CURRICULUM VITAE

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EDUCATIONAL BACKGROUND

- **University of Maryland, Baltimore**
  Maryland, Baltimore
  Masters in Pharmaceutical Health Services Research, Spring 2023
- **Bombay College Of Pharmacy**
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  Bachelor of Pharmacy
  Graduation: 2021

RESEARCH EXPERIENCE

- Experience in Manuscript writing, Systematic review, Literature review and Specific Aims page writing.
- Experience in performing retrospective cohort studies using Claims data.

WORK EXPERIENCE

- **University of Maryland, Baltimore** January 2022 - Present
  Graduate Research Assistant
  Team Projects:
  1. **"COMmunity Mistrust and Institutional Trustworthiness to advance health EQuity research (COMMIT-EQ)" Source: FDA (U01FD007563)**

  Primary role - Search strategist to conduct a systematic literature review. Developed and executed appropriate search strategies for both peer-reviewed and grey literature for a systematic literature review using Covidence. Accompanied team in analyzing over 500 full-text research papers and currently working as a co-author on manuscript drafting.

  2. **Assessing Health Equity in Cost-Effectiveness Analysis**

  Completed a review of final ICER evidence reports to assess the inclusion of health disparities in ICER value assessments conducted for pharmacological treatments in the US. Extracted and categorized information relevant to health equity from the Long-term Cost Effectiveness section of the report.

  3. **Exploring pharmacy student and graduate experiences with student debt, burnout, and loan relief.**

  Led semi-structured interviews with 20 recent pharmacy graduates to gather insights into their experiences with debt. Interview debriefing i.e., identified codes and appropriate themes relevant to the aim of the study. Completed data analysis using NVIVO and manuscript writing.

- **Applied Patient Experience, LLC** June 2022 – August 2022
  Research Intern, Patient-Centered Research
  Projects:
    1. **National Health Council - Identifying essential questions for patients to ask healthcare providers.**

  Contributed to a qualitative research study that aimed to understand the experiences of chronic disease patients in interacting with the U.S. healthcare system and provided suggestions for improving healthcare discussions and quality. My tasks included creating a codebook, analyzing transcripts, and interpreting and summarizing results with the project team.

    2. **Assessing Use FDA's Use of Patient Experience Data (PED) in Drug Approvals for the year 2022.**

  The purpose of this study was to evaluate how researchers across the FDA consider patient experience data in their approval decisions. My tasks included contributing to a data extraction table and collating data from all clinical or multidisciplinary reviews between 2018-2021.

PUBLICATIONS AND PRESENTATIONS

- Seo D, Patil D, Mattingly J. Inclusion of Considerations for Health Disparities in Cost-Effectiveness Analyses. (under review)
- Huffman M, Mcguirt D, Patil D, Mattingly J. Exploring pharmacy student experiences with student debt and perspectives on future burnout and loan relief. (under review)
- **Podium presentation for the ISPOR conference 2023** - Patil D, Oehrlein E, How Did FDA Consider Patient Experience Data in Regulatory Decisions Among Approved Drugs in 2022?

PROFESSIONAL SKILLS AND AWARDS

- Statistical Language: **SAS & R**
- Experience using **TreeAge** Pro Healthcare 2022 Software
- Experience using **Nvivo** – A qualitative data analysis program
- Experience using **Covidence** for systematic review
- Proficient in **MS Office** / MS Word / MS Excel / MS PowerPoint
- Bayer Scholar Award

LEADERSHIP

- Member of the ISPOR Student Network Event Planning Committee 2022-2023
- Secretary at UMB-ISPOR-Eboard 2021-2022
- Director at BCP-ISPOR-SC 2020-2022

ABSTRACT

Title: A cost-effectiveness analysis model framework for treatments of early-stage Huntington's disease patients in the United States

Divya Manoj Patil, Master of Science

Thesis Directed by: Mattingly, T. Joseph, PhD, MBA, Associate Professor, Pharmaceutical Health Services Research

Huntington's disease (HD) is a rare neurodegenerative condition caused by mutation in the huntingtin gene. The emergence of drugs such as Tominersen and AMT-130, which have the potential to treat HD, highlights the importance of evaluating their cost-effectiveness. This study aims to fill this gap and evaluate the incremental cost-effectiveness of these treatments compared with the current standard of care for HD. A health state transition Markov model was developed to estimate the costs and benefits of each treatment over a lifetime time horizon from a societal perspective. Our findings showed that Tominersen and AMT-130 were associated with higher costs but also provided greater benefits than the standard of care. AMT-130 was found to be a cost-effective option compared to standard of care and Tominersen, considering the willingness to pay threshold. This study provides valuable insights into the economic impact of HD which can inform healthcare policy and treatment decisions.

A Cost-Effectiveness Analysis Model Framework For Treatments Of Early-Stage Huntington's Disease Patients In The United States

by
Divya Manoj Patil

Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Master of Science
2023

Dedicated in the loving memory of my grandmother whose unwavering love, support, and encouragement have been my guiding light and source of strength throughout this journey.

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List of Abbreviations

AAV	Adeno-Associated Virus
ASOs	Antisense Oligonucleotides
CSF	Cerebral Spinal Fluid
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CAG	Cytosine-Adenine-Guanine Nucleotides
DVT	Deep Venous Thrombosis
DBZ	Deutetrabenazine
HSUV	Health State Utility Value
HTT	Huntingtin
HD	Huntington's Disease
HD-ADL	Huntington's Disease Activities Of Daily Living
HD-CAB	Huntington's Disease Cognitive Assessment Battery
UHDRS	Huntington's Disease Rating Scale
ICER	Incremental Cost-Effectiveness Ratio (ICER)
ICER	Institute For Clinical And Economic Review
MRI	Magnetic Resonance Imaging
MoCA	Montreal Cognitive Assessment
mtHTT	Mutant Huntingtin
OWSA	One-Way Sensitivity Analyses
OS	Overall Survival
PRISMA	Preferred Reporting Items For Systematic Reviews And Meta-Analyses
PBA-HD	Problem Behaviors Assessment For HD

QALY	Quality-Adjusted Life-Year
SAEs	Serious Adverse Events
SMA	Spinal Muscular Atrophy
SMN	Survival Motor Neuron
SUSARs	Suspected Unexpected Serious Adverse Reactions
TFC	Total Functional Capacity
TMS	Total Motor Score
USD	US Dollars
VMAT2	Vesicular Monoamine Transporter 2
VA	Veterans Affairs
wtHTT	Wildtype Huntingtin
WTP	Willingness-To-Pay

CHAPTER 1: UNDERSTANDING HUNTINGTON'S DISEASE

1.1 Disease Overview

Huntington's disease (HD) is a rare, yet devastating neurodegenerative disorder characterized by the progressive development of psychiatric manifestations, cognitive decline, and uncontrolled jerky movements known as chorea that include bothersome and potentially disabling excessive movement in finger, feet, face and torso.[1] These movements can get more intense when the person is nervous or distracted and as HD progresses, the these movements can become more extreme and obvious.[2]

Huntington's Disease is named after George Huntington, an American physician who described the disease in 1872. His description was based on observations of HD-affected families from the village of East Hampton, Long Island, New York (USA), where Dr. Huntington lived and worked. In the past, HD was often referred to as Huntington's chorea.[3]

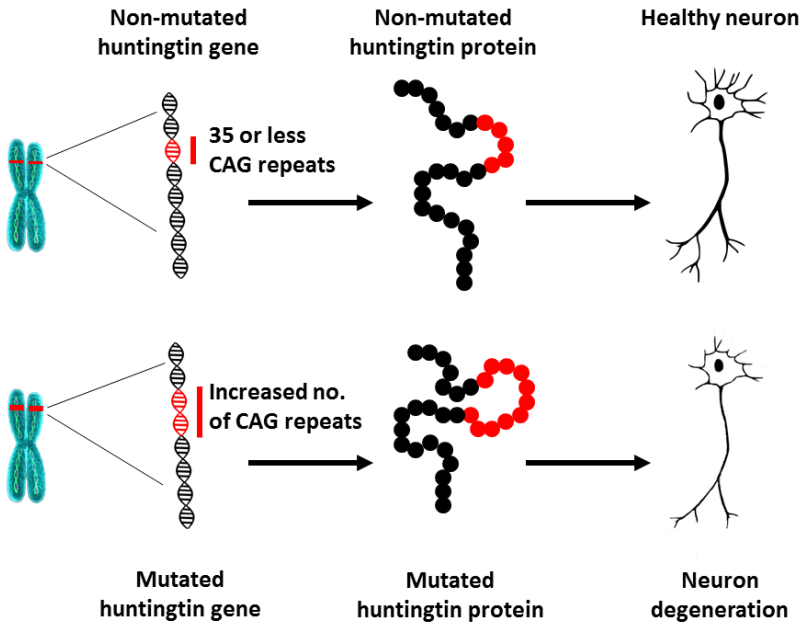
The Faulty Gene

The etiology of HD is attributed to DNA mutations present in the huntingtin gene. This gene, first identified in 1993, is universally present in all individuals, but only those who inherit the mutated form are characterized by an excessively repeated sequence of cytosine-adenine-guanine nucleotides (C-A-G) and are susceptible to developing HD and transmitting the condition to their offspring.[4,5]

Genes provide instructions to build proteins, which are responsible for the regulation of various bodily functions. The huntingtin gene provides instructions for the production of

the huntingtin protein, which plays an important role, especially during fetal brain development. The exact function of the huntingtin protein is not fully understood, but research indicates that the protein is large and seems to have many functions.[5] At one particular end of the huntingtin protein there is a stretch of repeats of one particular amino acid called glutamine and this distinctive feature is known as the polyglutamine repeat. Normally the polyglutamine repeat consists of up to 35 glutamine units, however, individuals with the HD mutation possess an expansion of this repeat sequence, consisting of at least 36 glutamine units (Figure 1).[3] The presence of this repeat expansion in the huntingtin gene is the underlying cause of HD, with all affected individuals developing the disease eventually, while their children have a 50% chance of inheriting HD.[4,5]

Figure 1: Etiology of Huntington's Disease

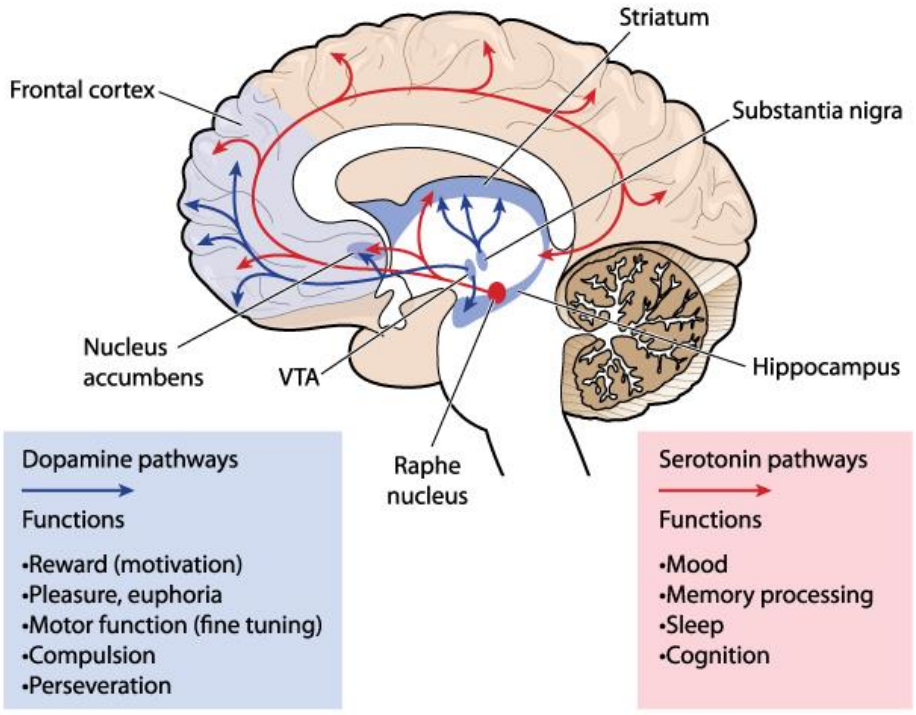


European Huntington's Disease Network. About Huntington's Disease. *ehdn.org*. https://ehdn.org/about-hd/

CAG repeats lead to an abnormal and excessively long huntingtin protein, hindering its proper functioning. Over time, the accumulation of mutant huntingtin protein in brain cells leads to their damage and death, resulting in the classic symptoms of HD.[4,5]

The striatum, comprising part of the basal ganglia, is particularly vulnerable to damage in HD (Figure 2). The striatum plays a pivotal role in regulating movement and is also involved in various other cognitive and emotional processes. As HD advances, it also impairs the cortex, which is the outermost and folded part of the brain, leading to cognitive decline. As time progresses, HD causes brain atrophy, ultimately affecting the overall functional capacity of the individual.[3]

Figure 2: Areas of the brain including the striatum, the most affected brain area.



