Statistical Challenges in Health Technology Assessment (HTA) for Rare Diseases

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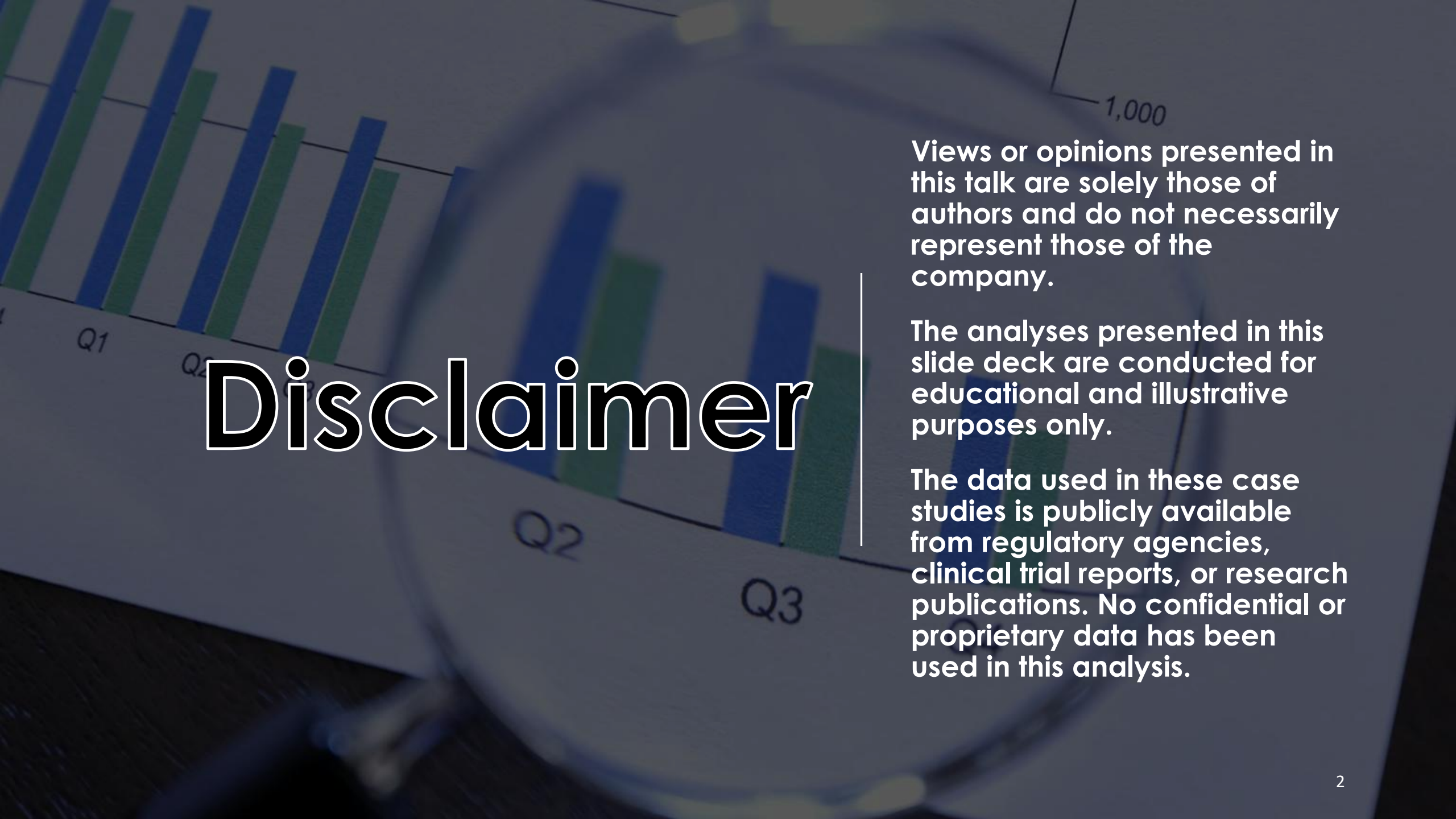

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The data used in these case studies is publicly available from regulatory agencies, clinical trial reports, or research publications. No confidential or proprietary data has been used in this analysis.

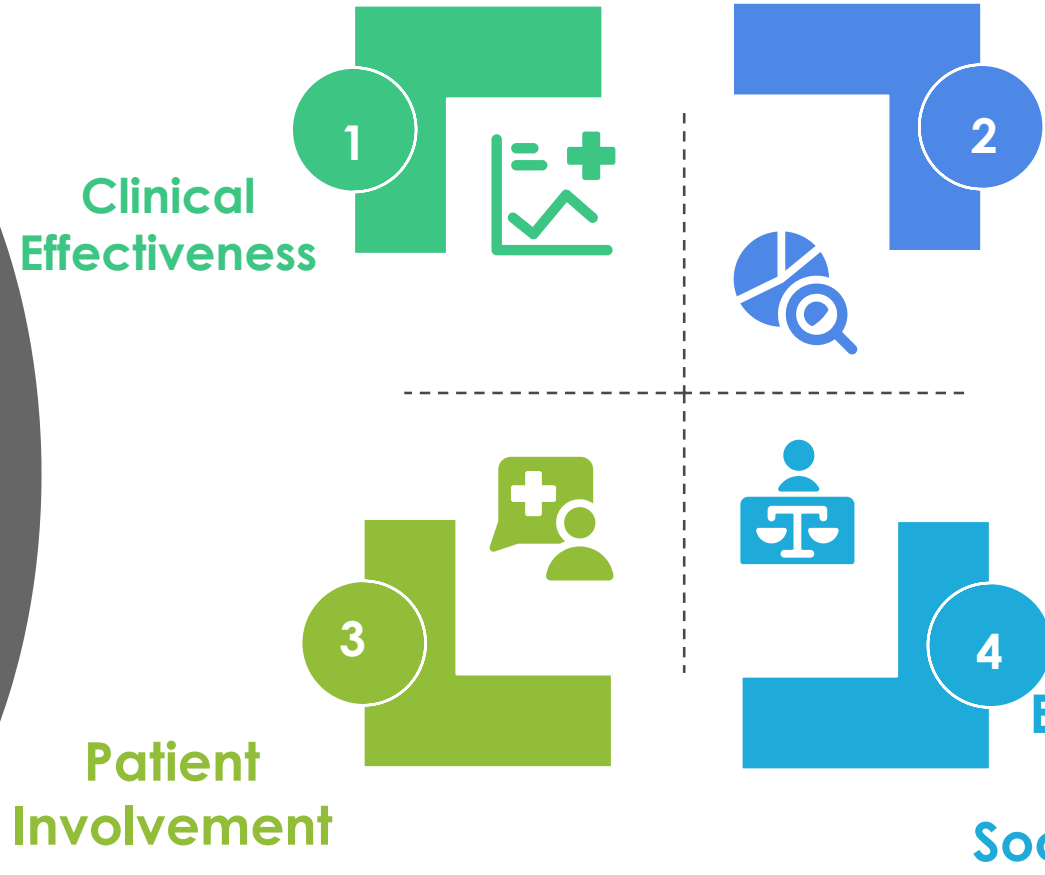
Outline

- Overview of Health Technology Assessment (HTA)
- Top Rare Diseases in the World
- Rare Diseases facts and Impact
- Unique Characteristics of Rare Diseases
- Key Statistical Challenges in HTA for Rare Diseases
- Importance of Health Technology Assessment (HTA)
- Ways to Handle Data Problems
- Adaptive Design
- Bayesian Methods

Overview of Health Technology Assessment (HTA)

HTA helps ensure that patients with rare diseases get access to effective treatments, while balancing affordability and evidence uncertainty.

