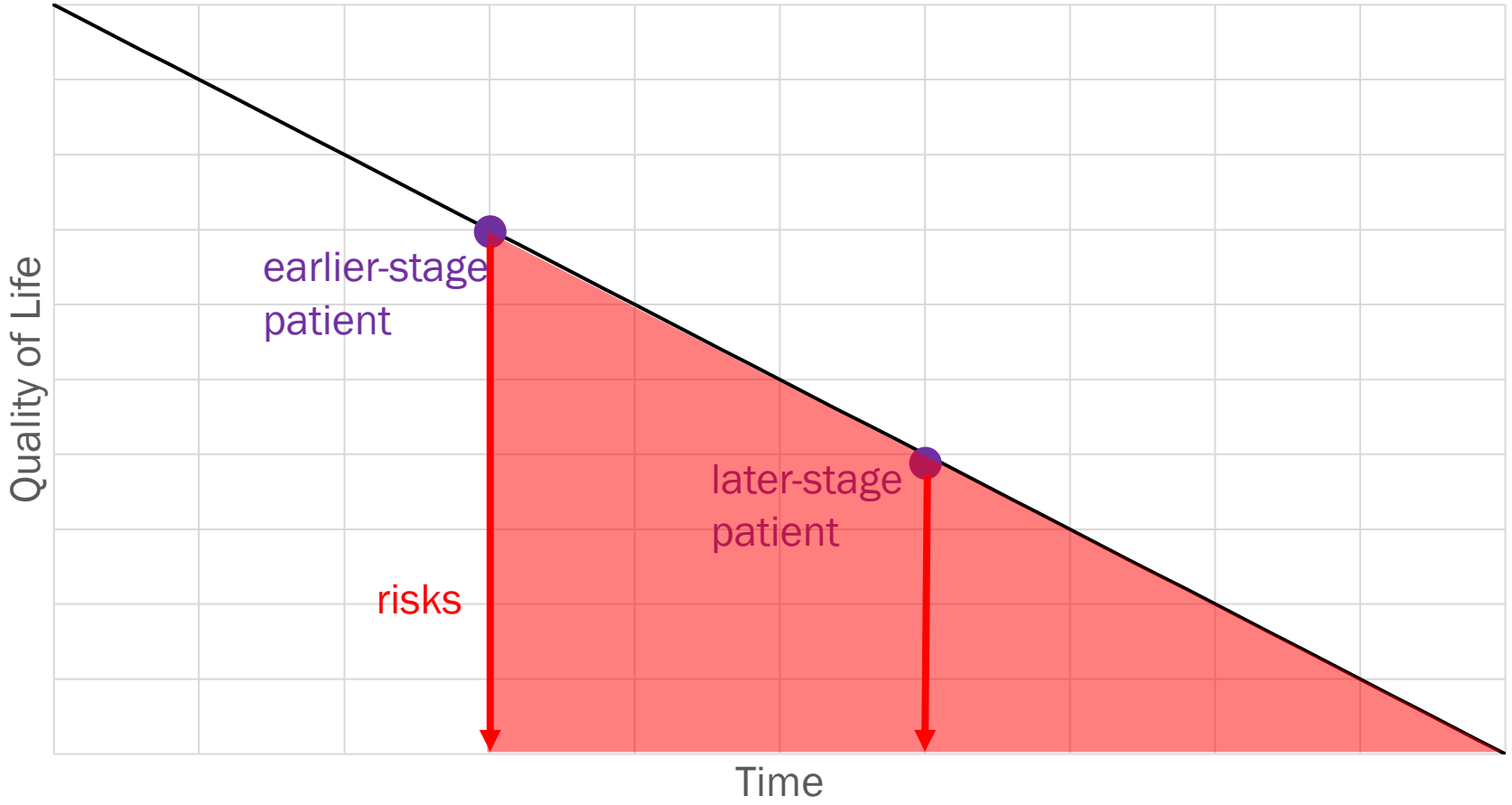
Black line represents a simplified disease trajectory of a patient with a progressive disease.