European Huntington's Disease Network. About Huntington's Disease. *ehdn.org*. https://ehdn.org/about-hd/

1.2 Symptoms of HD

Early signs of HD can vary widely, but often involve symptoms like personality changes, mood swings, depression, forgetfulness, impaired judgment, unsteady gait, involuntary movements (chorea), slurred speech, difficulty in swallowing and significant weight loss.[3,5]

Chorea being a prime symptom, can make it harder to walk and increase the likelihood of falling. Nevertheless, some people with HD do not experience chorea; instead, they may become rigid and move very little or not at all, known as akinesia. Additionally, some individuals may have unusual postures which are referred to as dystonia. Akinesia and dystonia can blend or alternate with each other.[3,6]

Other symptoms may include tremors, involuntary muscle movements, and unusual eye movements. Difficulties with speech, swallowing, and eating also may occur. Due to constant involuntary movement and feeding problems, swallowing issues, choking, and chest infections, a person with HD may lose a significant amount of weight. People with HD may also experience insomnia, loss of energy, fatigue, and seizures. Eventually, many individuals will a wheelchair or become bed-bound.[3]

Cognitive changes can include attention or judgment difficulties, as well as difficulty solving problems, making decisions, driving, prioritizing, and learning new things. Memory impairment and difficulties in answering questions and expressing thoughts may also occur. These cognitive changes worsen as the disease progresses until individuals are unable to function independently. When cognitive problems are severe enough to interfere with daily life, the condition is classified as dementia. Despite this, many people with HD remain aware of their surroundings and can express their emotions.[3,6]

Behavioral changes may include mood swings, irritability, apathy, depression, or anger. These symptoms may lessen as the disease progresses, but they can continue in some people and include outbursts, suicidal thoughts, deep depression, and psychosis. Moreover, people with HD may withdraw from social activities.[3,7]

Genetic Testing

Since 1993, a direct testing method for HD has been accessible, which enables a single individual to undergo the test.[6,8] The genetic variants tested are CAG repeats in chromosome 4p16.3 for Huntington's disease.[9] Previously, linkage analysis was the only available method, requiring DNA samples from multiple family members. Consequently, the dependence on family support and consensus has been eliminated. However, only 3% of people in the US currently at risk for HD, have undergone presymptomatic testing, with some fearing genetic discrimination.[6,8]

1.3 Measuring HD Severity

Several rating scales have been developed to assess various aspects of HD, including motor symptoms, cognitive function, and functional abilities. These scales are used to measure disease severity, track disease progression, and evaluate the effectiveness of treatments in clinical trials. The most commonly used scales for motor symptoms are the Unified Huntington's Disease Rating Scale (UHDRS)[10] Total Motor Score (TMS)[11]. For cognitive and functional abilities, the most widely used scales are the Montreal Cognitive Assessment (MoCA)[12] and the Huntington's Disease Activities of Daily Living (HD-ADL)[13,14] scale, respectively. These rating scales are essential tools for clinical research and patient care in HD.

The Unified Huntington's Disease Rating Scale (UHDRS)

The Unified Huntington's Disease Rating Scale (UHDRS), developed by the Huntington Study Group, is a semi-objective clinical rating scale. The scale assesses relevant clinical features of HD to allow comparisons of inter- and intraindividual clinical signs, disease progression, and effects of therapy. This scale comprises six distinct sections i.e., motor, cognitive, behavioral, functional assessment, independence scale, and total functional capacity.[10]

1. **Motor – Total Motor Score (TMS)**

   Motor abnormalities are a core feature of HD to such an extent that HD is also known as Huntington's chorea. These motor symptoms and signs continue to be used as the main reference for a clinical diagnosis of HD, both in clinical practice and research. Numerous rating scales have been developed to evaluate motor

symptoms and signs in Huntington's disease, with some of these scales designed specifically for this disease. They are utilized to determine the presence and severity of motor features, as well as to monitor changes over time or in response to therapeutic interventions during clinical trials.[7,11]

The total motor score assesses the severity and progression of motor symptoms in HD, including chorea, dystonia, bradykinesia, rigidity, and gait. TMS comprises 15 items and has a maximum score of 124 and the internal consistency of the UHDRS-TMS has been reported as highly reliable in manifest HD, with a Cronbach's α value ranging from 0.95 to 0.97. TMS is negatively correlated with the UHDRS-Total Functional Capacity scale, as well as with other UHDRS functional scales and with cognitive scales.[7,11]

2. **Cognitive - Huntington's Disease Cognitive Assessment Battery (HD-CAB)**

With cognitive dysfunction being an important aspect of HD that impairs quality of life, clinical trials are increasingly focusing on targeting cognitive outcomes.

Huntington's Disease Cognitive Assessment Battery (HD-CAB) scale consists of six tests that span a broad range of cognitive abilities known to decline in HD, including attention, processing speed, visuospatial processing, timing, emotion processing, memory, and executive function.[15]

In clinical trials focusing on HD, a range of cognitive tests have been utilized in addition to the HD-CAB, such as the Mini-Mental Status Examination (MMSE), The Montreal Cognitive Assessment (MoCA),[12] the Unified Huntington's Disease Rating Scale (UHDRS) cognitive assessment battery consisting of the phonetic verbal fluency test, Symbol Digit Modalities Test, and Stroop Test.

3. **Behavioral - Problem Behaviors Assessment for HD (PBA-HD)**

   This scale assesses psychiatric symptoms in HD, including depression, anxiety, irritability, and apathy. The PBA-HD scale adds up scores on Likert scales ranging from 0-4 to rate the frequency and severity of 11 behavioral symptoms including sadness, low self-esteem, guilt, disruptive/aggressive behavior, obsessions, hallucinations, and irritability, with higher scores indicating greater levels of behavioral problems.[16,17]

4. **Functional Assessment**

   The Katz Index of Independence in Activities of Daily Living (Katz) index is a tool used to assess a patient's ability to perform basic activities of daily living (ADLs), such as bathing, dressing, toileting, transferring, continence, and feeding.[14] In addition to the Katz Index, there is also a scale called the "Lawton Instrumental Activities of Daily Living (IADL) Scale", which is used to assess a patient's ability to perform more complex activities of daily living, such as using the telephone, managing finances, preparing meals, shopping, doing housework, and managing medications.[13]

5. **Independence Scale (IS)**

   This scale quantifies the level of dependence on others for ADLs and IADLs. The IS measures the level of independence by one single score between 10 and 100.[18]

6. **Total Functional Capacity (TFC)**

   This scale provides an overall assessment of functional capacity, taking into account all domains of HD. The Total Functional Capacity (TFC) scale is a Likert-based rating system used to assess the independence of individuals across five

domains, including occupation, ability to manage finances, ability to perform domestic chores, ability to perform personal activities of daily living, and setting for the level of care.[17]

The TFC score is calculated by summing the Likert responses (ranging from 0 to 3, or 0 to 2) for the five items. A higher score on the TFC indicates greater functional capacity, with scores ranging from 0 to 13. A score of 13/13 indicates complete functional independence for an individual with HD but no symptoms. The TFC is an important tool for evaluating the functional status of individuals with HD and is commonly used in clinical research to assess disease progression and evaluate the effectiveness of interventions.[17]

1.4 Defining Stages of HD

The Shoulson Fahn Staging

The TFC score is a tool that can be used to classify individuals with a neurodegenerative disorder into five disease stages, which are defined by the Shoulson-Fahn Functional Capacity Rating Scale.

In Stage I, which is the earliest stage, individuals have TFC scores ranging from 11-13. In Stage II, scores range from 7-10, and individuals may experience issues with work and some impairment with usual activities. In Stage III, scores range from 3-6 and individuals may have problems with activities of daily living and require some care support. Stage IV is characterized by the need for assistance with most activities of daily living, and 24-hour care may be appropriate. Stage V is indicative of requiring support with all activities of daily living, and the individual may be in the terminal phase of the condition. Individuals in Stage I can be pre-manifest, meaning they have been diagnosed with the condition via genetic testing but have no clinical expression.[17,19]

The Divino Staging Algorithm

In the Divino et al study, the authors developed an algorithm based on disease markers to assign disease stages and categorize clinically diagnosed HD patients into Early, Middle, and Late stages of HD (Table 1). The algorithm and markers were validated based on a review of the clinical literature and an exploratory analysis of the data.[20]

Table 1: Disease markers of Huntington's disease stage.[20]

Late-stage disease markers	Middle-stage disease markers
Nursing home	Home assistance
Feeding tube	Physical therapy
Incontinence	Dementia
Bedsore (e.g., Pressure Ulcer or Decubitus Ulcer)	Gait disorder
Hospice care	Dysarthria
Falls (evidence of two or more falls within one month)	Speech therapy
Dysphagia/swallowing	Falls

The study followed a hierarchical assessment in which Late-stage patients were identified first, based on the presence of any Late-stage marker, which are multiple and severe clinical characteristics such as residence in a nursing home or use of a feeding tube. Then, for patients with no markers of Late stage, Middle stage patients were identified based on the presence of any Middle stage marker, which are definitive clinical characteristics such as the use of physical therapy or home assistance. All remaining patients were classified as Early stage based on the absence of Late or Middle stage markers.[20] For the purpose of our study, we utilized the staging method developed by Divino et al. to categorize Huntington's disease patients into Early, Middle, and Late stages.

1.5 Impact of Huntington's Disease

Prevalence of HD

Understanding the manifest HD population is essential to accurately assess the burden of the illness and determine the resources required to address the needs of affected individuals.[21] Whilst a highly uncommon juvenile variant of the disorder exists, HD typically manifests during early to mid-adulthood. The estimates of HD prevalence display a difference of over ten times among various global regions.[1,22] This variance can be attributed to the average length of CAG repeats and frequency of diverse huntingtin (HTT) gene haplotypes present in the general population.[23] HD is characterized by onset in adulthood, typically occurring between the ages of 30 and 50 years, and an average disease duration ranging between 17 to 20 years. However, the onset age and disease progression rate may vary among individuals with HD. This variability in the clinical course of the disease highlights the heterogeneity of the HD population and underscores the need for personalized approaches to HD management.[20]

The prevalence rate of HD in predominantly Caucasian populations averages around 10 cases per 100,000 individuals, but this value shows considerable heterogeneity across individual estimates. The diagnosed prevalence of HD has exhibited a global increase of approximately 10 to 20% in each decade, which can be attributed to improved diagnostic testing and a rise in life expectancy. However, the actual prevalence of HD is probably underestimated, as some individuals with HD and those genetically predisposed to the disease remain undiagnosed due to social stigma and/or a lack of genetic testing.[24]

According to Yohrling et al. [24], the true US prevalence of HD is estimated to be 41,467, while the number of diagnosed cases is at least 21,331. The 2018 age-adjusted US prevalence of HD by age category is seen in Table 2. Applying age-specific prevalence rates to the 2018 US census data reveals that the highest HD prevalence of 2.3 per 100,000 occurs in the 55 to 59 age group. The study's authors suggest that the number of individuals with manifest HD in the United States may be as high as **40,000**, which contradicts the commonly cited figure of 30,000 individuals.[1,24]

Table 2: HD prevalence in the United States stratified by age.[24]

Age Categories	Percentage of total US population (2018)	Age-adjusted HD prevalence in US /100,000
15-19	6.4	0.1
20-24	6.7	0.1
25-29	7.2	0.1
30-34	5.4	0.3
35-39	6.6	0.4
40-44	6	0.9
45-49	6.3	1.2
50-54	6.4	1.8
55-59	6.7	2.3
60-64	6.2	2.0
65-69	5.2	1.4
70-74	4.1	1.2
75-79	2.8	0.6
80-84	1.9	0.4
85+	2	0
Total	**79.9**	**12.7**

Impact on caregivers

In a systematic literature Jan Domaradzki[25] review identifies several themes related to the caregiver's experiences. The most prevalent theme is the negative experiences caregivers have with health and social care services. Access to health services for individuals with HD and a lack of knowledge of HD from health professionals are identified as significant problems for many caregivers.[25,26]

Another theme identified in the literature is related to caregiver dissatisfaction with their role. In a study by Roscoe et al., over 65% of caregivers perceive their role as "very stressful."[27] The hereditary nature of HD further burdens caregivers, as they worry about the possibility of the disease developing in other family members, particularly their children which can lead to feelings of guilt and blame.[25,27]

Like other forms of dementia, maintaining a meaningful relationship with the affected relative can be challenging for HD caregivers. They often report the loss of a good friend and companion, with the marital relationship particularly affected. Caregivers may also find that HD has a significant impact on relationships within and outside the family.[25,28,29]

Finally, the literature identifies several strategies used by caregivers to deal with HD, including appreciation of positives, anticipatory mourning, setting boundaries, and using medications[25,29]

CHAPTER 2: TREATMENTS FOR HUNTINGTON'S DISEASE

2.1 Current Treatment for Huntington's Disease

As of today, there is no cure available for this disease, however, symptoms can be managed using a range of option including chorea medication, antipsychotic medication, antidepressants, mood-stabilizing medication as well as non-drug therapies.[30]