Multidisciplinary process that systematically evaluates the medical, social, economic, and ethical implications of a health intervention



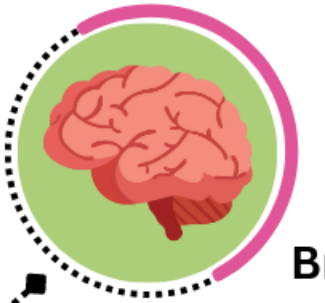
- Drug Approvals and Reimbursement Decisions
- Medical Device Assessments
- Public Health Interventions

Types of rare diseases

Blood

Metabolic

Brain/nervous system



Mobility

Connective Tissues

Intellectual disability

Miscellaneous Disease

Other

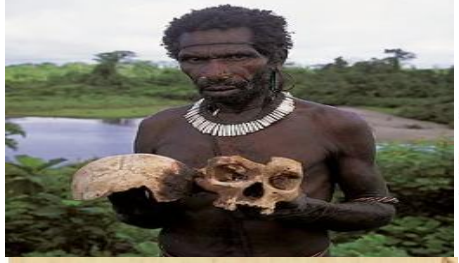
Cancer

Top Rare Diseases in the World You Never Heard About

Rare Diseases

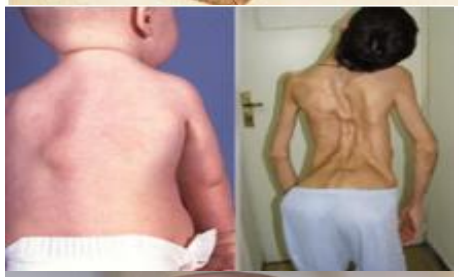
Methemoglobinemia
Rare condition causing bluish skin; treated with methylene blue.

Kuru Disease
Fatal prion disease with no cure; rapid progression.

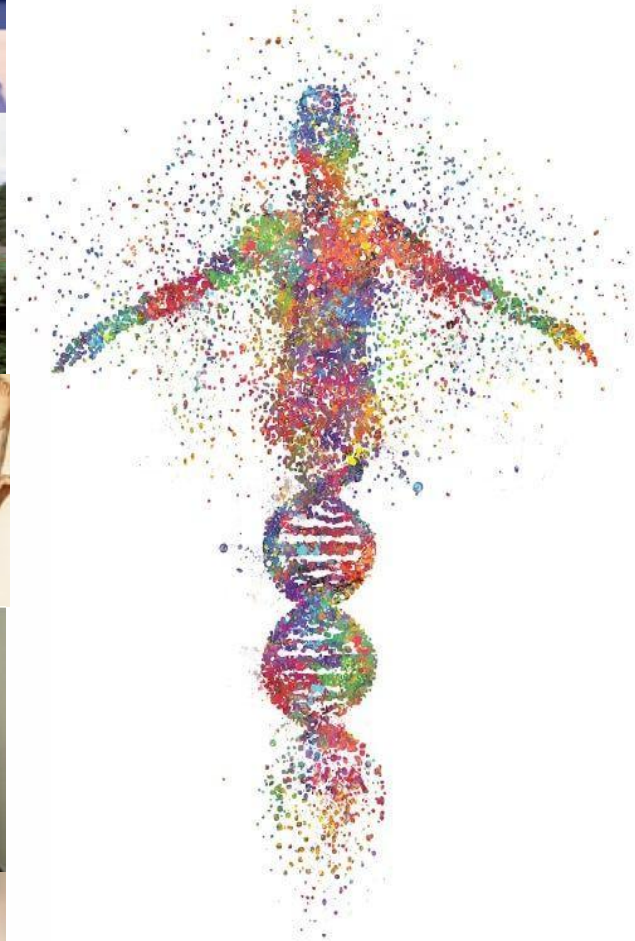


Harlequin Ichthyosis
Genetic disorder causing thick skin; isotretinoin aids treatment (1 in 0.3m).

Stone Man's Disease
Extremely rare condition where muscle turns to bone; no cure (1 in 2m).



Hutchinson Gilford Progeria Syndrome
Premature aging in children; ongoing research for cure (1 in 4m).



RARE DISEASES
FACTS AND IMPACT

Over
300 Million
people worldwide live with a rare disease

Approximately
1 in 20
individuals will be affected by a rare disease

Over
70%
of rare diseases have genetic origins

Only
5%
af rare diseases have an FDA-approved treatment

FDA

Over
7000
different rare diseases exist today

Long diagnostic journey
Averagee 5-7 years to receive correct diagnosis

Lack of specialists
Many patients go undiagnosed for years

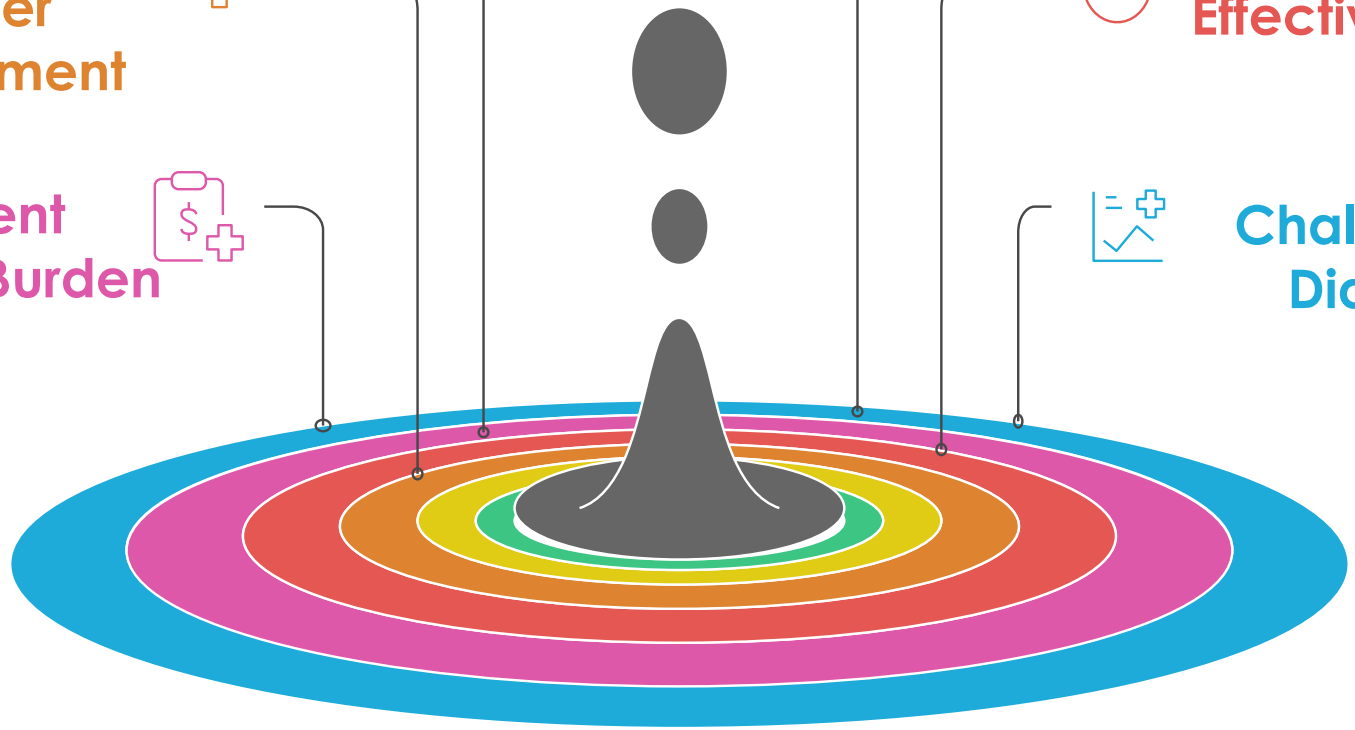
Long diagnostic journey
Average 5-7 years to receive correct diagnosis