What are the risks?



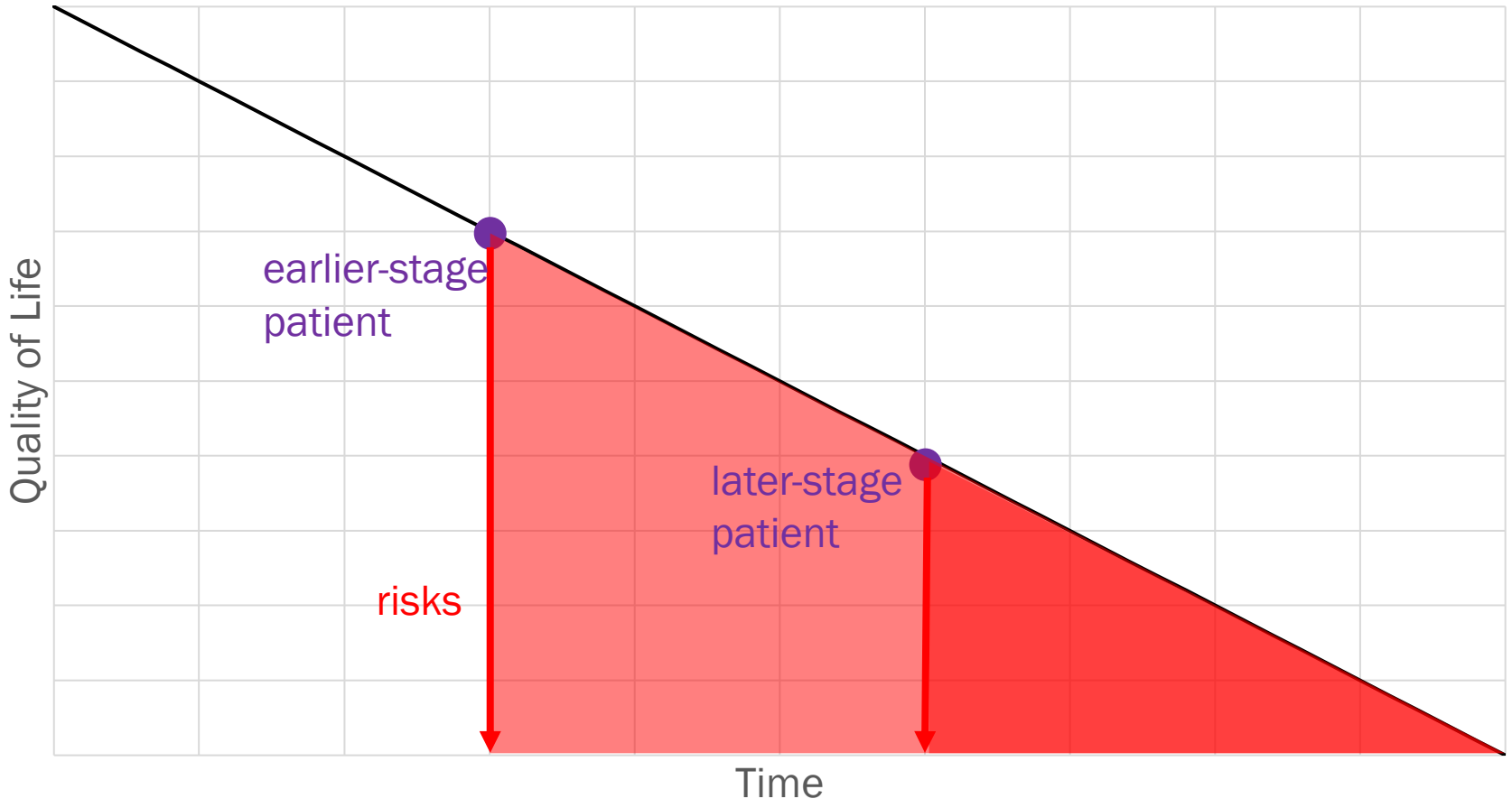
Red arrows represent the possibility of death (one potential risk).