The most commonly prescribed HD medications are targeted to reduce chorea. One of the major pathological hallmarks of HD is the degeneration of the basal ganglia and particularly the striatum, which has been linked to the development of chorea. The basal ganglia contribute to the initiation of movement and suppression of unwanted movements.[30]

The first US Food and Drug Administration (FDA)-approved drug for chorea associated with HD is tetrabenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor. VMAT2 inhibitors can improve hyperkinetic movements and are effective treatment options for the chorea of HD.[31] According to current understanding, tetrabenazine exerts its pharmacological effect by specifically depleting central monoamines from nerve terminals through reversible inhibition of human VMAT2. In a randomized controlled trial conducted by the Huntington's Study Group, it was determined that after 12 weeks, tetrabenazine led to a significant reduction in chorea severity of 5.0 units on the UHDRS scale, whereas the placebo treatment yielded only a 1.5-unit reduction.[30]

Another drug, Deutetrabenazine (DBZ) is a pharmacological agent that is FDA-approved to treat chorea associated with Huntington's disease. Structurally, DBZ is an isotopic isomer of tetrabenazine, wherein six hydrogen atoms have been replaced with deuterium atoms. This substitution renders DBZ chemically equivalent to tetrabenazine, but with a prolonged half-life due to the presence of deuterium atoms. Consequently, DBZ can be dosed less frequently.[30]

In addition to the aforementioned treatments, several other therapeutic approaches are employed in the management of symptoms. Psychiatric and neurologic professionals may prescribe drugs, such as anti-psychotics (e.g.Risperidone) and antidepressants (e.g.Citalopram), to mitigate psychosis, anxiety and depression while also ameliorating uncontrolled behaviors. Additionally, physical, and occupational therapies can promote balance, coordination and strength, while speech and language interventions and appropriate nutritional strategies can address communication difficulties, eating and swallowing impairments, and weight loss.[32]

2.2 Future Treatment Options for Huntington's Disease

Recurring Symptom-Managing Genetic Treatment - Antisense oligonucleotides

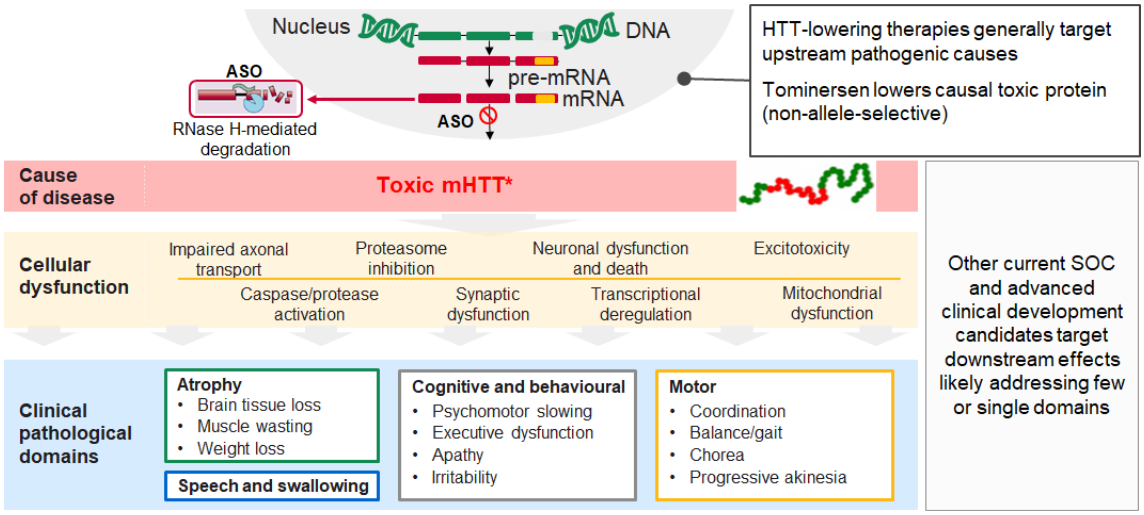
The Huntingtin (HTT) lowering strategy using Antisense oligonucleotides **(**ASOs) is the state-of-art. ASOs are small single-stranded chemically modified DNA molecules that use Watson Crick base pairing to bind RNA and catalyze downstream events.[33] Depending on the target sequence of the mRNA, they can prevent protein biosynthesis, block splicing, or inhibit the binding of proteins.[34]

In lieu of targeting the mutation selectively, a nonselective approach was adopted to partially suppress both wildtype huntingtin (wtHTT) and mutant huntingtin (mtHTT). In preclinical studies, 50% suppression of mtHTT is sufficient to provide benefit[35] and total HTT can be lowered by 50% without overt phenotype[36], suggesting that appropriately dosed nonselective ASOs could provide a potentially safe and effective therapy. Nonselective ASOs, like the Roche/IONIS ASO (Tominersen), target *HTT*, indiscriminately binding to both *wtHTT* and *mtHTT* transcripts, and degrade a portion of each. The nonselective approach is attractive as it offers a universal treatment option to the majority of the HD community, but the tolerability of such an approach has been called into question. The findings from the most recent trial, GENERATION HD1 [NCT03761849][37], indicate that Tominersen, at least at 120 mg, is not well tolerated.[38]

Thus, to identify the appropriate dose efficacy, Roche initiated a Phase II trial, GENERATION HD2 Trial, in the year 2023. GENERATION HD2 [NCT05686551][39] is a multicenter, double-blinded, placebo-controlled, randomized controlled trial that will investigate lower and less frequent doses of Tominersen. This study will evaluate the

safety, biomarkers, and efficacy trends of two different doses of Tominersen (Table 3) in younger adults with less disease burden.

Figure 3: ASOs mechanism of action for lowering the HTT.



MoA schema adapted from Wild EJ, Tabrizi SJ. Lancet Neurol. 2017; 16:837–847; Bates GP, et al. Nat Rev Dis Primers. 2015; 1:15005; Ross CA, et al. Nat Rev Neurol. 2014; 10:204–216; Roos R. Orphanet J Rare Dis. 2010; 20:5:40; Zuccato C, et al. Physiol Rev. 2010; 90:905–981; Zielonka D, et al. Front Physiol. 2014; 5:380.

The study time for this trial is at least 16 months including seven clinic visits and four interim phone consultations. It has a common close design wherein the first person enrolled will continue the study until the last person completes their 16-week last visit. Adults with very early subtle symptoms or early manifest HD will be included in the study. These individuals must also have CAP Score between 400-500 units. The clinical trial treatment will be given as an injection by lumbar puncture. This involves a needle being placed into the lower back between two lumbar bones (vertebrae), into the space (called the 'intrathecal space') where there is a fluid that surrounds the spinal cord and brain (cerebrospinal fluid) which then flows in this fluid up to the brain. This is a common medical procedure known as 'intrathecal injection'.

Table 3: Description of GENERATION HD2[39] treatment arms

Comparators	Dosage	Frequency	Administration	Study Population
Tominersen	100 mg	Every 4 months	Intrathecally	120
Tominersen	60 mg	Every 4 months	Intrathecally	120
Placebo		Every 4 months	Intrathecally	120

The primary endpoints are the number and seriousness of any side effects; changes in laboratory results from the cerebrospinal fluid, including in the amount of mtHTT protein; changes in results from the brain magnetic resonance imaging (MRI) scan; changes in function (for example, the ability to move, think and perform daily activities); changes in the amount of an indicator of nerve damage in cerebrospinal fluid and the effects of Tominersen on the immune system.[39] Success of this trial, will help in finding answers to questions about the possibility of using ASO based Tominersen as a treatment for Huntington's, focusing on the safety profile of the drug as well as its efficacy in engaging the target protein, huntingtin.

ASOs are a promising treatment option because they can bind to both mRNA and pre-mRNA, increasing the availability of targetable RNA sequences for selection. ASOs are also favorable as therapies because of their extensive distribution in the central nervous system and long half-lives.[40]

Onetime Disease Modifying Gene Therapy - AAV-mediated RNAi Therapy

The main task of gene therapy is to selectively replace, repair, or control the expression of mutant genes by the transfer of genetic material to the target cells that are responsible for each disease. Clinical trials have primarily utilized viral vectors such as an adeno-associated virus (AAV), lentivirus (LV), adenovirus (Adv), and retroviruses for gene replacement as they can express full-length genes. Even though there are some adverse events associated with the administration of AAV therapy[41], it has become the most common type of virus utilized as a vector in human gene therapy.

Recombinant adeno-associated viral (AAV) vectors help achieve the stable expression of the therapeutic gene. These vectors have advantages over other viral vectors, including their non-pathogenicity, inability to replicate in the host, and lack of integration into the host genome.[42] Bilateral intraparenchymal infusion can be used to deliver viral vectors to specific brain regions. The striatum is the most severely affected brain region in Huntington's disease and the most common target for AAV-mediated delivery.

Clinical trials of AAV-mediated RNAi therapy in HD are already underway.[43] UniQure's AMT-130 is being evaluated in an ongoing Phase I/II clinical trial [NCT04120493][44] in patients with early manifest HD. This is a randomized, double-blinded, and sham-controlled study. The AMT-130 trial is evaluating the safety, tolerability, and efficacy of bilateral injections in patients with early-stage HD.[43] The trial includes two dose cohorts of 26 patients each, with the first cohort having 10 patients (6 receiving AMT-130 and 4 receiving imitation surgery) and the second cohort having 16 patients (10 receiving AMT-

130 and 6 receiving imitation surgery). An additional cohort exploring the use of an alternative stereotactic navigation system will include up to 18 randomized patients.[44]

Patients receive a single intrastriatal injection administration of AMT-130 using MRI-guided, convection-enhanced stereotactic neurosurgical delivery directly into the striatum. A Phase Ib/II open-label study of AMT-130 is also ongoing in Europe, enrolling 15 patients with early manifest HD across two dose cohorts. Both studies aim to establish safety, proof of concept, and the optimal dose of AMT-130.[45]

The data demonstrated that a single administration of AMT-130 resulted in a dose-dependent and sustained reduction of mtHTT in the deep structures of the brain including the striatum. the putamen, and the cortex. At 12 months of follow-up on these patients, the lower dose was generally well-tolerated with no serious adverse events related to treatment. In the four treated patients with evaluable data from this cohort, mean levels of mutant Huntingtin protein (mtHTT) in the cerebral spinal fluid (CSF) declined at all time points compared to baseline and decreased by **53.8%** at 12 months of follow-up. In the three control patients with evaluable data, mean levels of mtHTT showed an increase compared to baseline at one, three, six, and nine months of follow-up, and decreased by 16.8% at 12 months of follow-up.[46]

2.3 Specific Aims

Huntington's disease has a significant financial impact on patients, caregivers, and the healthcare system, however, a limited number of attempts have been made to quantify this impact. There are very few studies that determine the cost of care for HD and to understand how costs may vary as the disease progresses through the early, middle, and late stages. There is a lack of comprehensive direct and indirect medical cost data for HD. Thus, there is a need for a study using a representative sample of the US population to determine the current standard of care cost of comprehensive direct and indirect medical care for HD.

Moreover, the emergence of promising drugs such as Tominersen and AMT-130, which have the potential to significantly treat or possibly even cure HD, highlights the importance of evaluating their cost effectiveness and relative merits. To date, no study has been conducted to estimate the incremental cost-effectiveness of these two treatments as compared to standard of care. Thus, this study aims to fill this knowledge gap and contribute to the scientific understanding of HD treatment through the following aims.

Aim 1: Identify the cost and burden associated with Huntington's Disease by stage.

Conduct a systematic review to identify economic evaluations using multiple databases. Identify cost-of-illness estimates stratified by disease severity i.e., early, middle, and late-stage HD. Cost identified will be categorized as inpatient costs, outpatient costs, pharmacy costs, indirect costs, etc.

Aim 2: Develop a Markov model to assess the cost-effectiveness of potential treatments for Huntington's disease.

Utilizing the cost estimates identified through the systematic review, we aim to develop a Markov model comparing "AMT-130" (disease-modifying one-time treatment) and "Tominersen" (recurring symptom managing treatment) with the current standard of care for early-stage Huntington's disease in the United States.

Overall, this study has the potential to provide valuable insights into the economic impact of HD and the incremental cost-effectiveness of different potential treatment options. This information can be used to inform healthcare policy, resource allocation, and treatment decisions related to HD.