Unique Characteristics of Rare Diseases

Low Occurrence
Trial challenges

Limited Clinical
Data hamper
effective treatment

High Treatment
Costs Financial Burden



Heterogeneity Complicates
research

Urgent need of
Effective treatments

Challenges in
Diagnosis

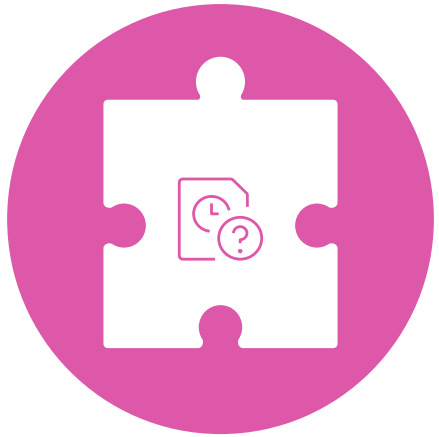
Key Statistical Challenges in HTA for Rare Diseases

Small Sample Size

Limited analysis & low power biased conclusions.

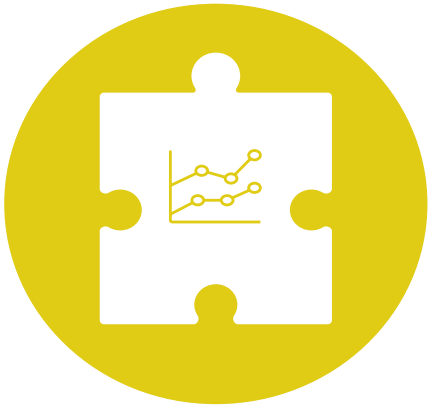
Disease Diversity

Limited applicability across populations delays comparisons.



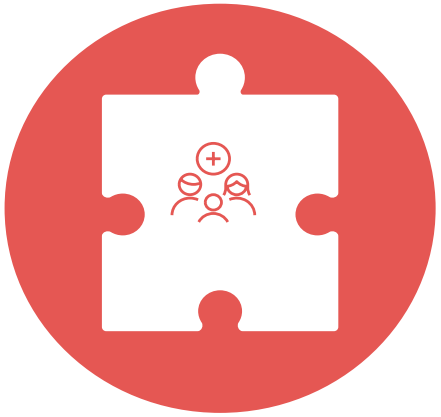
Lack of RCTs

Ethical concerns lead to support on weaker study designs.



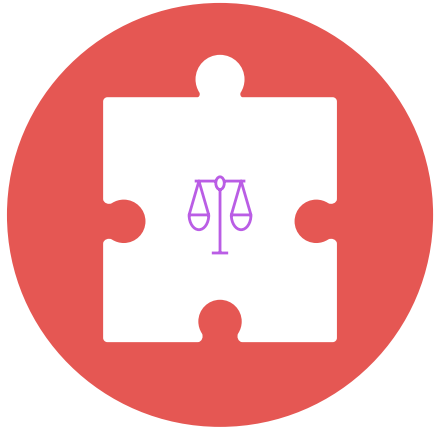
Lack of Trial Data

Uncertain effects hamper detecting clinical impact..



Missing Long-Term Data

Inability to assess value or predict outcomes hampers care planning.



Importance of Health Technology Assessment (HTA)

Supports evidence based decisions for policy funding & reimbursement.

Promotes access to safe, effective & high-impact care.

Encourages cost-effective care & avoids low value interventions.

Drives innovation & Provides a framework To evaluate new Technologies

Balances clinical value with economic impact.

Ways to Handle Data Problems

Traditional trials often fail for rare diseases

Innovative Trial Designs

- Adaptive Trials
  - ❑ Modify design as data accumulates
  - ❑ Needs fewer participants
  - ❑ Increases chance of success
- Basket Trials
  - ❑ One drug, multiple diseases with shared biomarkers
  - ❑ More efficient than individual trials

FDA supports and is developing guidance for these designs.

Advanced Stats: Bayesian Methods

- Bayesian approaches help overcome limited data issues
  - ❑ Use prior knowledge in analysis
  - ❑ Update continuously with incoming data
  - ❑ Effective for small sample sizes

FDA allows Bayesian borrowing in rare disease trials.

BLAZE-1 Trial: Adaptive Design in COVID-19 (Rare Subsets)

- **Condition:** COVID-19 (targeting rare/immunocompromised subgroups)
- **Intervention:** Bamlanivimab and Etesevimab (monoclonal antibodies)
- **Design:** Adaptive, randomized, double-blind, placebo-controlled
- **Goal:** Evaluate the effectiveness of monoclonal antibodies in reducing viral load and preventing disease progression.

The trial initially targeted general COVID-19 patients but used an adaptive design to expand enrollment to include rare, high-risk subgroups, such as:

- Immunocompromised patients (rare due to low representation in standard trials).
- Patients with genetic variants linked to poor COVID-19 outcomes

Demonstrates how adaptive design can be applied to rare diseases by efficiently **expanding subgroups**, optimizing dosing, and accelerating trial completion.

Statistical Results Bamlanivimab and Etesevimab for COVID-19

- **Primary Efficacy Results:**

  - **Endpoint:** Change in viral load from baseline at **Day 11**.
  - **Bamlanivimab (700 mg) + Etesevimab (1400 mg)** vs. **Placebo:**

Parameter	Treatment Group	Placebo Group	Difference (95% CI)	p-value	Statistical Significance
Mean change in viral load	−3.81 $\log_{10}$ copies/mL	−3.38 $\log_{10}$ copies/mL	−0.43 $\log_{10}$ copies/mL (−0.63 to −0.23)	< 0.001	Yes (Statistically significant)

- **Hospitalization and Death Rate:**

Parameter	Treatment Group	Placebo Group	Difference (95% CI)	p-value	Statistical Significance
Hospitalization or death by Day 29	2.1% (11/518)	7.0% (36/517)	ARR: 4.9% RRR: 70%	< 0.001	Yes (Significant reduction)