What are the risks?



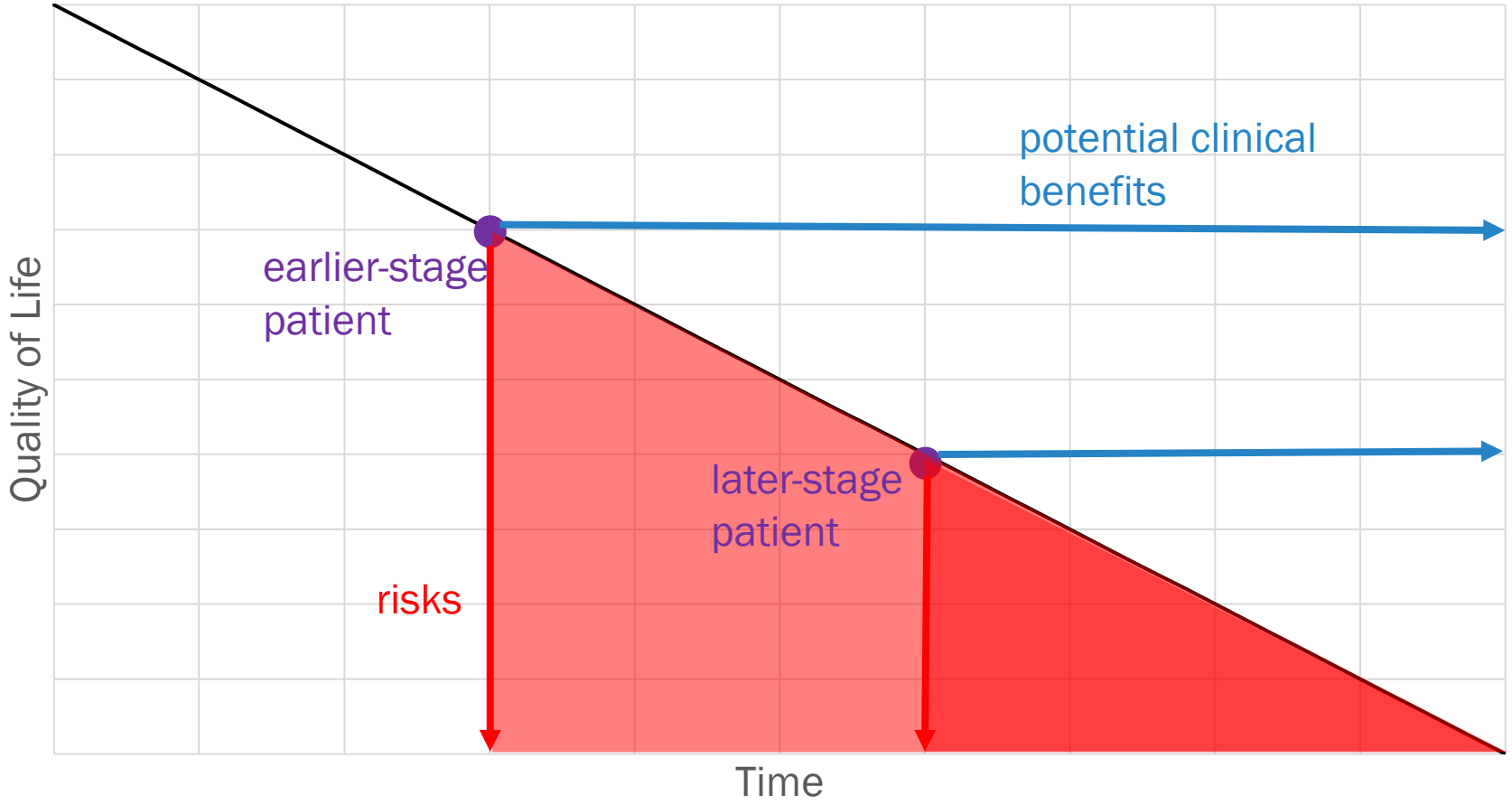
Light red area represents the quality of life lost over time (in case of death) for a patient with earlier-stage disease.