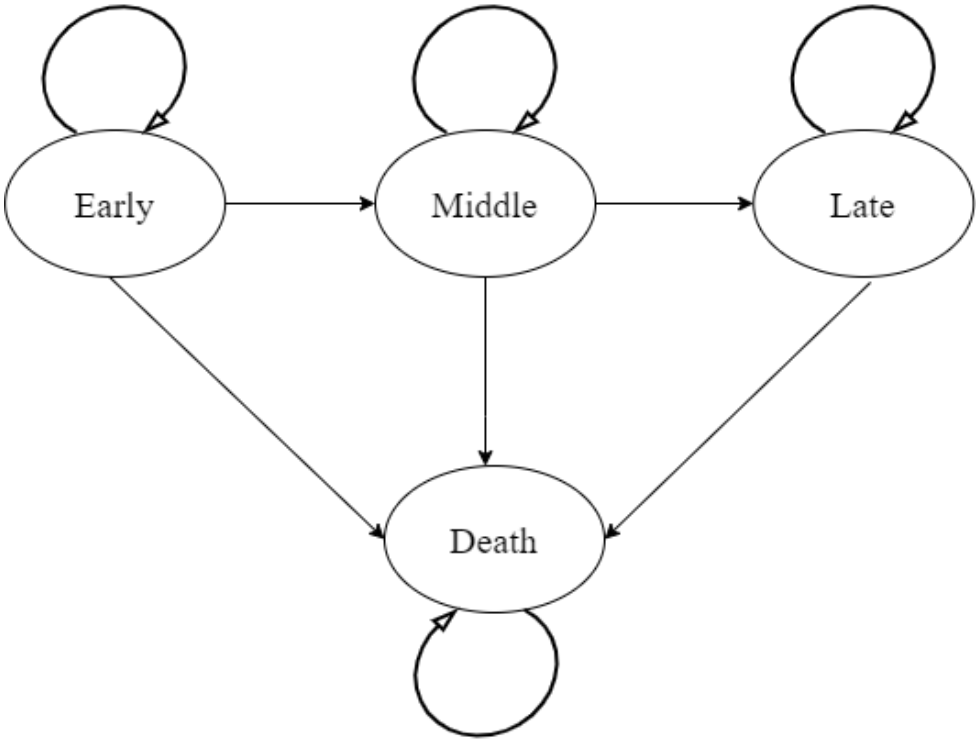
CHAPTER 3: METHODS

3.1 Model Overview

A health state transition Markov model (Figure 4) was used to determine the incremental cost-effectiveness of the potential genetic treatment (Tominersen) and the one-time genetic therapy (AMT-130) compared with the current standard of care for Huntington's disease in the United States. The model was used to estimate the costs and benefits of each treatment option over a lifetime time horizon from a societal perspective, taking into account the probability of disease progression and associated health states. The model consisted of four stages, Early, Middle, Late and Death based disease markers, using a modified algorithm. This algorithm was developed and validated in the Divino et al study.[20] The cycle length for each period was one year with an annual discount rate of 3% used for all costs and effects. A half-cycle correction method was used for this model. The model was built and analyzed using TreeAge Pro Healthcare 2023 software. A systematic review was performed to identify the cost associated with HD. Data extraction and mathematical calculations were carried out using Microsoft Excel.

To determine the key drivers of model outcomes, we conducted one-way sensitivity analyses (OWSA) by varying individual input parameters over a conservative range based on published data and expert opinion. The ranges used for each parameter are listed in tables 7 and 8. Furthermore, we performed a scenario analysis to examine the effect of an additional "value of hope"[47] on the base-case utility values for both treatments.

Figure 4: Stage Transition Diagram - The states are represented by ovals and possible transitions between states are shown by arrows.



3.2 Costs

Identifying Cost

We performed a comprehensive literature search on August 17, 2022, to identify economic evaluations using the following databases: Embase (Embase.com), Cochrane Library (WileyOnline), Medline (Ovid), and Scopus (Scopus.com). The search strategies were developed by a health sciences librarian, Emily Gorman and reviewed for accuracy and relevance by another health sciences librarian. The strategies combined key words and subject headings related to Huntington's disease and economic burden. The search strategy for each database is provided in **Appendix 1.** All abstracts were reviewed using Covidence[48] systematic review software.

Selection Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines were used for study eligibility criteria, quality assessment, and analysis of results.[49,50] The following inclusion criteria were used to screen articles:

1. Articles reporting juvenile and adult (65 years) HD cases.
2. Articles must report economic information including costs specific to HD burden.
3. Any experimental/observational study including case reports or case series related to HD must be included.
4. Articles must be written in English.

Data Extraction and Evidence Synthesis

Data extraction included the following variables: article citation details (year, author, title), study type, study description, country, population description, comparators, the measure of effectiveness – quality-adjusted life-year (QALY) or life-years gained (LYG), description of costing methods, time horizon, discount rate, currency, year of cost reported, description of sensitivity analysis, costs reported, and effectiveness reported. Using these extracted data, we identified the cost of illness of HD for utilization of every healthcare resource.

Costs identified were categorized as direct healthcare costs, direct non-healthcare costs, indirect costs, and total all-cause costs. Direct healthcare costs included inpatient costs, outpatient costs, pharmacy costs, diagnostic costs, costs pertaining to medical devices, etc. Direct non-healthcare costs included transportation costs, informal caregiver costs, and costs required for aids and adaptations. These reported costs were adjusted to US dollars (USD) using currency conversion and then inflated to USD as per the year 2022.[51,52]

Cost Classification by Disease Stage

Not all costs identified from peer-reviewed papers were stratified according to Divino et al stages, i.e. Early, Middle, and Late-stage HD. Jones et al[53] reported cost according to the Shoulson Fahn stages, which are Stage 1 (least severe) to Stage 5 (most severe) whereas Silva Pardes et al[54] defined stages according to the Barthel score, i.e., Barthel 1 (most severe) to Barthel 5 (least severe). To adapt these costs to our study, we used the approach described by Wild et al in Premanifest and Early Huntington's Disease chapter[55] (Table 4 and Table 5).

Table 4: Huntington's disease stages conversion - Shoulson Fahn Stages

TFC Score	Shoulson Fahn Stages	Stages based on disease markers
11-13 7-10	1 2	Early
4-6	3	Middle
1-3 0	4 5	Late

Table 5: Huntington's disease stages conversion - Barthel Index Stages

Barthel score	Barthel Index Stages	Stages based on disease markers
100 (total independency)	5	Early
60-99	4	
40-55	3	Middle
20-35	2	
<20 (total dependency)	1	Late

Therefore, the mean annual cost reported for *Shoulson Fahn Stages 1 and 2* or *Barthel 4 and 5* were combined to estimate the cost for *early-stage HD*. Similarly, mean annual costs reported for *Shoulson Fahn Stage 4 and 5* were combined to estimate the cost for *late-stage HD* whereas *Barthel 2 and 3* were combined to estimate the cost for *middle-stage HD*. For instance, while combining the costs for *Shoulson Fahn Stage 1 and 2*, we first found the total annual cost for Stage 1 and Stage 2 from the mean annual cost reported. The total annual costs found were later used to find the annual **weighted average costs** for Early-

Stage HD. This methodology was used considering that the number of individuals for stage 1 and stage 2 was different and therefore, it would have been inappropriate to simply take the mean of two means with different denominators (number of individuals).

Table 6: Steps used for finding the mean cost of early-stage HD from reported mean costs of Shoulson Fahn Stages 1 and 2.

Shoulson Fahn Stages	**Step 1:** Mean Annual Costs Reported ($n_1 \neq n_2$)	**Step 2:** Finding Total Annual Costs	**Step 3:** Annual Weighted Average Cost for Early-Stage HD
Stage 1	$x_1 = t_1 / n_1$	$t_1 = x_1 * n_1$	$\bar{X}_w = (t_1 + t_2) / (x_1 + x_2)$
Stage 2	$x_2 = t_2 / n_2$	$t_2 = x_2 * n_2$	

Similarly, **weighted standard deviation(sd_w)** was calculated using the below-mentioned formula where x_i represents the individual means, $\bar{x}_w$ is the weighted average, N' is the number of non-zero mean values and w_i represents the weights for each cohort.

$$sd_w = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x}_w)^2}{\frac{(N' - 1)\sum_{i=1}^{n} w_i}{N'}}}$$

We calculated a 95% confidence interval for most of the cost variables using weighted mean and weighted standard deviations. However, for some cost variables such as transportation cost, indirect cost, and cost for medical devices that were based on small cohorts from Silva Pardes et al[54], the lower limit of the confidence interval was negative. In these cases, we decided to set the lower limit to zero because negative costs are not meaningful or possible.

3.3 Age

For our study, we focused on calculating the mean age for the early-stage HD cohort since all the patients in the model entered at the early stage. The mean age for early-stage HD was determined using the estimates reported in the Crowell et al study.[21] As the mean age was reported according to the Shoulson Fahn stages in the Crowell study we used the same methodology as described above to estimate the mean age. Weighted mean age was calculated for *early-stage HD* by combining the mean age for *Shoulson Fahn stages 1 and* 2 and was found to be approximately 50 years. The range for early-stage age was estimated by using the minimum and maximum age reported for *stage 1 and stage 2* respectively, as the lower and upper limits of age for early-stage HD.

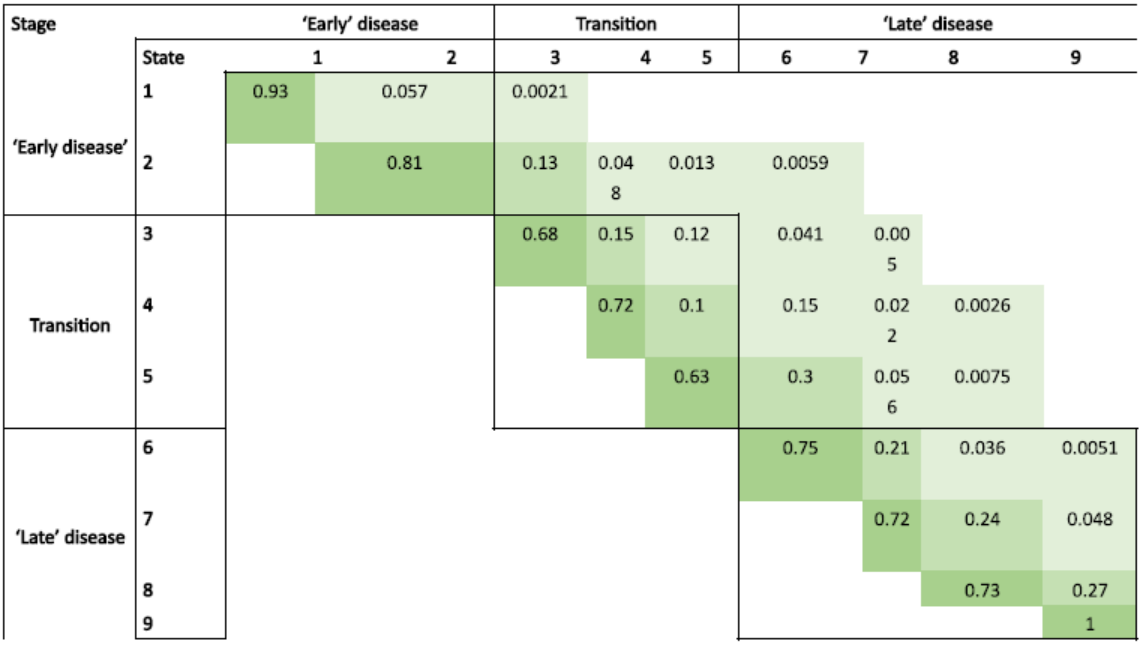
3.4 Disease Progression Probabilities

All patients entered the model in the early stage, and at the end of each cycle, they could transition into a different health stage, stay in the early stage, or experience death. Transition to a more severe HD stage could only happen one cycle at a time and only to the next severe HD stage (i.e., patients in the early stage could not skip the middle stage and move directly to late-stage HD). Existing literature was used to identify disease mortality rates and stage transition probabilities.

Transition Probabilities

To identify transition probabilities, we referred to the Mohan et al study.[56] Authors in the study used probabilistic machine learning methods to develop and validate a model of Huntington's disease progression. Nine states of HD were identified based on the distribution of four clinical reference measures such as UHDRS DCL levels, CAP*age product (CAP) score, UHDRS-total functional capacity (TFC) score, and UHDRS-Total Motor Score (TMS). Transition probability matrix (Figure 5) was calculated for these nine states using a Markov model. Moreover, the authors also separated these nine states were s into three periods – States 1 and 2 were identified as the early disease phase; states 3-5 as the middle phase, and states 6-9 as the late disease phase.[56]

Figure 5: Annual transition probabilities through successive states.



Mohan A, Sun Z, Ghosh S, Li Y, Sathe S, Hu J. RESEARCH ARTICLE A Machine-Learning Derived Huntington's Disease Progression Model : Insights for Clinical Trial Design Probabilistic disease progression modeling. 2022;37(3):553-562. doi:10.1002/mds.28866

For the purpose of our study, we computed the cumulative probabilities of transitioning between disease stages by applying the probability-rate-probability conversion method to the individual state transition probabilities derived from the Mohan et al. model.[56]

Initially, we converted the individual state probabilities to rates because rates can be added mathematically, while probabilities cannot. Next, we added these rates based on the stage categories: early, middle, and late-stage HD (note that in our study, we refer to the transition stage as middle stage HD). We then converted the resulting cumulative rates back to probabilities. Since these probabilities were derived from different sources, the sum of each row was sometimes greater than 100%. To address this issue, we applied the probability normalization method[57] and computed the disease transition probabilities for each stage.