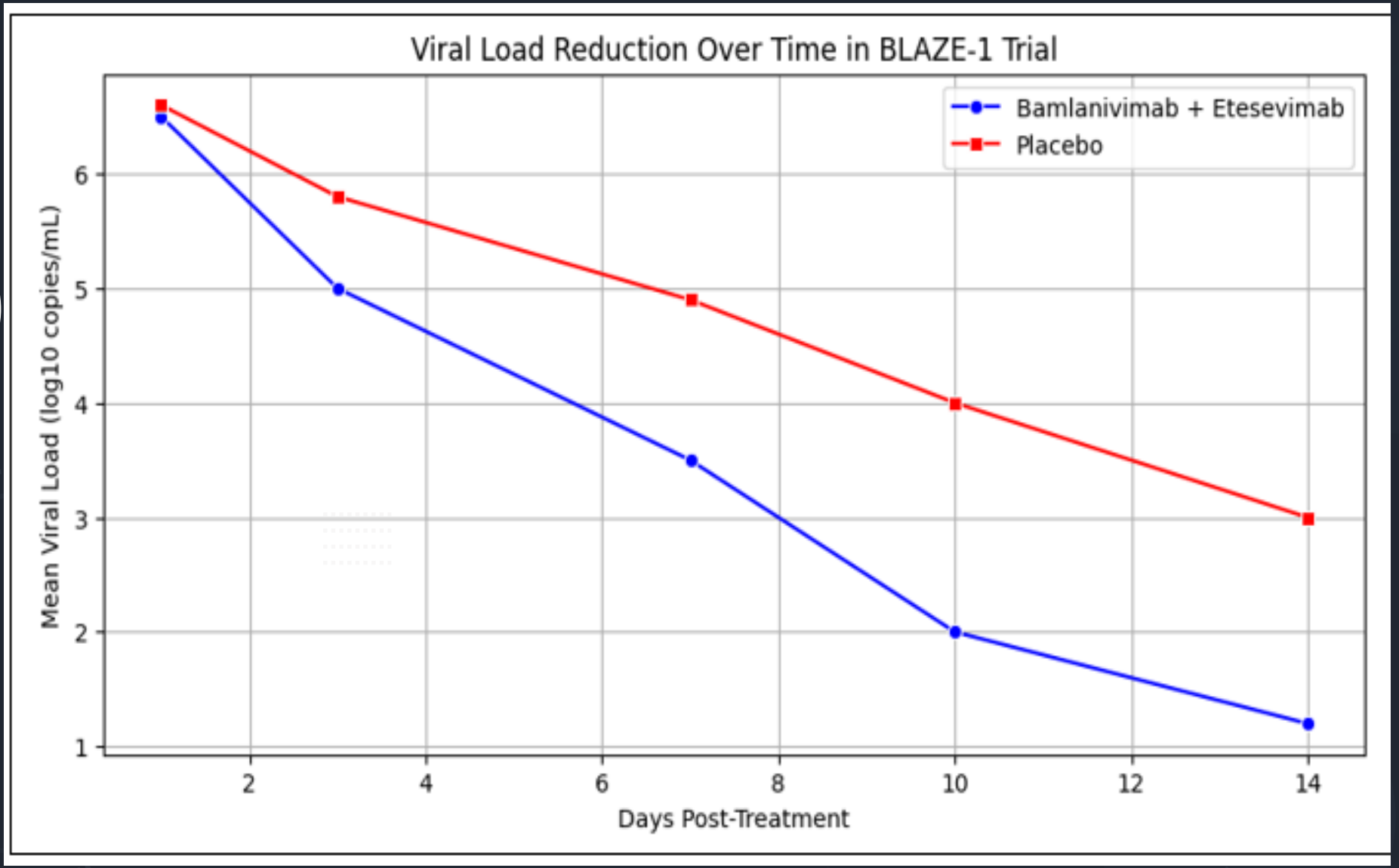
Statistical Results Bamlanivimab and Etesevimab for COVID-19

- **Subgroup Analysis: Rare/High-Risk Patients:**
  - **Immunocompromised or rare condition subgroup:**

Parameter	Treatment Group	Placebo Group	Relative Risk Reduction	p-value	Statistical Significance
Hospitalization or death (event rate)	4.4%	15.0%	~71%	< 0.001	Yes (Statistically significant benefit)

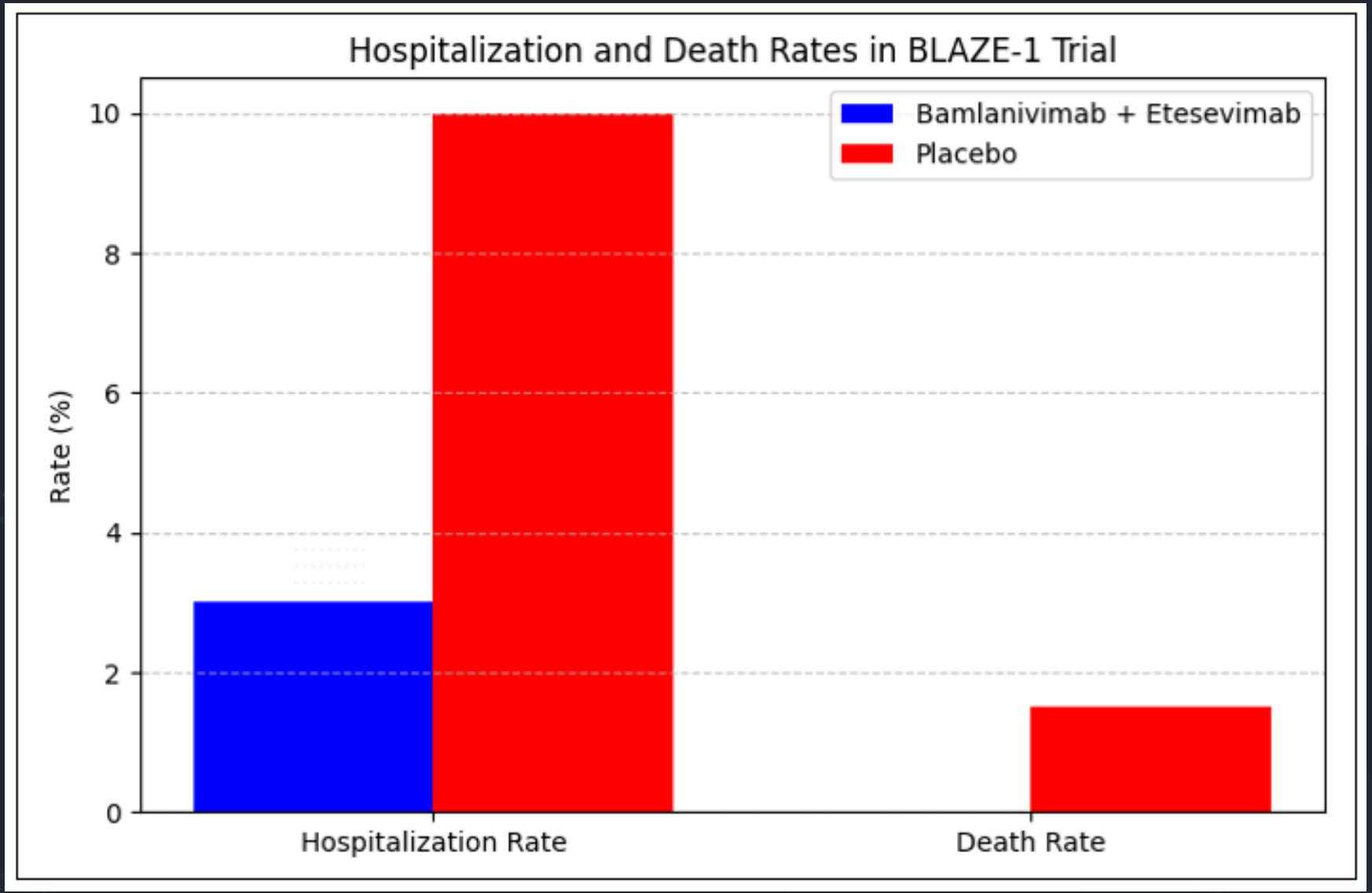
  - **Interim Analysis Impact:**
- After the first interim analysis, the trial expanded to **include rare/high-risk patients**, contributing to the **early stopping** for efficacy

Viral Load Reduction Over Time (Line Graph)



Highlight the **statistical significance (p-values)** for reductions.