What are the risks?



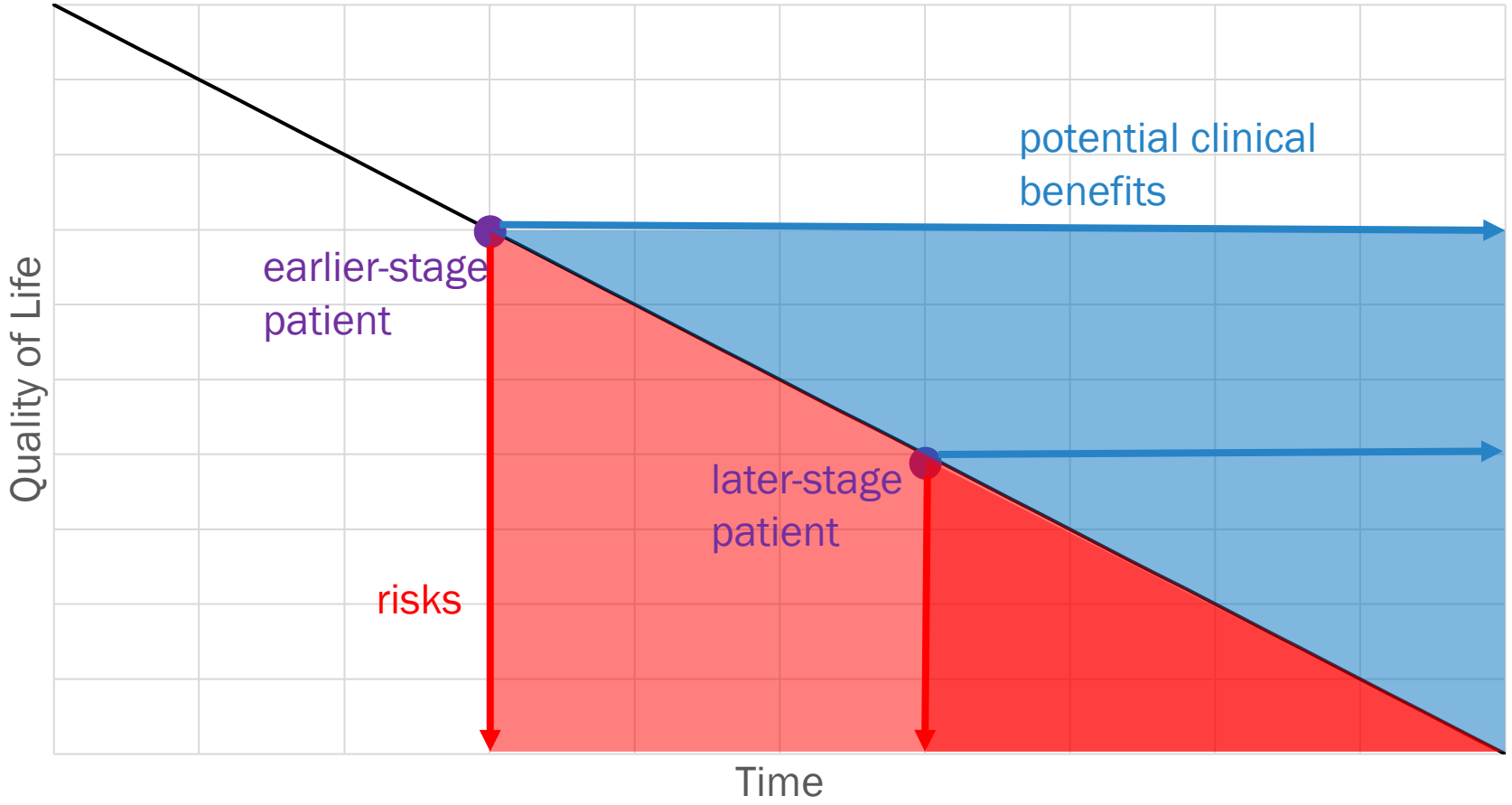
Dark red area represents the quality of life lost over time (in case of death) for a patient with later-stage disease. Patient with later-stage disease risks losing less quality of life over time in case of death (compared to patient with earlier-stage disease).