Mortality Rate

The mortality rates for early, middle, and late-stage HD were estimated using the one-year probability of overall survival (OS) estimates reported in the Crowell et al study.[21] The OS estimates were reported according to the Shoulson Fahn stages and therefore, we had to combine them in order to align with our study. We first converted the reported probabilities to rates using the below-mentioned equation since rates can be mathematically manipulated (addition/multiplication) while probabilities cannot.[58]

$$Rate = \frac{-ln(1 - Probability)}{t}$$

Later, the mean of rates for *Shoulson Fahn stages 1 and 2* was calculated to estimate the one-year overall survival rate for *early-stage HD*. Likewise, the mean of rates for *Shoulson Fahn stages 4 and 5* was calculated to estimate the one-year overall survival rate for *late-stage HD*. These rates were now converted back to probabilities using the following equation.

$$(Survival)Probability = 1 - \exp\text{^}(-rate * time)$$

Finally, to obtain the death probability, i.e., the probability of transitioning directly from early/middle/late to death, the complement of the one-year overall survival probability estimates was taken for each stage.

$$(Death)Probability = 1 - \text{Survival Probability}$$

However, these were HD stage-specific mortality rates and we needed to incorporate the age-specific mortality rates to estimate the final mortality rates for each stage. The rationale

for this was that, with each one-year cycle, the age of the patient increases as well, and therefore a mortality rate specific to that age is applied for that cycle. The general population age-specific mortality rates for the United States in the year 2020 were obtained from the National Vital Statistics Reports[59] and are listed in Appendix 2-Table 13. A mortality factor was calculated based on the HD-specific mortality rate and the general population mortality rate. This mortality factor accounted for the high mortality rate associated with HD in comparison to the general population.

$$Mortality\ Factor = \frac{HD\ stage\ specific\ death\ probability}{General\ population\ mortality\ rate\ for\ a\ 50\ year\ individual}$$

For example, for early-stage HD patients, the death probability was calculated to be 0.01 and the general population mortality rate for a 50-year individual was found to be 0.005.[59] Therefore, the mortality factor for the early-stage population was calculated to be 0.01/0.005 = 2. Likewise, the mortality factor for middle-stage and late-stage HD was calculated to be 6.6 and 20 respectively. These mortality factors were then multiplied by the age-specific mortality rates (starting at 50 years) to estimate the age-specific mortality rate for each stage.

3.5 Health State Utility Values

Health outcomes are often evaluated in terms of quality-adjusted life-years (QALYs), which measure the quantity and quality of life in a single metric. QALYs take into account the duration of life as well as the quality of life during that time, as represented by a weight or score called a health state utility value (HSUV). These HSUVs can be determined using preference-based measures, such as the EQ-5D or SF-6D, which are widely used around the world.[17] For our study, we referred to the Hawton et al study that used SF-6D preference based to identify the HSUV for Huntington's disease by stage.

The SF-36 is a questionnaire consisting of 36 self-reported questions that evaluate the patient's functional health and well-being over the past four weeks from their perspective.[60] In the Hawton study,[17] researchers transformed the responses provided by the participants to the SF-36 into SF-6D values using the method developed by Brazier et al.[61] The SF-6D is a preference-based measure that assigns HSUV, which ranges from 0.3 to 1.0, with 0.3 indicating the poorest health state and 1.0 representing the best health state.[61]

In the Hawton et al study, SF-6D health state utility values by Shoulson Fahn disease stage were further stratified by countries. In the context of our research, we considered the "all countries" combined estimates. However, since the values were identified according to the Shoulson Fahn stages in the Hawton et al study, we used the same methods as described for costs, to adapt the HSUVs to our study, We calculated the weighted mean and weighted standard deviation values for *early-stage HD* by combining the *Shoulson Fahn stages 1 and 2* HSUVs. While the values described for *Shoulson Fahn Stage 3 and 4/5* were simply classified as *middle-stage and late-stage* HD HSUVs respectively.

Table 7: Full list of inputs used in the economic model for the standard of care arm.

Input	Base Case	Range	Source
GENERAL			
Discount Rate	0.03		
Total cycles	30		
Age (mean years)			
Early	50	45 – 53	[21]
RATES AND PROBABILITIES			
Transition Probabilities			
Early to Middle	0.16	0.1 – 0.2	[56]
Middle to Late	0.32	0.3 – 0.4	[56]
Mortality Rate			
Early to Death	0.01	0 – 0.05	[21]
Middle to Death	0.02	0 – 0.05	[21]
Late to Death	0.1	0 – 0.15	[21]
At Age 50	0.005	0 – 0.1	[59]
COSTS			
Healthcare Direct			
Early			
Inpatient	$1,136	$1,114 - $1,159	[20,53,54,62]
Outpatient	$3,805	$3,724 - $3,886	[20,53,54,62]
Pharmacy	$10,682	$10,279 - $11,085	[20,53,54,62]
Medical Devices	$46	$4 - $89	[54]
Middle			
Inpatient	$4,315	$4,280 - $4,349	[20,53,54,62]
Outpatient	$9,947	$9,886 - $10,008	[20,53,54,62]
Pharmacy	$12,484	$12,131 - $12,838	[20,53,54,62]
Medical Devices	$63	$0 - $187	[54]
Late			
Inpatient	$18,427	$18,181 - $18,672	[20,53,54,62]
Outpatient	$17,229	$16,921 - $17,573	[20,53,54,62]
Pharmacy	$18,516	$18,157 - $18,876	[20,53,54,62]
Medical Devices	$1,211	$0 - $2,471	[54]
Non – Healthcare Direct			
Early			
Caregiver	$5,877	$5,874 - $5,881	[53,54]
Transportation	$258	$126 - $391	[54]
Adaptations/aids	$2,537	$1,691 - $3,383	[53]
Middle			
Caregiver	$37,202	$32,688 - $41,717	[53,54]
Transportation	$102	$13 - $191	[54]
Adaptations/aids	$3,450	$710 - $6,190	[53]

Table 7 continued: Full list of inputs used in the economic model for the standard of care arm.

Input	Base Case	Range	Source
COSTS			
Non – Healthcare Direct			
Late			
Caregiver	$108,911	$79,581 - $1,38,242	[53,54]
Transportation	$317	$0 - $701	[54]
Adaptations/aids	$6,072	$1,123 - $11,021	[53]
Indirect Cost			
Early	$1,319	$734 - $1,904	[54]
Middle	$2,202	$887 - $3,518	[54]
Late	$1,324	$0 - $3,918	[54]
HEALTH STATE UTILITIES			
Early	0.73	0.7 – 0.9	[17]
Middle	0.63	0.5 – 0.7	[17]
Late	0.57	0.4 – 0.6	[17]

3.6 Key Assumptions

Assumption Regarding Treatment Costs

This study compares the incremental cost-effectiveness of Tominersen and AMT-130, two treatments currently undergoing clinical trials for HD, along with the current standard of care. For the purpose of our study, we will limit our key assumptions to early-stage HD patients, as the efficacy of these treatments is expected to be restricted to this group. Key assumptions were made using a best-case scenario approach based on clinical trial information and manufacturer data to estimate annual costs and disease progression probabilities for these treatments. Since no cost findings were available, we utilized existing cost estimates of treatments for Spinal Muscular Atrophy (SMA). The rationale behind using these SMA cost estimates was the similarity of the existing SMA treatment with these HD treatments.

Similarities in HD and SMA

SMA, like Huntington's disease, is an inherited rare genetic neurodegenerative disease. The most common form is caused by mutations in a gene called SMN1, although there are several other forms. The disease causes the progressive death of motor neurons in the spine and brain stem. As the disease progresses this leads to the atrophy of the muscles throughout the body – although the severity is highly variable depending on the age of onset. Similar to HD, juvenile cases of SMA exist due to mutation in the survival motor neuron 1 (SMN) gene.[63]

HD and SMA can have very different prognoses, however, they share a similar method of attack against the body since they both cause the deterioration and death of neurons in the motor pathway. Therefore, many drug candidates featuring neuroprotective mechanisms are sometimes tested simultaneously.[63]

Similarities in Tominersen and Nusinersen (Spinraza®)

Nusinersen (SPINRAZA®) is a prescription medicine used to treat SMA in children and adult patients.[64] It is marketed by Biogen and is the first FDA-approved therapy to treat SMA. It is an SMN-enhancing therapy that works by targeting the SMN2 gene, causing it to make a more complete protein. SMA patients who began Nusinersen as soon after diagnosis as possible had better results than those who waited to begin treatment. Patients receive four "loading doses" within the first 2 months of treatment. Once those loading doses are completed, they receive a maintenance dose every 4 months for the duration of the individual's life.[65]

Tominersen and Nusinersen, both are antisense oligonucleotide drugs. They have the same mechanism of action. Both drugs aim to reduce the expression of disease-causing proteins by promoting the degradation of the targeted mRNA or altering its splicing pattern. Additionally, both drugs are administered through intrathecal injection into the cerebrospinal fluid.[37,39,64]

Considering the similarities between Tominersen and Nusinersen, we assumed that the unit price of 60 mg of Tominersen would be equivalent to that of Nusinersen. A cost-effectiveness study found that the wholesale acquisition cost for a single intrathecal injection of 12 mg of Nusinersen was $125,000.[66,67] However, to account for typical mark-

ups observed for hospital outpatient treatments, we applied a 15% regular payer discount.[67] The purpose of this was to estimate the potential cost associated with administering Tominersen in a hospital setting. As a result, the estimated cost for a single injection of 60 mg Tominersen was $106,250.

The clinical trial protocol for Tominersen indicates that each injection will be given every 4 months.[39] This means that for an HD patient, three injections of Tominersen will be required annually. As a result, we estimated that the annual cost of Tominersen for an early-stage HD patient would be **$318,750.**

We estimated the potential range for the cost of Tominersen by calculating both the lower and upper limits. For the lower limit, we applied the current 35% discount offered by the Department of Veterans Affairs (VA) on Nusinersen,[68] which is available to eligible veterans and active military members. Based on this calculation, we estimated the lower limit for the cost of Tominersen to be $207,188. For the upper limit, we considered the annual undiscounted cost of Tominersen, which is $375,000. By utilizing both the VA discount and the wholesale acquisition cost[67] of a similar drug as reference points, we were able to estimate a potential range for the cost of Tominersen.

Moreover, we assumed that the cost of administering Tominersen would be the same as that of Nusinersen, which was determined to be $1,209.[67] Based on this assumption, we estimated the annual cost of administering Tominersen to be **$3,627.**

Similarities in AMT-130 and Onasemnogene abeparvovec (Zolgensma®)

Zolgensma® is a prescription gene therapy designed to target the genetic root cause of SMA by replacing the function of the missing or nonworking SMN1 gene. Currently, it is used to treat children less than two years old with spinal muscular atrophy, however, a new study shows that the treatment may be more effective for adults than previously believed.[69]

Similar to AMT-130, Zolgensma® is a one-time-only dose therapy. AMT-130 and Zolgensma® both use viral vectors to deliver genetic material to the patient's cells in order to treat a genetic disease. AMT-130 uses an adeno-associated virus (AAV) vector to deliver a small interfering RNA (siRNA) while Zolgensma® uses an AAV vector to deliver a functional copy of the SMN1 gene to treat SMA. A 2021 cost-utility study investigated the list price of Zolgensma®, which was determined to be $2,125,000.[70,66]

Owing to these similarities, the cost for AMT-130 was assumed to be the same as the list price for Zolgensma®. The regular payer discount of 15% was then applied to the list price, as was done for Tominersen. Therefore, based on these assumptions and calculations, the estimated cost for a one-time dose of AMT-130 as of 2022 was estimated to be **$1,806,250.** However, it's important to note that this is an estimate, and actual prices may vary depending on factors such as location, insurance coverage, and other individual circumstances.

To estimate the potential range for the cost of AMT-130, we calculated the lower limit by applying a 35% discount offered by the Department of Veterans Affairs on Zolgensma®. This discount is available to eligible veterans and active military members.[68] Using this method, we estimated the lower limit for the cost of AMT-130 to be $1,381,250. We

estimated the upper limit of the potential cost range for AMT-130 to be the initial undiscounted list price of a Zolgensma®, i.e., $2,125,000[70]. In summary, by using both the VA discount and the list price of a similar drug as reference points, we estimated a potential range for the cost of AMT-130.

Furthermore, we must also account for the cost required to perform the complex stereotactic neurosurgery to administer a single intrastriatal injection of AMT-130. The estimated national average cost to perform this surgery was found to be **$23,516** per patient.[71]

Willingness-to-Pay

According to an Institute for Clinical and Economic Review (ICER) report on Spinraza® and Zolgensma® for SMA, ICER observed that the cost per the QALY is above the conventional cost-effectiveness thresholds of 100,000 - 150,000 USD per QALY used in the US.[66] However, payers may consider broader impacts and use higher thresholds when assessing the value of treatments for ultra-rare diseases.[72] ICER considered such factors and includes analyses with the willingness to pay thresholds of up to 500,000 USD per QALY while evaluating rare diseases.[54,55,56] Therefore, considering these facts, we decided to set the willingness to pay for our study at **500,000 USD per QALY**.