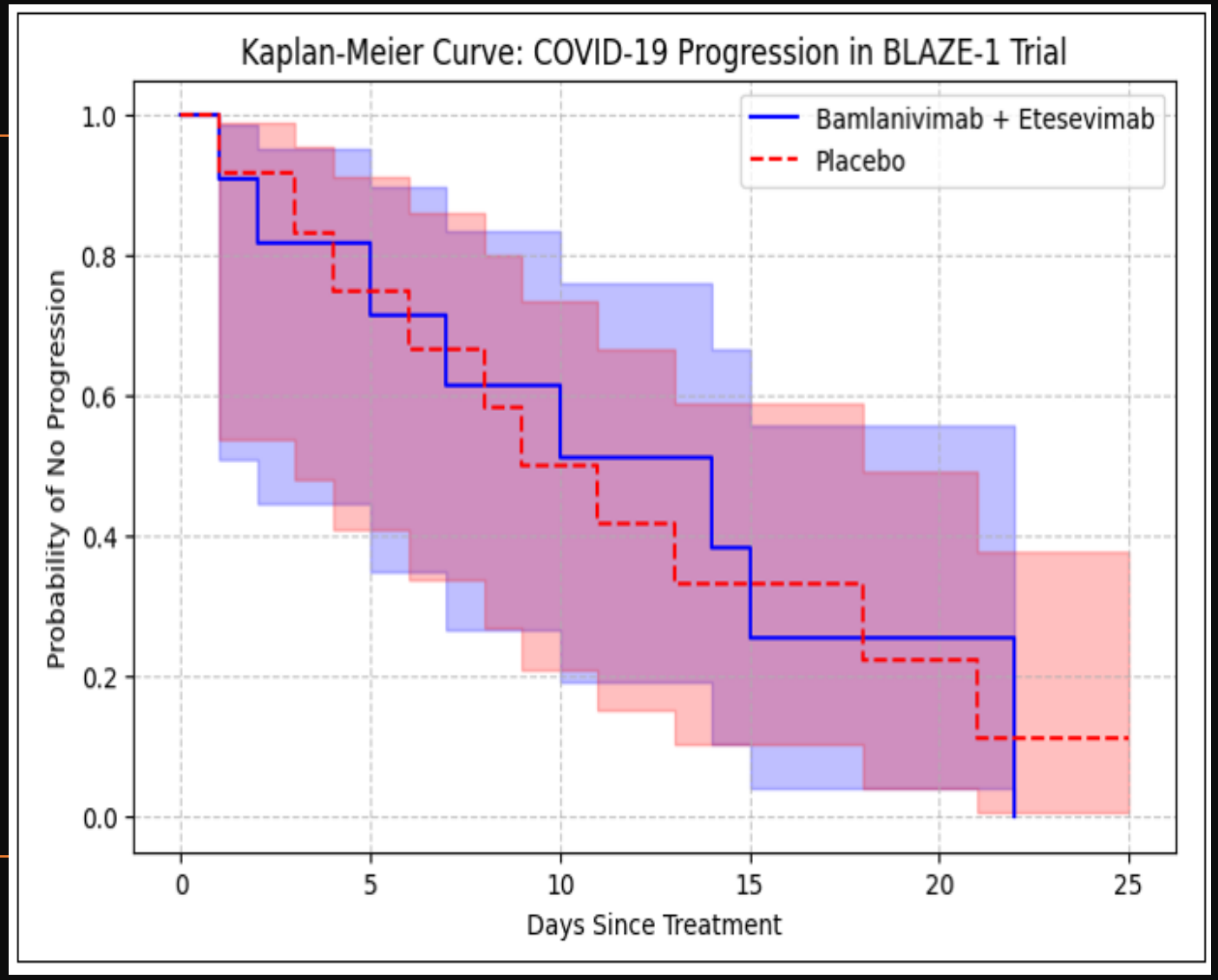
Hospitalization and Death Rates (Bar Chart)



- The **treatment group shows a significant reduction** in hospitalization (3% vs. 10%) and death (0% vs. 1.5%).
- This supports the **efficacy of Bamlanivimab + Etesevimab** in reducing severe COVID-19 outcomes.

Cumulative Incidence of COVID-19 Progression (Kaplan-Meier Curve)

- **Kaplan-Meier Curves** estimate the probability of **not experiencing disease progression** over time.
- The **treatment group (blue solid line)** shows a **lower progression risk** compared to the **placebo group (red dashed line)**.
- **Confidence intervals (CI)** are included to indicate uncertainty in the estimates.



Key Takeaway Adaptive Design in COVID-19 (Rare Subsets)

Adaptive Platform Design

- Empowering rapid, evidence-based decisions during health crises.

High-Risk Focus

- Targeted mild-to-moderate COVID-19 patients at high risk of progression (age, comorbidities).

Early Efficacy Signal

- Primary endpoint was viral load reduction by Day 11.

Real-World Relevance

- Generated timely evidence to support emergency use decisions.

Rare Subset Insights

- Demonstrated how adaptive designs can support analysis in rare or hard-to-reach populations.

Bayesian Design in Rare Disease HTA

- **Case Study: Strensiq (Asfotase Alfa)**
  - **Condition:** Hypophosphatasia (HPP)
    - A rare, genetic metabolic disorder affecting bone mineralization.
    - Extremely low prevalence (~1 in 100,000 live births).
  - **Drug:** Strensiq (Asfotase Alfa)
  - **Goal:** Assess the long-term effectiveness and safety of Strensiq using Bayesian statistical methods to address the small sample size and data uncertainty.

Bayesian Methodology in the Trial

1. **Borrowing Historical Data:**
   - Rarity of HPP - trial with **limited patient data**.
   - **Bayesian hierarchical models**:
     - **Incorporate historical control data** into the analysis.
     - Improve precision & reduce uncertainty by **borrowing strength** from previous studies.
2. **Bayesian Prior Distribution:**
   - **Informative priors** were based on:
     - Data **history studies** of untreated HPP patients.
     - Preclinical and observational data.
   - Helps stabilize the estimates, making the small-sample analysis more robust.
3. **Posterior Probabilities for Efficacy:**
   - The Bayesian model calculated **posterior probabilities** for treatment efficacy.
   - Allow the trial to **quantify uncertainty** around the treatment effect, providing a probabilistic interpretation of results.

