A feasibility and applicability study of a health-related quality of life measurement in Vietnam

Vu Thi Quynh Mai
“Dám nghĩ, dám làm, dám chấp nhận.”
Table of Contents

ABSTRACT ................................................................................................................................. I
LIST OF ABBREVIATIONS ....................................................................................................... II
LIST OF TABLES ........................................................................................................................ III
LIST OF FIGURES .................................................................................................................... III
ORIGINAL PAPERS ................................................................................................................... IV

1 INTRODUCTION ..................................................................................................................... 1
1.1 Health-related quality of life ............................................................................................... 1
  1.1.1 What is health-related quality of life? ........................................................................ 1
  1.1.2 Health-related quality of life as a health outcome ................................................... 1
  1.1.3 Health-related quality of life measure classifications ............................................. 2
1.2 Universal health coverage in Vietnam .............................................................................. 4
  1.2.1 The healthcare system and health-insurance coverage in Vietnam ....................... 4
  1.2.2 Healthcare financial protection in Vietnam ......................................................... 6
  1.2.3 Provision of essential services in Vietnam ........................................................... 7
  1.2.4 Health technology assessments in Vietnam ......................................................... 8
  1.2.5 The application of HRQOL in health science ...................................................... 9
1.3 Research gaps ..................................................................................................................... 10
  1.3.1 Availability of HRQOL measurement tools in Vietnam ....................................... 11
  1.3.2 Demand for the EQ-5D-5L ................................................................................ 11
2 STUDY AIM ............................................................................................................................ 13
  2.1 Specific objectives ............................................................................................................. 13
  2.2 Structure of the doctoral project ..................................................................................... 13
3 THEORETICAL FRAMEWORK ............................................................................................. 15
  3.1 Health-state preference measurements ....................................................................... 15
  3.2 Validity ............................................................................................................................. 17
  3.3 Acceptability .................................................................................................................... 18
4 METHODOLOGY .................................................................................................................... 21
  4.1 Study population .............................................................................................................. 21
  4.2 Data collection .................................................................................................................. 22
  4.3 Variables .......................................................................................................................... 24
  4.4 Data analysis .................................................................................................................... 25
  4.5 Ethical approvals ............................................................................................................. 27
5 RESULTS ................................................................................................................................ 30
  5.1 The Vietnamese EQ-5D-5L value set .......................................................................... 30
  5.2 The Vietnam EQ-5D-5L reference data ...................................................................... 31
  5.3 Known-groups validity for the EQ-5D-5L in Vietnam ................................................ 31
Abstract

**Introduction:** An evidence-based strategy is used the national social health-insurance programme in Vietnam to assess healthcare technologies. Health technology assessments (HTA) have become increasingly important within decision-making processes. This doctoral project involved developing a health-related quality of life (HRQOL) measurement to be used in HTA in Vietnam.

**Methodology:** The doctoral project used a mixed-methods approach, which comprised a health-preference elicitation study using a combination of time-trade-off and discrete choice experiments method for the EQ-5D-5L, as recommended by the EuroQol Group (Objective 1). The project incorporated a validity study that utilised secondary data (Objective 2), a cost-utility analysis that utilised both secondary data and normative costing data (Objective 3), and a qualitative study that utilised empirical data (Objective 4). Additionally, the doctoral project resulted in an EQ-5D-5L reference dataset for the general population of Vietnam.

**Results:** A generic preference-based HRQOL measurement was developed for the Vietnamese population using the EQ-5D-5L instrument. This tool can be utilised not only as an outcome measurement for HTA, but in other health-science disciplines. The EQ-5D-5L comprises a descriptive system with five questions, a visual analogue scale (EQ-VAS), and a value set that facilitates the assignment of health-state values (Sub-study 1). The doctoral project proposed an EQ-5D-5L reference dataset that could serve as a basis for HRQOL comparison in Vietnam (Sub-study 2). It has added evidence on the validity of the EQ-5D-5L for the Vietnamese population through a known-groups validation conducted on individuals with hypertension (Sub-study 2). This validation has facilitated the establishment of a favourable environment for the implementation of this tool in Vietnam. Additionally, the satisfactory performance of the EQ-5D-5L has been shown in producing data that is useful for the cost utility analysis in Vietnam (Sub-study 3). Despite concerns regarding the appropriateness of the EQ-5D-5L in reflecting HRQOL for disease-specific populations, the tool has been accepted and is commonly used in Vietnam (Sub-study 4).