Assumptions Regarding Cost and Rates of Adverse Events

In addition to considering the cost and probability of disease transition, we also took into account the cost and rates of adverse events for these treatments. As reported in the interim results of the AMT-130 clinical trials, no adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs) were found to be associated with the use of AMT-130. However, during the peri-operative period (Day 0 to 13), two out of ten individuals (20%) experienced serious adverse events (SAEs) unrelated to AMT-130. These events included a *deep venous thrombosis (DVT)* in the upper arm of one patient, which was successfully treated with anticoagulants, and *transient post-operative delirium* in another patient, which was resolved with supportive care.[73] Therefore, based on the observed 20% rate of serious adverse events unrelated to AMT-130 during the peri-operative period, we assumed a **0.2** probability of observing overall adverse events associated with AMT-130 treatment.

Estimating the costs associated with HD-related adverse events for the AMT-130 trial is challenging due to the ongoing nature of the trial and thus, we relied on existing literature to estimate the cost of adverse events. Specifically, we examined the costs associated with deep venous thrombosis and transient postoperative delirium. The annual all-cause cost of DVT was obtained from the Fernandez et al[74] and MacDougall[75] studies and was determined to be $53,100 in the year 2004. To account for inflation[51], this cost was adjusted to $93,580 in 2022. Similarly, the annual cost for transient post-operative delirium adverse events was obtained from the Franco et al study[76] and was estimated to be $7903.65 in the year 2022. As a result, the total cost associated with adverse events for AMT-130 was

calculated to be **$101,484** per annum per patient, with a 95% confidence interval used to estimate the range.

Additionally, in order to address potential adverse events associated with Tominersen treatment, we referred to the preliminary findings of the GENERATION HD 1 trial.[77] We specifically took into account the SUSAR cases, serious adverse events, and events that were potentially related to the study drug or lumbar puncture as reported by the investigators. Overall, a total of 57.1% adverse events were observed for patients who received 120 mg of Tominersen every 16 weeks. Based on these findings, we estimated the probability of adverse events to be **0.4** for patients who received 100 mg of Tominersen every 4 months in the GENERATION HD 2 trial.

The cost resulting from adverse events due to Tominersen was computed by referring to pre-existing literature which had assessed the expenses related to adverse events due to Nusinersen since the adverse events observed for Tominersen were almost similar to that observed for Nusinersen. In the study by Droege et al[78], the expenses incurred from SMA-related events associated with Nusinersen were estimated to be $46,723 as of 2018. We utilized this estimated cost to evaluate the costs resulting from adverse events related to Tominersen. Consequently, the cost of adverse events related to Tominersen was adjusted to account for inflation up to the year 2022[51] and was calculated to be **$73,139**. Furthermore, a 95% confidence interval was computed to determine the potential range of the estimated cost.

Assumptions Regarding Treatment Disease Progression

As mentioned earlier, in preclinical studies, **50%** suppression of mtHTT is sufficient to provide benefit[38] and would result in disease reversal independent of wild-type levels.[35] In a statement released by UniQure[46] on August 08, 2022, they announced that *"12-month data on the lower-dose cohort of AMT-130 in Huntington's disease showed the investigative gene therapy was generally well tolerated at this dose with a mean reduction of **53.8%** of mtHTT observed in the cerebral spinal fluid."*

Considering these two study findings and the success of the trial, we assume that the administration of a single dose of AMT-130 gene therapy, which leads to over 50% reduction of mtHTT, may result in the cessation of disease progression among individuals with early HD. However, a complete cure cannot be guaranteed, and hence the probability of transition from the early to the middle stage was assumed to decrease from 0.16 to 0, accounting for the possibility of remaining in the early stage. The age-specific mortality rates[59] remained the same as those calculated for the standard of care arm.

In the case of Tominersen, according to the phase I/IIa of Generation HD1 trial [NCT03761849][37], high doses (90mg – 120 mg) of Tominersen achieved **40%** mean CSF mtHTT lowering, within putative trough target range to cover deep brain regions with ASO modality.[77] Given that the reduction in mtHTT levels was below 50%, disease reversal was not postulated. Nevertheless, we made an assumption based on expert opinion that the probability of disease progression from the early stage to the middle stage would reduce from 0.16 to 0.1 for the base case model. Similar to AMT-130, we employed age-specific mortality rates[59] for patients in the early stage of Huntington's disease who received

Tominersen. The disease progression and mortality rates for middle and late-stage HD patients were assumed to be the same as those applied to the comparator.

Assumptions Regarding Utility Values

In the base case Markov model, we used the same utility values for early-stage AMT-130 and Tominersen arms as those employed for the early-stage standard of care arm. This decision was made because it was challenging to estimate incremental utilities for drugs that were still undergoing clinical trials. Nonetheless, a scenario analysis was carried out to assess the effect of an additional 0.07 "value of hope"[79] on the initial health state utility. The concept of "value of hope" in health economics literature refers to the notion that in specific circumstances, a rational individual may deviate from their typical risk-averse behavior and undertake calculated risks that have the potential to yield favorable outcomes, such as a cure.[80] Therefore, it is possible that their health state utility increases owing to the hope of improvement or a cure associated with the treatment. However, utility values for middle and late-stage HD remained the same for all three arms.

Table 8: Full list of inputs used in the economic model for treatment arms for the early-stage HD cohort.

Input	Base Case	Range	Source
RATES AND PROBABILITIES			
Transition Probabilities			
Tominersen			
Early to Middle	0.10	0 – 0.16	Assumptions
AMT-130			
Early to Middle	0	0 – 0.16	Assumptions
Adverse Events Probability			
Tominersen	0.4	0.3 – 0.5	Assumptions
AMT-130	0.2	0.1 – 0.3	Assumptions
COSTS			
Tominersen			
Annual Drug Cost - 3 IV injections of 60 mg (Low dose)	$318,750	$207,188 - $375,000	Assumptions
Administration Cost	$3,627		Assumptions
Adverse Event Cost	$51,967	$28,712 - $75,221	
AMT-130			
One-time Drug Cost (Low dose)	$1,806,250	$1,381,250 - $2,125,000	Assumptions
Administration Cost	$23,516		Assumptions
Adverse Event Cost	$101,484	$90,000 - $110,000	
HEALTH STATE UTILITIES			
Tominersen	0.73	0.7 – 0.9	Assumptions
AMT-130	0.73	0.7 – 0.9	Assumptions

CHAPTER 4: RESULTS

In the case of early-stage HD patients receiving Tominersen, the total cost of Tominersen treatment (including the cost of the drug and administration) as well as the total cost associated with early-stage HD patients were discounted at a rate of 3%. A half-cycle correction was applied throughout the lifetime horizon to account for the timing of costs and benefits since Tominersen is a recurring treatment for HD.

In contrast, for early-stage HD patients receiving AMT-130, the total discounted cost of AMT-130 treatment (including the cost of the drug and administration) was only applied to the first cycle, and a half-cycle correction was not used since AMT-130 is a one-time treatment option for HD. However, the additional discounted total cost associated with early-stage HD patients was applied throughout the lifetime horizon, and a half-cycle correction was used to account for the timing of costs and benefits.

4.1 Base Case Results

The base case outcomes for the three comparator arms – Standard of care, Tominersen, and AMT-130 are presented from a societal perspective over a lifetime horizon. Tables 9 and 10 along with the cost-effectiveness plane (Appendix 3, Figure 6) provide a summary of the total cost, QALYs, and incremental cost-effectiveness ratio (ICER) for both treatments compared with the standard of care.

For the early-stage population of individuals with Huntington's disease, the total cost associated with the Tominersen arm was approximately **$2.92 million**, which represents a cost nearly four times greater than that of the standard of care arm, which had a total cost

of approximately **$717 K**. However, the Tominersen arm was found to have a greater number of QALYs at **7.03** QALYs, compared to the standard of care arm, which had **6.11** QALYs. As a result, the incremental cost per QALY gained for Tominersen over the standard of care was approximately **$2.3 million per QALY**.

Table 9: Base-case results for Tominersen versus standard of care in early-stage HD

Intervention	**Total**		**Incremental[a]**		**ICER = Incremental Cost / Incremental QALYs**
	Cost	**QALYs**	**Cost**	**QALYs**	
Standard of Care	$716,997	6.11			
Tominersen	$2,923,143	7.03	$2,206,146	0.93	$2,384,006 / QALY

[a]Incremental = Cost or QALY of Tominersen - Cost or QALY of Standard of Care

Similarly, for the early-stage population of individuals with Huntington's disease, the total cost associated with the AMT-130 arm was approximately **$2.68 million**, which represents a cost more than 3.5 times that of the standard of care arm, which had a total cost of approximately **$717K**. However, the AMT-130 arm was found to have a greater number of QALYs at **11.34 QALYs**, compared to the standard of care arm, which had **6.11 QALYs**. As a result, the incremental cost per QALY gained for AMT-130 over the standard of care was approximately **$375.4K per QALY**.

Table 10: Base-case results for AMT-130 versus Standard of Care in early-stage HD

Intervention	**Total**		**Incremental[a]**		**ICER = Incremental Cost / Incremental QALYs**
	Cost	**QALYs**	**Cost**	**QALYs**	
Standard of Care	$716,997	6.11			
AMT-130	$2,681,115	11.34	$1,964,119	5.23	$375,484 / QALY

[a]Incremental = Cost or QALY of AMT - Cost or QALY of Standard of Care

4.2 Scenario Analysis

We performed a scenario analysis to test an additional 0.07 "value of hope" to the early-stage health states utility for Tominersen and AMT-130 treatment arms. As the effectiveness of the two treatment arms was the only parameter that was altered, there were no variations in the incremental cost estimates. Nevertheless, the ICERs for Tominersen and AMT-130 in comparison to the standard of care have been revised due to changes in the incremental QALYs.

After considering the additional value of hope to the base case utility value, the total QALYs for Tominersen increased from 7.03 to **7.49**, and for AMT-130, it increased from 11.34 to **12.43**. The incremental QALYs increased by 0.45 for Tominersen and by 1.09 for AMT-130. As a result, the ICER value decreased significantly from $2.38 million per QALY to **$1.59 million per QALY** for Tominersen, and for AMT-130, it changed from $375.4K per QALY to **$310.8K per QALY**. Table 11 provides a comparison between the results obtained in the base case analysis and the scenario analysis. Additionally, a cost-effectiveness plane (Appendix 3, Figure 7) has also been presented to illustrate the costs and effectiveness of the comparators for the scenario analysis.

Table 11: Comparing Base Case and Scenario Analysis Results

Intervention	**Total QALYs**		**Incremental QALYs**		**ICER[a] ($/QALY)**	
	Base Case	**Scenario**	**Base Case**	**Scenario**	**Base Case**	**Scenario**
Standard of Care	6.11					
Tominersen	7.03	7.49	0.93	1.38	2,384,006	1,597,869
AMT-130	11.34	12.43	5.23	6.32	375,484	310,870

[a]Incremental cost for Tominersen vs Standard of Care and AMT-130 vs Standard of Care remained the same as the base case.

4.3 Sensitivity Analysis

To assess the robustness of our results, we performed a series of sensitivity analyses by varying key parameters over a plausible range. One-way sensitivity analysis was conducted for the base case scenario, where key input parameters were varied individually. The list of parameters and their impact on ICER has been listed in Table 12. The results of the sensitivity analysis are presented in tornado diagrams in Appendix 4 (Figures 8 and 9).

The analysis showed that our conclusions were not sensitive to changes in most of the input parameters, except for the cost and early-stage utility values of AMT-130 and Tominersen. Varying the cost of these treatments resulted in significant changes in the ICER, suggesting that the cost and early-stage utility values of these treatments are the key drivers of the model's results. The ICER for AMT-130 remained below the willingness-to-pay (WTP) threshold of $500,000 per QALY, whereas, for Tominersen the ICER exceeded the WTP threshold across all tested scenarios.

Table 12: Summary of one-way sensitivity results: List of parameters and their impact on ICER.