Statistical results

- **Primary Efficacy Outcomes (Survival Rates):**
  - **Endpoint: Overall survival** and **ventilation-free survival** at **5 years**.
  - **Bayesian Posterior Mean Estimates:**

Parameter	Strensiq Group	Historical Control Group	Bayesian Posterior Probability of Superiority	Statistical Significance
Survival rate	95.0% (Posterior mean)	42.0%	>99.9%	Very high confidence Strensiq improves survival
95% Credible Interval (CrI)	89.2% – 98.4%	30.5% – 54.7%		

This indicated a very high probability that Strensiq was superior to no treatment.

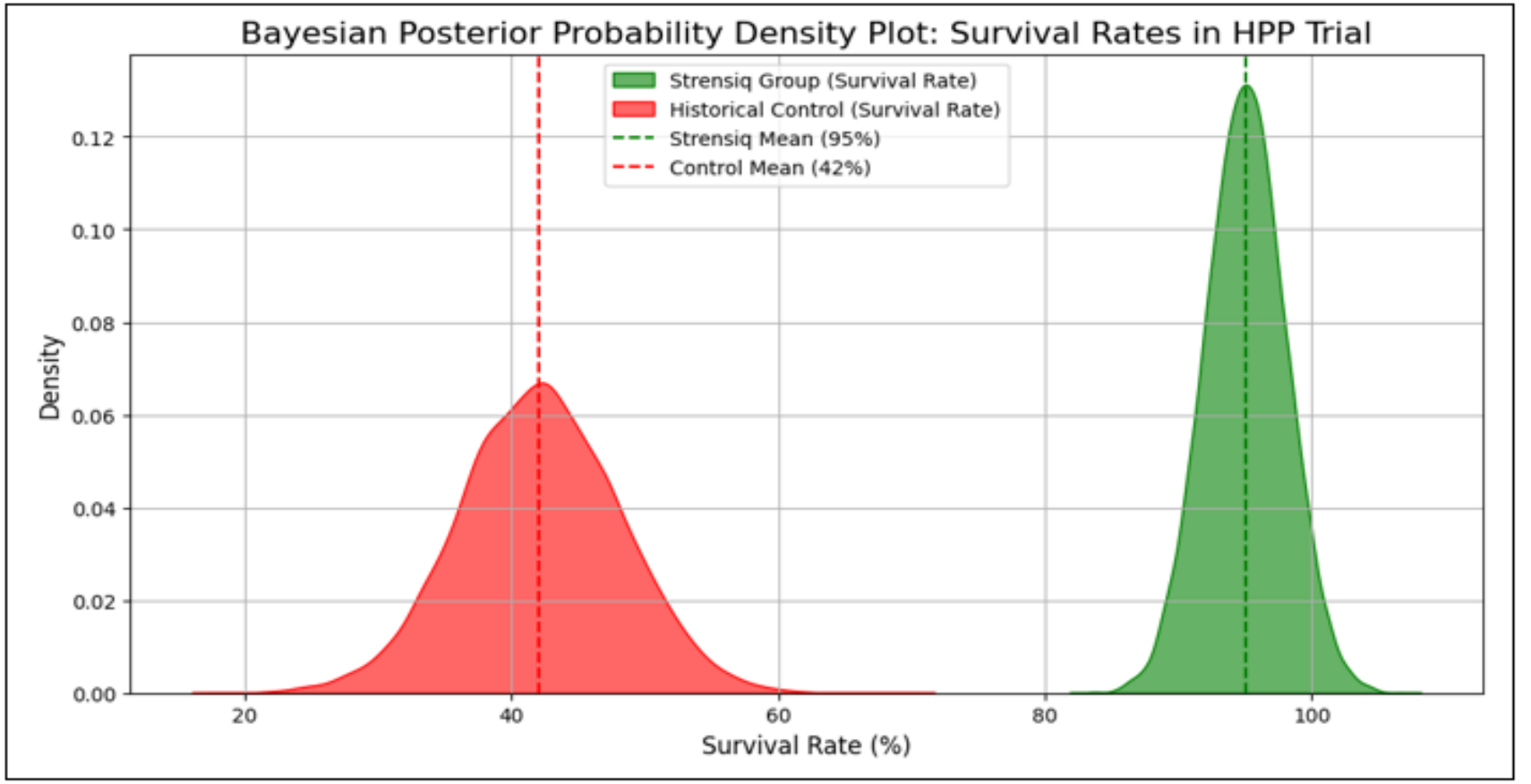
Statistical results

- **Ventilation-Free Survival (Key Secondary Endpoint)**

- **Patients not requiring mechanical ventilation:**

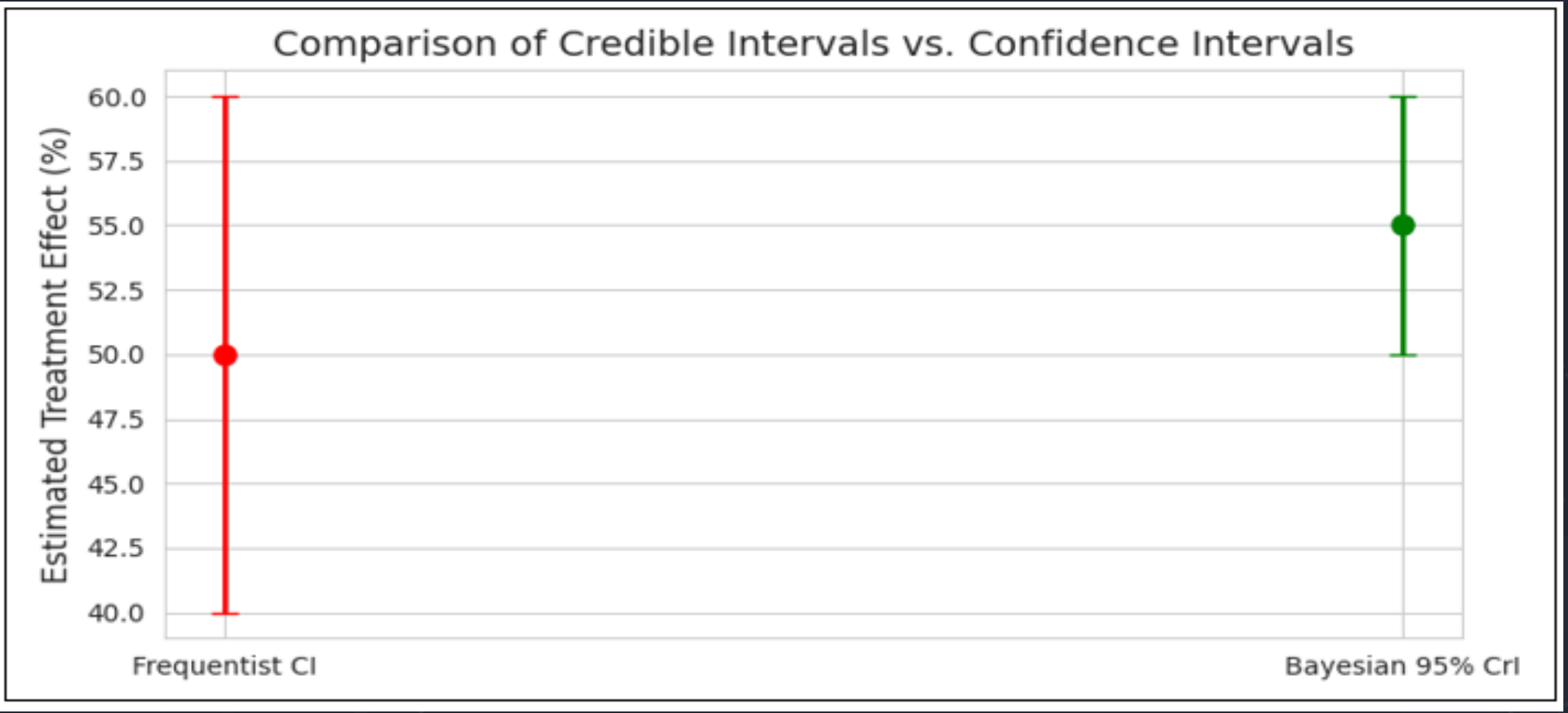
Parameter	Strensiq Group	Historical Control Group	Bayesian Posterior Probability of Superiority	Statistical Significance
Ventilation-free survival rate	89.0%	27.0%	>99.5%	Strong evidence of improved ventilation-free survival
95% Credible Interval (CrI)	82.5% – 94.3%	15.9% – 39.8%		