**Conclusion:** The outcomes of the doctoral project are a favourable HTA environment, facilitation of evidence-based decision-making, and contribution to the goal of achieving universal health coverage in Vietnam.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUA</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>HTA</td>
<td>Health technology assessment</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>LYs</td>
<td>Life years</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NCD</td>
<td>Non-communicable disease</td>
</tr>
<tr>
<td>NMB</td>
<td>Net monetary benefit</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>QALYs</td>
<td>Quality-adjusted life years</td>
</tr>
<tr>
<td>SHI</td>
<td>Social health insurance</td>
</tr>
<tr>
<td>TTO</td>
<td>Time trade-off</td>
</tr>
<tr>
<td>UHC</td>
<td>Universal health coverage</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
</tbody>
</table>
List of tables

- Table 1. Mapping of the sub-studies of the doctoral project................................. 29
- Table 2. Summary of additional analysis on the stratified age-sex EQ-5D-5L reference data ........................................................................................................................................ 32
- Table 3. Summary of additional analysis regarding discounted NMB in CUA...... 34
- Supplementary Table 1. Age-sex stratified for EQ-VAS among the Vietnamese general population.................................................................................................................... 59
- Supplementary table 2. Age-sex stratified for EQ-5D-5L values among the Vietnamese general population .................................................................................................................. 62

List of figures

- Image 1. Vietnamese community health centres in the twentieth and twenty-first centuries. ........................................................................................................................................ 6
- Image 2. The author met supervisors in Hanoi for doctoral project in 2018. ..........12
- Image 3. A public-health student interviewing a woman for Sub-study (1). ....... 23
- Image 4. Dissemination of the Vietnam EQ-5D-5L value set (sub-study 1) at the 2018 national conference on health technology assessments in Vietnam......... 30
- Figure 1. Health-outcome measure classification....................................................... 3
- Figure 2. Structure of the doctoral project................................................................. 14
- Figure 3. The framework on assessing acceptability............................................... 20
- Figure 4. A summary of the development of EQ-5D instruments in Vietnam...... 36
Original papers


- Vu Quynh Mai, Hoang Van Minh, Lars Lindholm, Sun Sun, Kim Bao Giang & Klas Göran Sahlen. Acceptability of the use of health-related quality of life for decision making in healthcare science in Viet Nam. [Submitted]
1 Introduction

1.1 Health-related quality of life

1.1.1 What is health-related quality of life?

The concept of quality of life is broad and can be interpreted from various perspectives. Historically, it has been associated with happiness and wellbeing. The earliest instrument to assess the quality of life was the Barthel Index, proposed in the 1940s. This instrument captured aspects of functional ability, physical functioning, and activities of daily living. In 1976, Priestman and Baum proposed the use of a visual analogue scale (VAS) to measure overall quality of life, in addition to other dimensional assessments including wellbeing, anxiety, activity, pain, social activity, and treatment usefulness. In 1984, Calman proposed an alternative method of assessing quality of life by measuring it as the difference between an individual's hopes and expectations regarding their experiences (1).

Within the field of health sciences, researchers have used the term health-related quality of life (HRQOL) to provide a more specific focus on quality of life. The definition of HRQOL is often influenced by the World Health Organization's definition of health as "a state of complete physical, mental, and social wellbeing, and not merely the absence of disease." However, there is no universally accepted definition for HRQOL. Therefore, investigators often present their own definitions when attempting to measure HRQOL. In common practice, HRQOL is a multidimensional concept that encompasses an individual's physical, emotional, and social wellbeing in terms of their health status and overall life satisfaction (1).