What are the potential benefits?



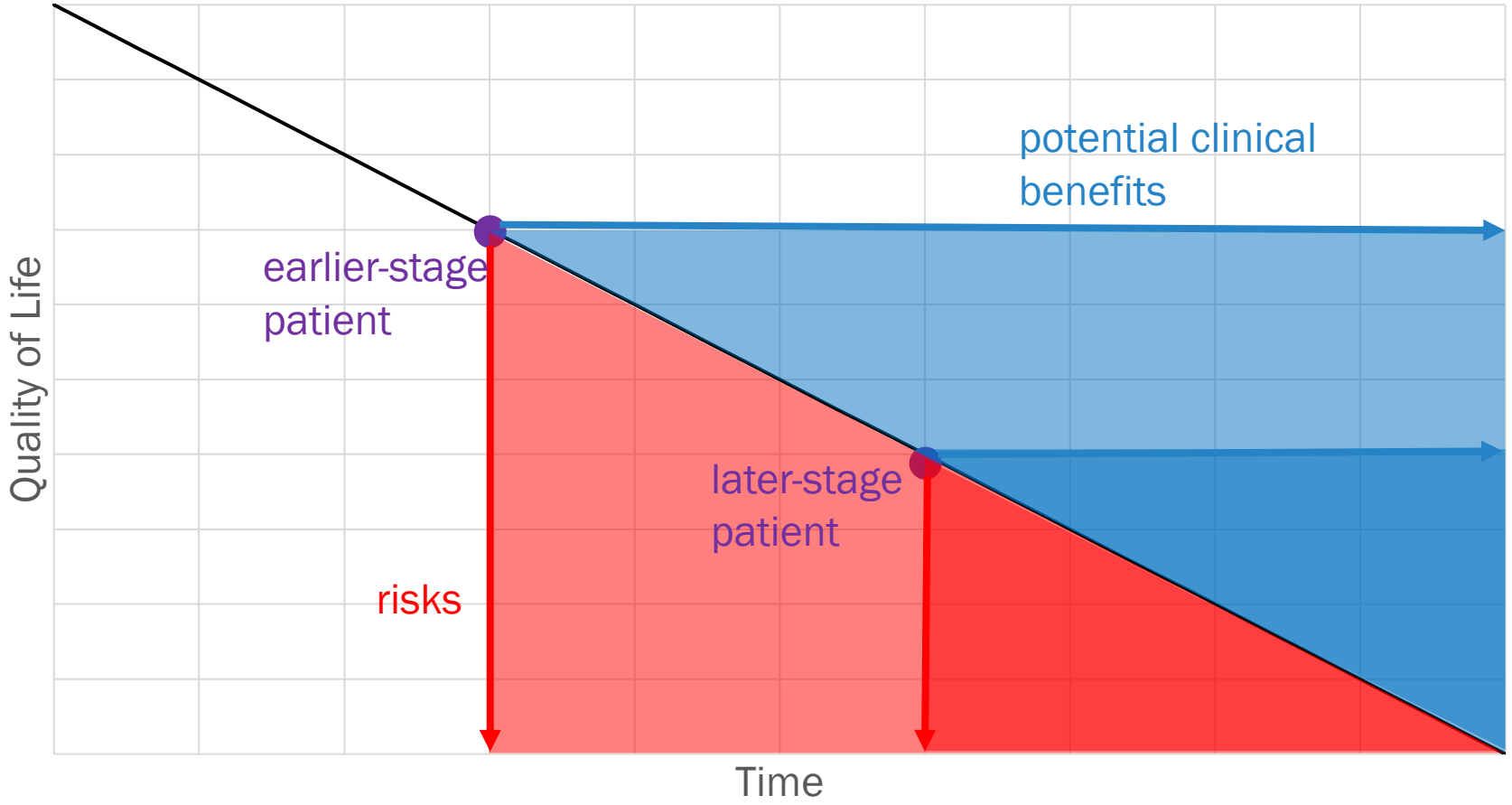
Blue arrows represent the possibility of halted disease progression (patient remains at current quality of life).