Variable Description	Variable Base	Variable Low	Variable High	Change in ICER
Cost of AMT-130 drug	1,806,250	1,381,250	2,125,000	Increase
Cost of Tominersen drug	318,750	207,188	375,000	Increase
Cost associated with Adverse Events for AMT-130	101,484	90,000	110,000	Increase
Cost associated with Adverse Events for Tominersen	51,967	28,712	75,221	Increase
Utility for middle stage	0.63	0.5	0.7	Increase
Utility for late-stage	0.57	0.4	0.6	Increase
Adaptations/Aids Cost of Early-Stage	2,537	1,691	3,383	Increase
Indirect Cost of Early	1,319	734	1,904	Increase
Caregiver Cost of Early-	5,877	5,874	5,881	Increase
Utility for early-stage	0.73	0.7	0.9	Decrease
Caregiver Cost of Late-Stage	108,911	79,581	138,242	Decrease
Adaptations/Aids Cost of Late-Stage	6,072	1,123	11,021	Decrease
Caregiver Cost of Middle	37,202	32,688	41,717	Decrease
Adaptations/Aids Cost of Middle Stage	3,450	710	6,190	Decrease
Indirect Cost for Late	1,324	0	3,918	Decrease
Indirect Cost for Middle	2,202	887	3,518	Decrease

CHAPTER 5: DISCUSSION

The results of this study provide valuable insights into the incremental cost-effectiveness of Tominersen and AMT-130 compared with the current standard of care for early-stage HD patients. The results indicated that Tominersen when compared to the standard of care, was associated with markedly higher costs but offered greater health benefits than the current standard of care for HD. However, since the ICER exceeded the WTP threshold, the current standard of care would be considered preferable over Tominersen for early-stage HD patients.

In contrast, the results of the analysis showed that AMT-130 was associated with higher costs but also provided greater health benefits compared with Tominersen and the standard of care. The ICER for AMT-130 compared with the standard of care was within the range of what is typically considered cost-effective at a $500,000 WTP threshold indicating AMT-130 treatment to be a better option compared to the current standard of care for early-stage HD patients.

Moreover, Tominersen when compared with AMT-130, was found to be dominated, meaning that it was more expensive and less effective than AMT-130. These findings suggest that while **AMT-130** may be a cost-effective option compared with the current standard of care and Tominersen, however, further research is needed to determine its relative value compared with other treatment options for Huntington's Disease.

Furthermore, the sensitivity analyses performed in this study identified the key drivers of model outcomes and provided insights into the robustness of the results. The one-way sensitivity analyses showed that the model outcomes were sensitive to changes in certain

input parameters such as the utility values and drug costs. The scenario analysis testing the effect of additional “value of hope” also provided important insights into the potential impact of including non-clinical benefits in the analysis.

5.1 Limitations

It should be noted that this study has some limitations. The model relied on several assumptions and simplifications due to the lack of clinical trial data for the two treatments. While the assumptions were based on expert opinion and published literature, the results may not fully represent the real-world situation. This could introduce uncertainty into the results of the model, as the assumptions made may not accurately reflect the true outcomes and costs associated with the treatments.

Moreover, there is limited evidence on the durability of the treatment effect for AMT-130 and Tominersen. The model relied heavily on the assumption of sustained benefit for both treatments beyond the data. It was assumed that patients responding to treatment would maintain the highest functional status observed in the early stage for the remainder of the 30-year model time horizon until their death. Furthermore, the short-term comparative clinical efficacy of AMT-130 and Tominersen with the standard of care is uncertain. The statistical generalizability or the comparative efficacy of AMT-130 and Tominersen with the standard of care cannot be assessed.

Besides, systematic review limitations must also be considered. Due to translation limitations, this study only included studies with full-text available in English, which could introduce publication bias and limit the generalizability of the review's findings. These

limitations highlight the need for further research and evaluation of the long-term clinical and economic outcomes of AMT-130 and Tominersen for the treatment of early-stage HD.

5.2 Strengths

While this study has some limitations as discussed above, we took several measures to mitigate them and ensure the robustness of our findings. One of the key strengths of this study is its use of a comprehensive economic model to assess the cost-effectiveness of Tominersen and AMT-130 compared to the current standard of care for early-stage HD patients. To our knowledge, this is the first incremental cost-effectiveness study comparing AMT-130 and Tominersen with the current standard of care for early-stage Huntington's disease. The model incorporated a range of inputs, including clinical trial data, published literature, and expert opinion, to simulate disease progression and estimate the long-term costs and health outcomes associated with each treatment.

Additionally, the model was subject to extensive sensitivity and scenario analyses to test the robustness of the results and identify the key drivers of model outcomes. This approach provides a rigorous and transparent framework for evaluating the potential value of emerging therapies in a complex disease like HD.

Moreover, this study adds to the growing body of literature on the economic evaluation of HD treatments, and its findings may inform future decision-making regarding the allocation of healthcare resources for HD patients.

CHAPTER 6: CONCLUSION

In conclusion, this study aimed to evaluate the incremental cost-effectiveness of Tominersen and AMT-130 compared with the current standard of care for early-stage HD patients. Our findings showed that Tominersen and AMT-130 were associated with higher costs but also provided greater health benefits than the current standard of care, however, AMT-130 was found to be a cost-effective option compared with both the standard of care and Tominersen considering the WTP threshold. It is important to note the limitations of this study, particularly concerning the assumptions made due to the lack of clinical trial data for the two treatments. However, we have taken steps to mitigate these limitations through the use of conservative ranges and scenario analyses.

The relatively low prevalence of HD compared to other neurological disorders, such as multiple sclerosis and Parkinson's disease, underscores the need for further research into this devastating disease. There is a pressing need to educate and raise awareness of HD and its complexity. Furthermore, despite the relatively small number of cases, HD has a significant impact on both patients and caregivers, necessitating the investigation of potential treatment options. Understanding the impact of HD and in light of our findings, we recommend that future research should focus on collecting more data on the clinical effectiveness and durability of treatment effects of AMT-130 and Tominersen, as well as comparing their relative value with other treatment options for HD. Additionally, future research should explore the cost-effectiveness of other interventions aimed at improving the health outcomes of HD patients.

APPENDICES

Appendix 1: Systematic Review Search Strategies

Search strategies developed by Emily F. Gorman, MLIS and reviewed by Katherine Downton, MLIS

Final searches run on 17 August 2022
Total references on 17 August 2022: 616 references
Total following de-duplication in Covidence: **388** references

Filters / Limits: none

MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (Ovid, 1946 – August 16, 2022) – 91 references retrieved
Multi-line search run in the Advanced Search interface:

1. exp huntington disease/
2. ((huntington* adj2 (chorea or disease)) or chorea major or hereditary chorea or chronic progressive chorea).ti,ab,kw.
3. 1 or 2
4. exp "costs and cost analysis"/
5. (((health* or health care or medic* or direct or indirect or patient* or disease or illness or huntington*) adj3 (cost* or expenditure* or economic*)) or economic burden* or cost burden* or burden* of illness).ti,ab,kw.
6. 4 or 5
7. 3 and 6

Embase (Embase.com) – 305 references retrieved
One-line search run in the Quick search tab of the Embase.com interface:

('huntington chorea'/exp OR ((huntington* NEAR/2 (chorea OR disease)):ti,ab,kw) OR 'chorea major':ti,ab,kw OR 'hereditary chorea':ti,ab,kw OR 'chronic progressive chorea':ti,ab,kw) AND ('cost'/exp OR 'cost of illness'/exp OR (((health* OR 'health care' OR medic* OR direct OR indirect OR patient* OR disease OR illness OR huntington*) NEAR/3 (cost* OR expenditure* OR economic*)):ti,ab,kw) OR 'economic burden*':ti,ab,kw OR 'cost burden*':ti,ab,kw OR 'burden* of illness':ti,ab,kw)

Cochrane Library (WileyOnline; Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register) – 10 references retrieved (0 reviews, 10 trials)
Using Search Manager in Advanced Search:

1. [mh "huntington disease"]
2. ((huntington* near/2 (chorea or disease)) or "chorea major" or "hereditary chorea" or "chronic progressive chorea"):ti,ab,kw

3. #1 or #2
4. [mh "costs and cost analysis"]
5. (((health* or "health care" or medic* or direct or indirect or patient* or disease or illness or huntington*) near/3 (cost* or expenditure* or economic*)) or (economic next burden*) or (cost next burden*) or (burden* next "of illness")):ti,ab,kw
6. #4 or #5
7. #3 and #6

Scopus (Scopus.com) – 210 references retrieved
One-line search run in the Advanced Search interface:

TITLE-ABS-KEY((huntington* W/2 (chorea or disease)) or "chorea major" or "hereditary chorea" or "chronic progressive chorea") AND TITLE-ABS-KEY(((health* or "health care" or medic* or direct or indirect or patient* or disease or illness or huntington*) W/3 (cost* or expenditure* or economic*)) or "economic burden*" or "cost burden*" or "burden* of illness")

Appendix 2

Table 13: Age-Specific Mortality Rate obtained from National Vital Statistic Reports[59]

Age	Probability	Age	Probability	Age	Probability	Age	Probability
0	0.005849	25	0.001840	50	0.005985	75	0.039507
1	0.000403	26	0.001899	51	0.006450	76	0.043893
2	0.000259	27	0.001966	52	0.007004	77	0.048013
3	0.000208	28	0.002050	53	0.007657	78	0.053409
4	0.000155	29	0.002148	54	0.008381	79	0.058234
5	0.000144	30	0.002251	55	0.009115	80	0.064014
6	0.000132	31	0.002351	56	0.009859	81	0.070301
7	0.000121	32	0.002448	57	0.010668	82	0.077280
8	0.000109	33	0.002539	58	0.011568	83	0.086551
9	0.000096	34	0.002627	59	0.012548	84	0.095951
10	0.000091	35	0.002722	60	0.013599	85	0.107089
11	0.000107	36	0.002827	61	0.014668	86	0.116675
12	0.000159	37	0.002931	62	0.015723	87	0.130906
13	0.000255	38	0.003033	63	0.016751	88	0.146410
14	0.000385	39	0.003140	64	0.017793	89	0.163192
15	0.000529	40	0.003264	65	0.018910	90	0.181227
16	0.000676	41	0.003411	66	0.020241	91	0.200462
17	0.000831	42	0.003580	67	0.021617	92	0.220810
18	0.000991	43	0.003769	68	0.023122	93	0.242150
19	0.001152	44	0.003983	69	0.024700	94	0.264330
20	0.001320	45	0.004231	70	0.026327	95	0.287167
21	0.001483	46	0.004515	71	0.028145	96	0.310455
22	0.001620	47	0.004831	72	0.030318	97	0.333969
23	0.001717	48	0.005181	73	0.032487	98	0.357477
24	0.001785	49	0.005570	74	0.036455	99	0.380747
						100	1.000000