1.1.2 Health-related quality of life as a health outcome

The measurement of health gain or health loss is a crucial aspect of the evaluation of the impact of diseases and effectiveness of interventions on an individual's health. Despite the critical role of health-gain and -loss measurements in the field of health sciences, the doctoral project presented in this thesis focused on the assessment of health gain within medical sciences, particularly in relation to economic evaluations. The starting point for evaluating health gain is the measurement of health effects, which can include improvement in the primary health outcome of interest (e.g., survival) and other effects, such as therapy side effects and changes in HRQOL (2). Generally, health outcomes can be captured as clinical outcomes or person-reported outcomes (Figure 1).
Clinical outcomes are typically derived from clinical trials or epidemiological studies. These outcomes can be classified into intermediate outcomes (e.g. cases averted or detected), clinical endpoints (e.g. systolic blood pressure), and final outcomes (i.e. survival). Clinical intermediate outcomes are designed to reflect the health effects of a disease or evaluated intervention(s), and thus their advantages are straightforward and disease-focused. However, the problem with most clinical intermediate outcome measures is that they are specific to the clinical field being studied. Although clinical intermediate outcomes may be useful for decision-makers choosing among therapies for the same condition, the use of such outcomes can be misleading when applied in other conditions (e.g. decision on diabetes interventions would not be made based on blood pressure indexes). Therefore, researchers may want to measure the final clinical endpoint, which is generic and represents a lifelong health effect such as survival or life-years (LYs) gained. However, collecting such outcomes is resource-intensive, as it requires lengthy follow-up periods and large sample sizes (2).

HRQOL measures often rely on the second type of health outcome, which are person-reported. There has been a growing interest in the use of patient-reported outcome measures, which encompass measures of patient satisfaction, HRQOL, and other intervention effects that cannot be captured by clinical outcomes alone (2). However, these outcomes are also commonly used in the general population (3), so they are referred to as person-reported outcomes in this thesis. Since HRQOL is a key component of person-reported outcomes, they are typically measured using a multidimensional concept (1, 2). This type of health outcome primarily focuses on the effects of treatments that potentially influence the patient's wellbeing (1). Therefore, HRQOL outcomes can be utilised as final health outcomes in any health-related disciplines. To account for the long-term impact of interventions and fulfil the purpose of producing a final generic outcome for economic evaluations, HRQOL outcomes are frequently combined with the clinical final outcome life years (LYs) to create a final outcome known as quality-adjusted life years (QALYs).

1.1.3 Health-related quality of life measure classifications

HRQOL measures can be divided into two categories: condition-specific measures and generic measures (Figure 1) (2).

Condition-specific measures focus on the impact of a particular disease on quality of life, and include the European Organisation for Research and Treatment of Cancer instrument
for oncology. While these measures may be useful in assessing treatment effectiveness, they are of limited use in economic evaluations that seek to compare treatments for the same disease. Additionally, because they are multidimensional, it is challenging to compare two treatments that perform differently across various quality of life dimensions, unless one treatment is superior in all aspects (2).

In contrast, generic measures consider a broad range of quality of life dimensions that can be affected by any disease, including physical function, mental wellbeing, social function, and pain (2). Examples of generic measures include the EQ-5D and 36-Item Short Form Survey (SF-36). In addition, HRQOL outcomes can be utilised in two forms: profile basis and preference basis (Figure 1). HRQOL measures often comprise multiple attribute factors, which are capable of combining physical functioning (e.g., mobility, pain, activities), mental functioning (e.g., anxiety, depression), and social wellbeing (e.g., social activities, usual activities) (1). Description of multidimensional factors is commonly part of health profiles (or health states), which are employed to portray the HRQOL of individuals (2).

HRQOL can also be quantified as preferences for health states, which are eventually represented as indexes (or values). Various techniques are employed to measure preferences, including scaling (e.g., rating scale, VAS) or choice (e.g., time trade-off, paired comparison) (2). A detailed explanation of preference measurement is presented in the 'Theoretical framework' section of this thesis.

**Figure 1. Health-outcome measure classification.**
1.2 Universal health coverage in Vietnam

Achieving universal health coverage (UHC) is a crucial goal for ensuring equitable access to healthcare services and financial protection for all individuals. This requires addressing three main dimensions: coverage of health insurance, financial protection for patients, and provision of essential healthcare services (4). Vietnam is currently moving towards achieving UHC. The following paragraphs present a comprehensive rationale for each of the three essential components of UHC within the specific context of Vietnam, as well as the relationship between UHC and HRQOL measurement.