Bayesian Posterior Probability Density Plot



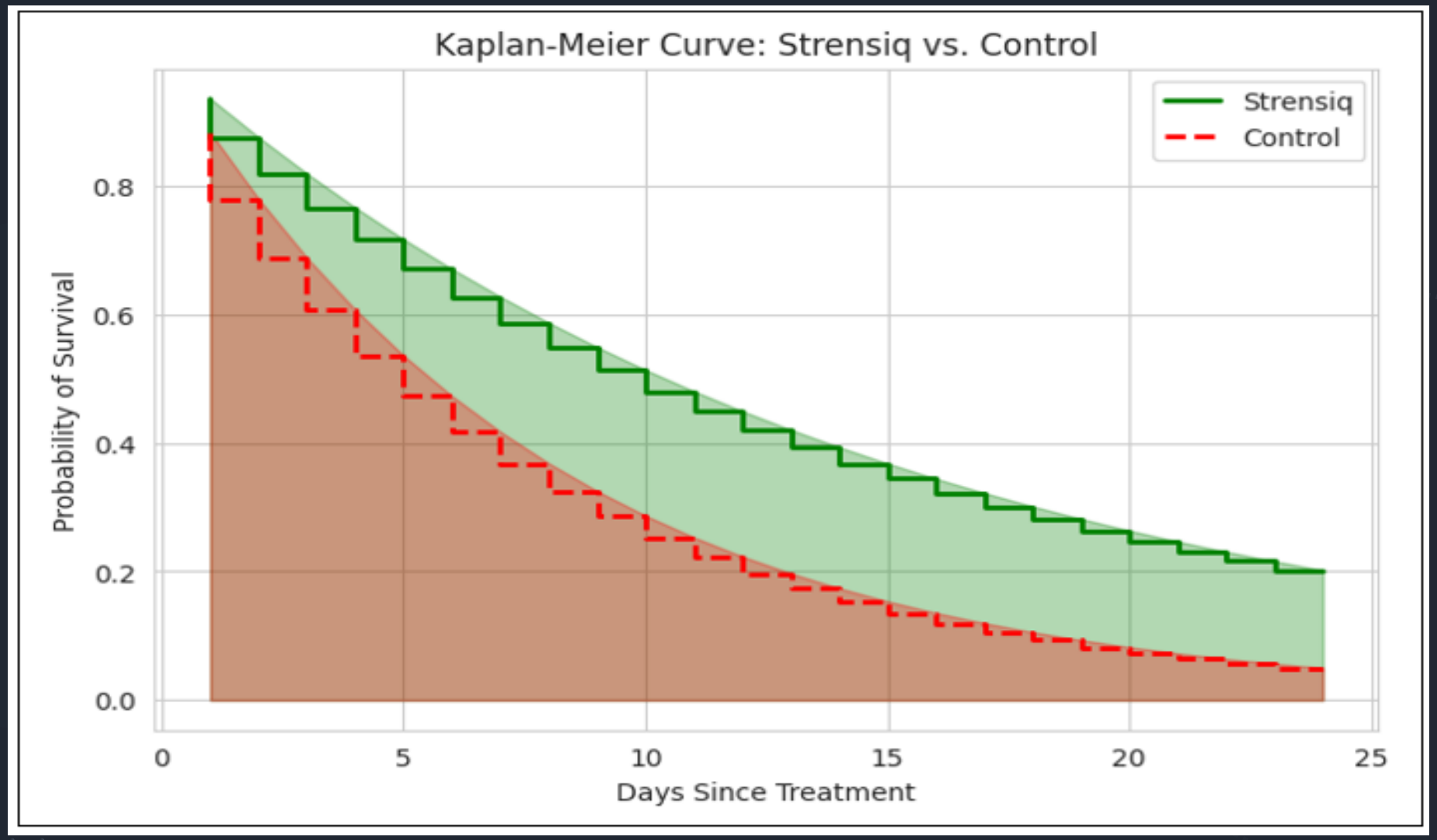
- The **Strensiq group** has a survival rate distribution that is significantly higher than the control group.
- The **control group's survival rate distribution is centered around 42%**, as indicated by the red dashed line.
- The **Strensiq group's survival rate distribution is concentrated near 95%**, as indicated by the green dashed line.
- The **posterior distributions are well-separated**, showing a clear advantage of the Strensiq treatment over the historical control.

Credible Intervals (CrI) vs. Confidence Intervals (CI)