Appendix 3: Incremental Cost-Effectiveness Analysis Results

Figure 6: Cost Effectiveness Plane for Base Case Results

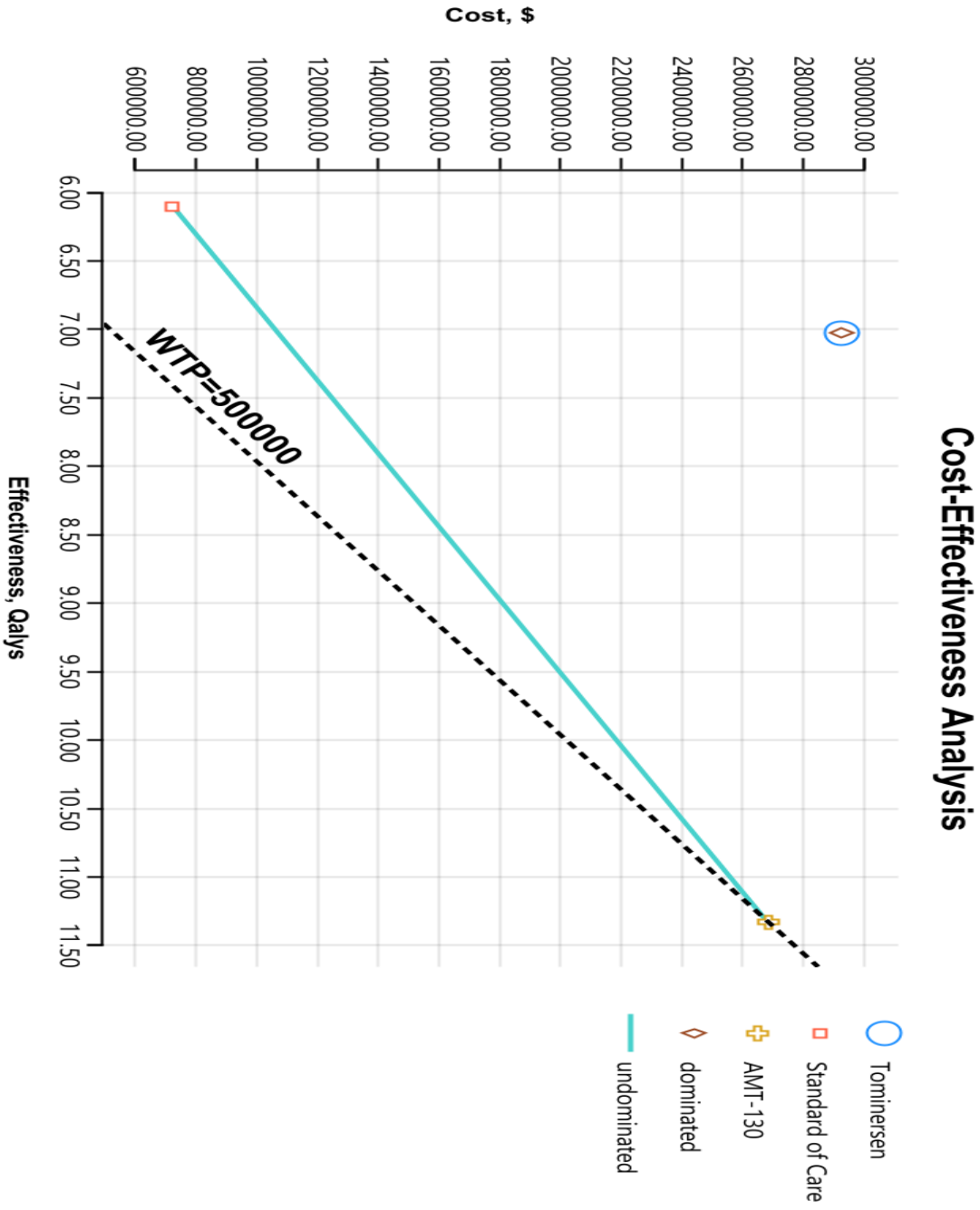
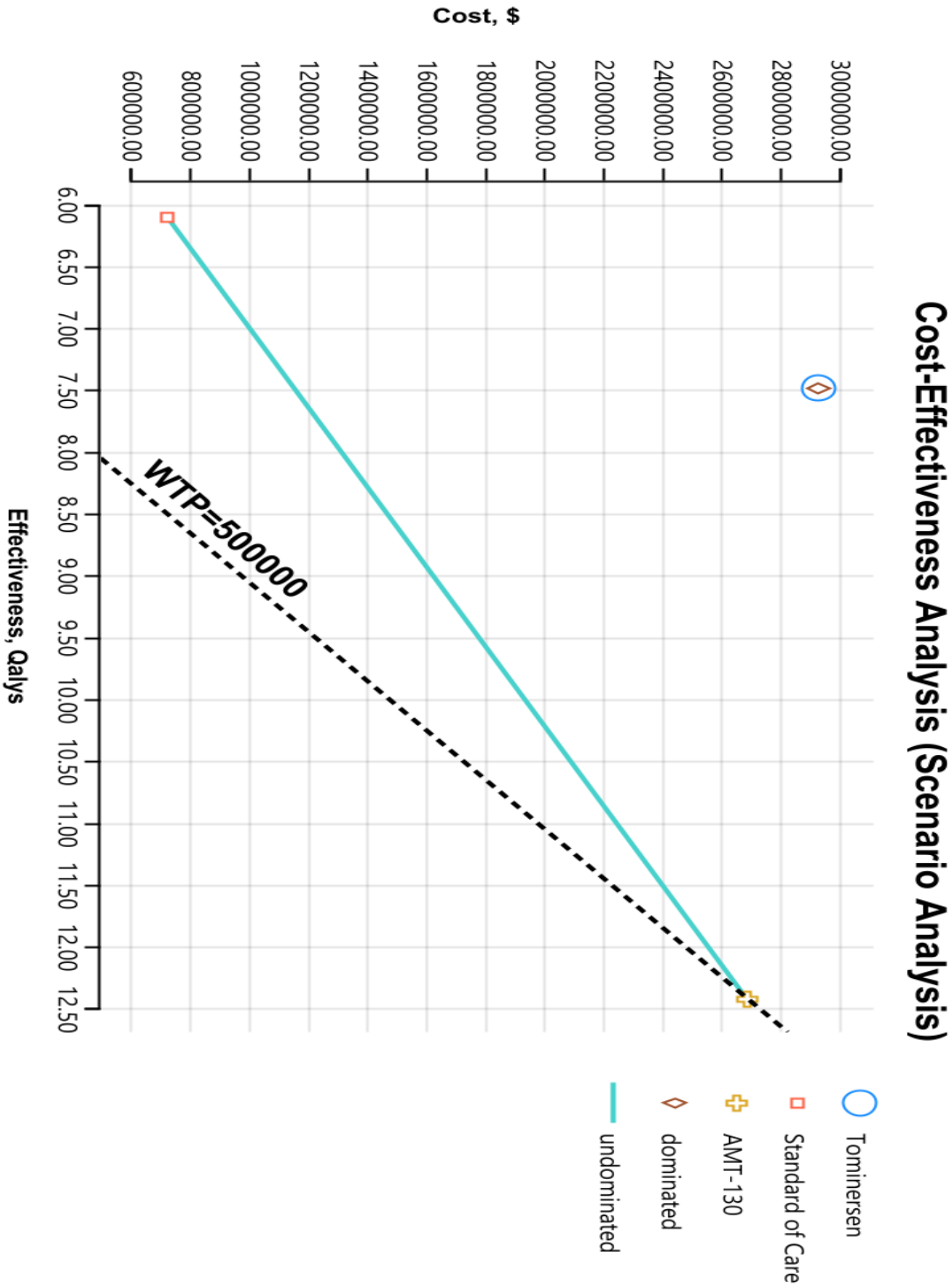


Figure 7: Cost Effectiveness Plane for Scenario Analysis Results



Appendix 4: Results from Deterministic Sensitivity Analyses

Figure 8: Tornado diagram with most sensitive inputs in one-way sensitivity analyses for AMT-130 vs Standard of Care

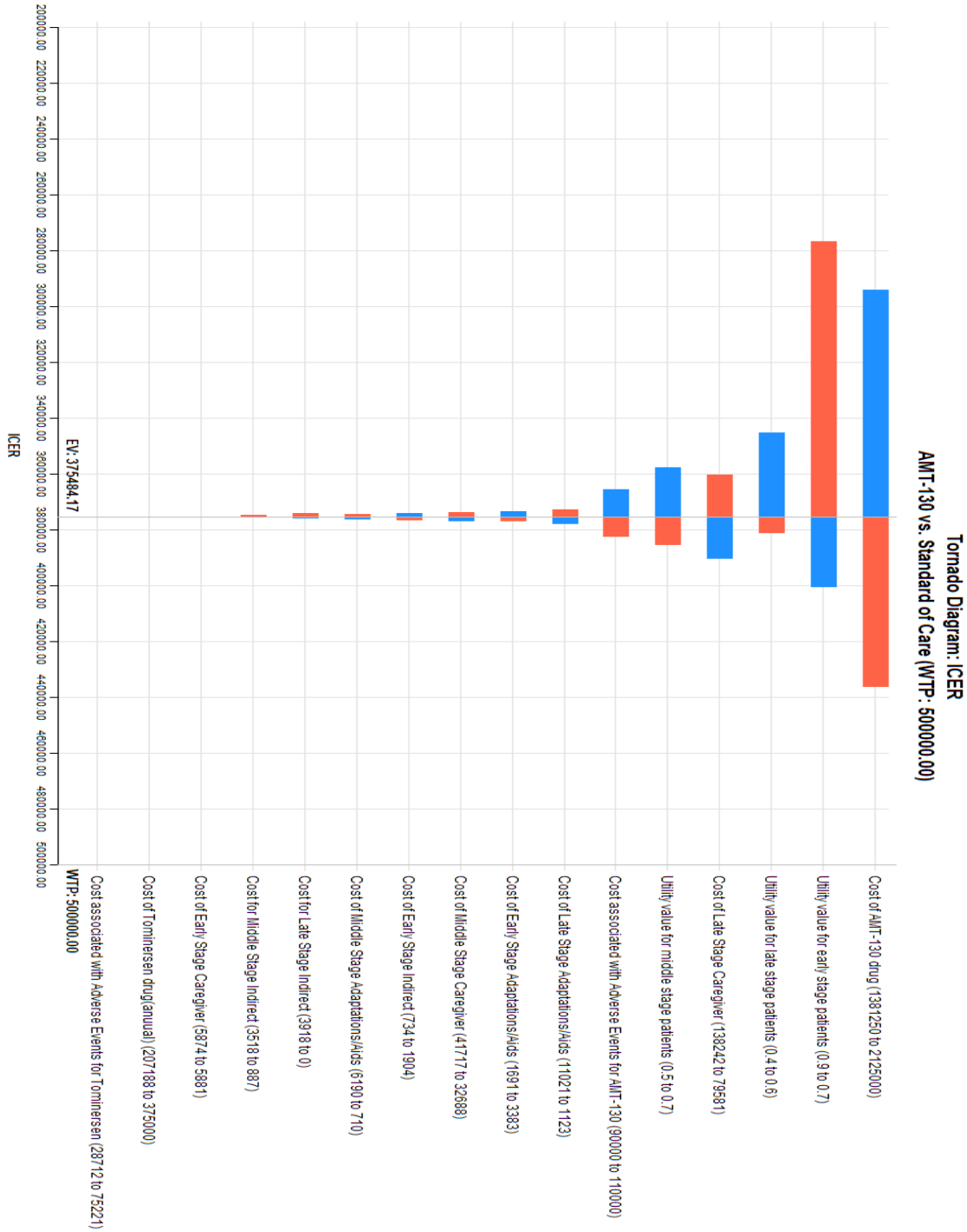
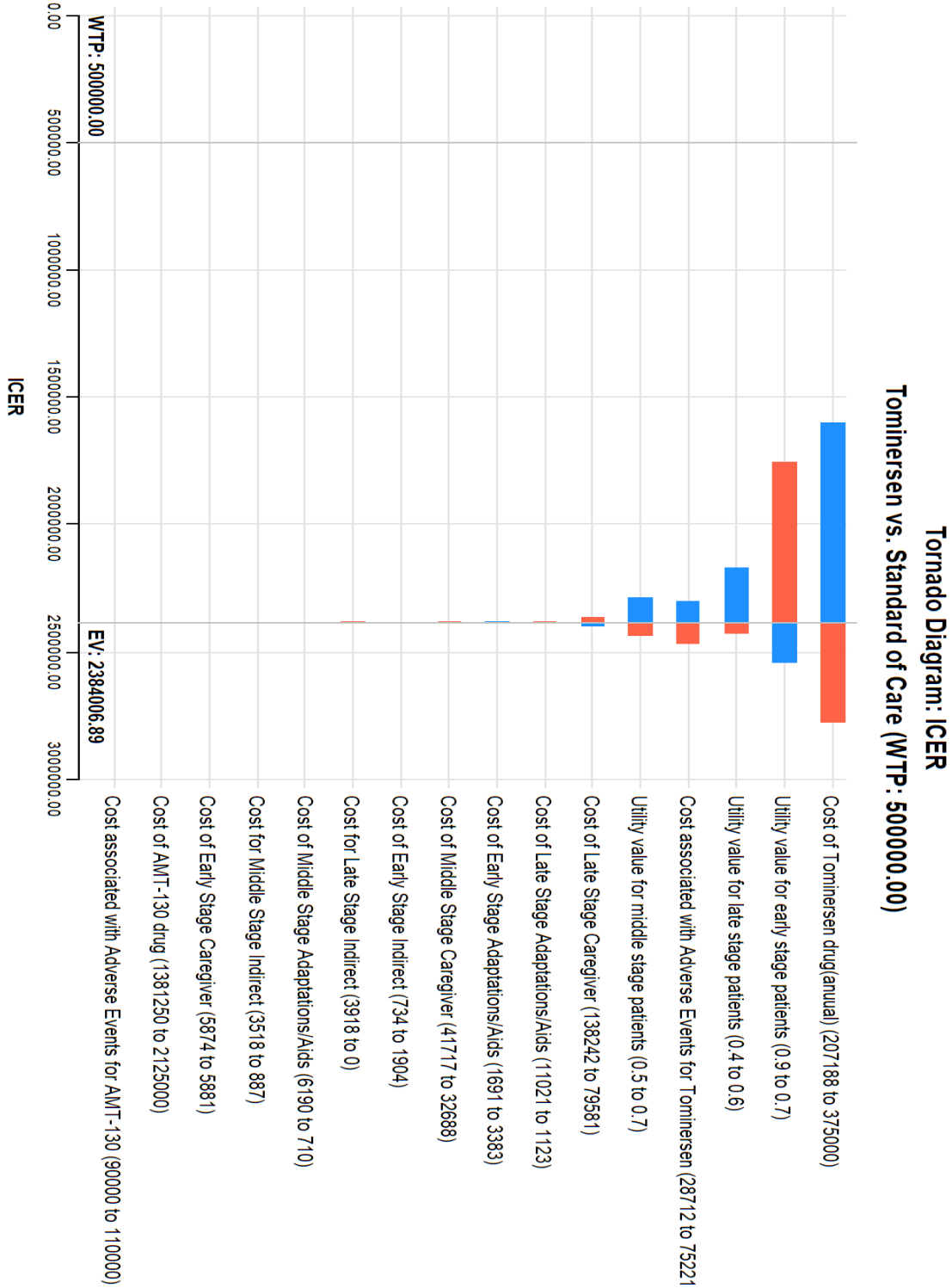


Figure 9: Tornado diagram with most sensitive inputs in one-way sensitivity analyses for Tominersen vs Standard of Care



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