What are the potential benefits?



Light blue area represents the quality of life gained over time for a patient with earlier-stage disease.

What are the potential benefits?



Dark blue area represents the quality of life gained over time for a patient with later-stage disease. Patient with later-stage disease may gain less quality of life over time compared to patient with earlier-stage disease.

Further Complexity

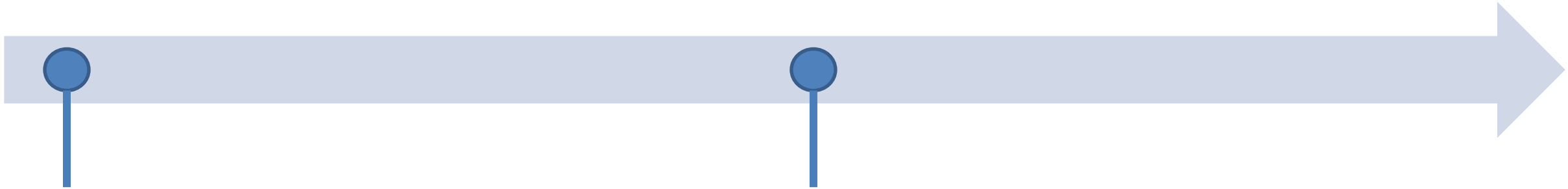
- Graphs showed the *magnitudes* of risks and potential benefits, but the analysis is more complex:
  - Early-stage patient: higher *probability* of benefit (GT is more likely to modify healthier nerve tissues)
  - Early-stage: lower *probability* of harm (better able to cope with any complications of GT)
  - Early-stage: higher scientific and social value (higher likelihood of benefit makes it easier to detect an efficacy signal)
  - Late-stage: possible 'only chance' to enroll in potentially beneficial research

Evaluating the Trade-Off

Earlier-stage patients	Later-stage patients
• Higher magnitude and likelihood of clinical benefit • Lower probability of harm • Social value - higher chance of detecting a potential efficacy signal	• Lower magnitude of harm • Only chance to receive potentially therapeutic GT • Lower risk of damaging societal trust in research due to a serious adverse event affecting a healthier patient

Participant selection in the GAN GT Trial

- Investigators designed eligibility criteria broadly, prioritizing among eligible patients when the trial became high-demand



Trial outset: Prioritized later-stage patients

- High uncertainty about GT risks
- Main priority = reduce risk of serious adverse event affecting a healthier patient (risk-benefit consideration)

As trial progressed: Prioritized earlier-stage patients

- After preliminary signs of GT safety
- Increase potential benefits (risk-benefit consideration)
- Increase knowledge about GT efficacy (social value consideration)

Points to Consider for Evaluating Differential Risk-Benefit Profiles

1. Risks and potential benefits may differ depending on stage of disease

2. Investigators may carefully consider which participants to enroll based on these differential risk-benefit profiles

3. Dosing participants in sequence rather than in parallel can allow investigators to adjust how they weigh the various risks and potential benefits based on relevant trial developments

Please feel welcome to contact me directly with any questions.

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