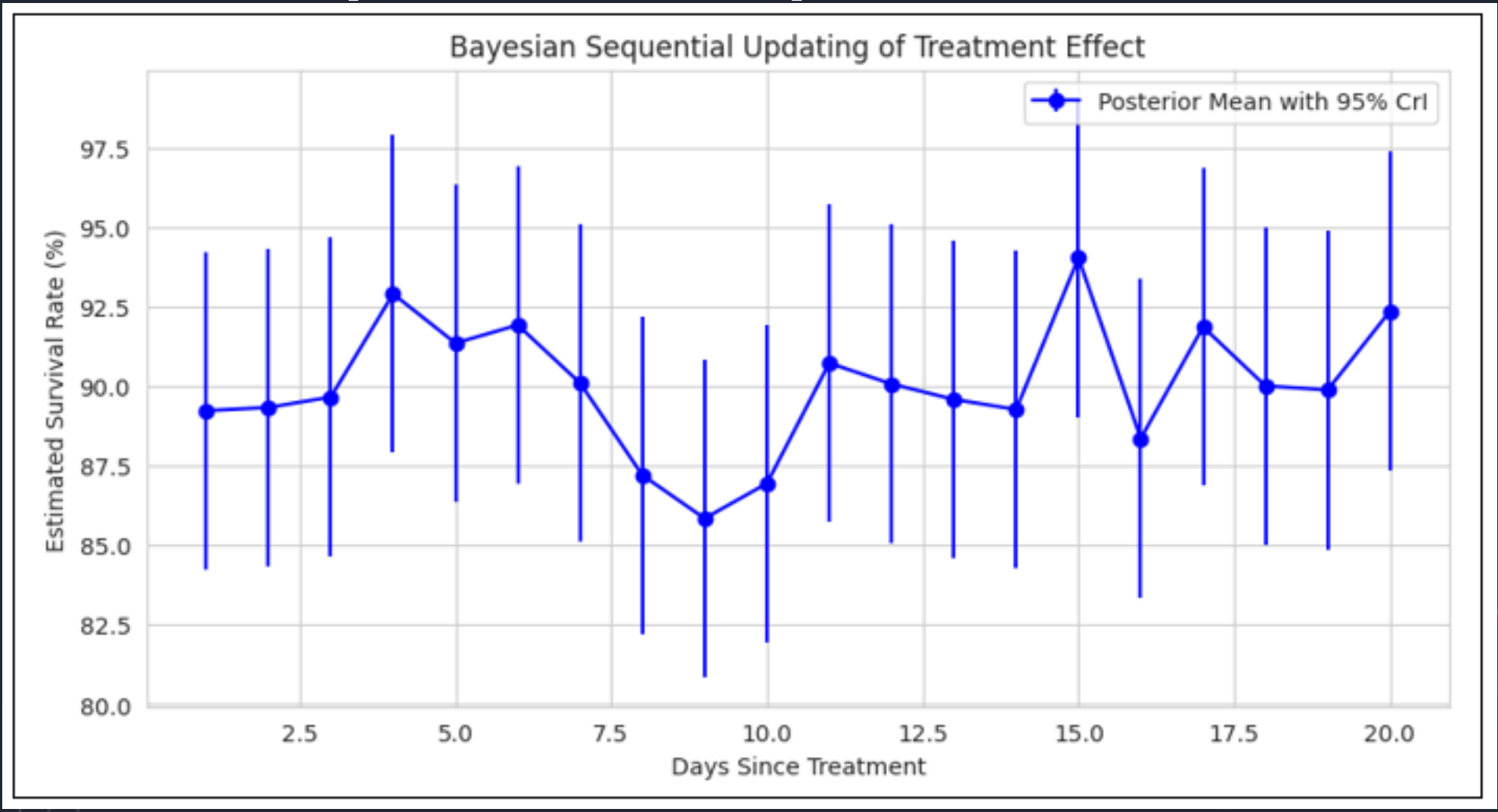
- The **95% CrI for Strensiq** shows a high degree of certainty in its superior survival rate.
- The **Bayesian CrI is narrower** than the Frequentist CI, showing reduced uncertainty due to prior information.

Survival Probability (Kaplan-Meier Curve)



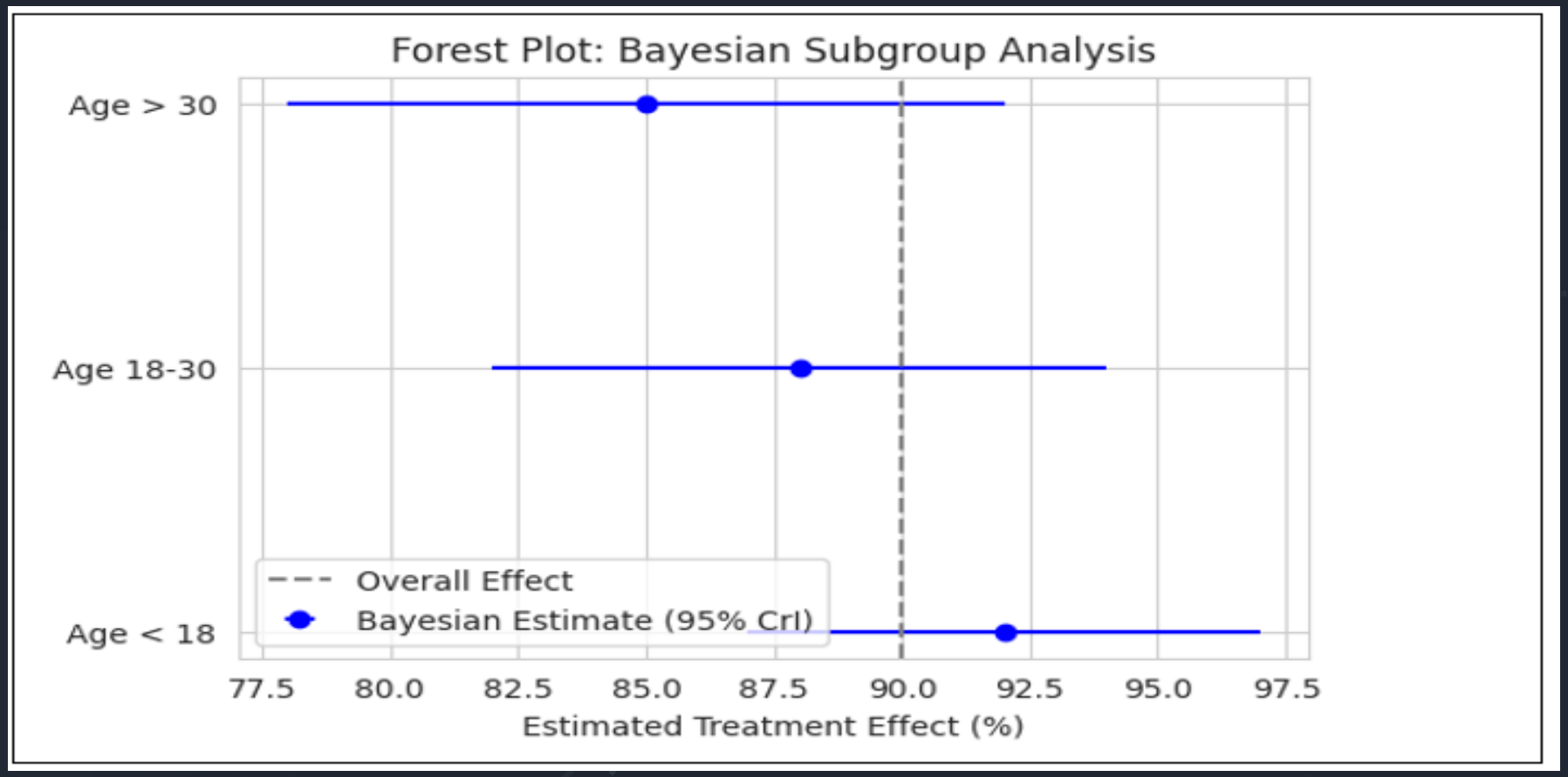
Strensiq group maintains a **higher survival probability** across all time points

Bayesian Sequential Analysis



- Shows how Bayesian methods **continuously update the treatment effect estimate** over time.
- Estimates become more **precise with additional data**.

Forest Plot for Subgroup Analysis



- Shows estimated treatment effects for **different patient subgroups** with **95% CrI error bars**.
- All subgroups benefit from **Strensiq**, but younger patients have slightly better effects.
- **Subgroup analysis** shows effectiveness **across different age groups**.

Key Takeaway - Bayesian Design

How Bayesian methods can effectively handle data inadequacy in rare disease HTA by

Bayesian Approach

- Enabled better analysis in rare disease with limited data.

Borrowed strength

- From historical controls to supplement sparse trial data.

Used posterior probabilities

- To reduce uncertainty and support efficacy claims.

Informed HTA and reimbursement

- Decisions with increased confidence.

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Thank you for your time!

Any Questions?

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