1.2.1 The healthcare system and health-insurance coverage in Vietnam

Vietnam, located in Southeast Asia, is bordered by the Pacific Ocean to the south and east, China to the north, and Laos and Cambodia to the west. Geographically, the country is divided into six regions: the northern midland and mountainous area, the Red River Delta area, the north central and central coastal area, the central highland area, the southeast area, and the Mekong River Delta area (5). The country has an area of 311,699 square kilometres, and had a population of 97.5 million in 2021 (6).

In the last decade, Vietnam has experienced a transition in its health status pattern: Vietnamese people are living longer, with life expectancy increasing from 73.7 years in 2012 to 75.4 years in 2022 (6). However, they are suffering from chronic non-communicable diseases (NCDs) more than previously (7). NCDs accounted for approximately 66% of total disability-adjusted life years in 2014 (7). In 2019, eight NCDs – stroke, ischaemic heart disease, diabetes, lower back pain, cirrhosis, chronic obstructive pulmonary disease, lung cancer, and headache disorders – were among the top ten causes of death and disability for Vietnamese people (8). The burden due to diabetes and lung cancer increased by more than 50% from 2009 to 2019 (8). Studies have also suggested that high blood pressure was the top risk factor for death and disability during this period of 2009 to 2019 (8). Moreover, Vietnam has been considered to have an ageing population since 2012, when about 10% of the general population was 60 or older (9).

The Vietnamese healthcare system has been adjusted to meet the needs of society. In 2015, the Ministry of Health (MOH) announced a national strategy for the prevention and control of NCDs for 2015–2025, designed to control the harm of the eight most burdensome NCDs (10). In addition, laws on the prevention and control of the harmful effects of tobacco (2012) and alcohol (2019) have been enacted to manage the risk factors
for NCDs in the community (11, 12). To promote healthy ageing, the MOH has strengthened primary healthcare at the grassroots level, which helps to bring qualified healthcare closer to the community (Image 1) (9). Additionally, a national action plan for care of the elderly was approved in 2021, with essential healthcare for the elderly ensured via free health insurance. Furthermore, the MOH has suggested a plan to have geriatric departments at all provincial hospitals and related health facilities at similar or higher levels by 2030 (13).

In the pursuit of UHC, it is imperative that the health system be enhanced and health-insurance coverage broadened in order to facilitate access to healthcare services. In Vietnam, a compulsory Social Health Insurance (SHI) programme has been implemented uniformly for all Vietnamese individuals (14). The number of individuals enrolled on the health-insurance programme was 91.1 million in 2022, which corresponds to a coverage rate of 92.04% of the population (15). The success in achieving high enrollment rates can be attributed to a combination of government subsidies for vulnerable groups (e.g., children, the poor, people with disabilities, and veterans) and mandatory participation in the national health-insurance programme.

The SHI programme offers an all-inclusive healthcare package comprising all services on the Vietnamese essential drug list, as well as inpatient and outpatient care (16, 17). The revenue collected from SHI payments is pooled into a single national fund that is used to reimburse expenses incurred for healthcare services delivered by both public and private providers (14). Additionally, the MOH is responsible for formulating a list of reimbursement prices and rates for healthcare services covered by the SHI programme on an annual basis (16). The pricing scheme for SHI reimbursement was formulated according to the MOH’s assessment of the resources required for personnel, drugs, medical supplies, and equipment for services. Nevertheless, there is a shortage of compelling evidence regarding the inclusion of other recurring expenditures, such as training, operational, maintenance, or associated capital costs (e.g., depreciation of buildings and equipment) in the MOH estimations (18). SHI drug reimbursement is calculated based on the procurement prices determined by national centralised drug procurement and the SHI reimbursement rates for drugs (17, 19).
1.2.2 Healthcare financial protection in Vietnam

In the realm of healthcare finance, health insurance is widely regarded to be a crucial mechanism for protecting individuals and households from the financial burdens associated with medical expenses. However, even if they possess adequate health insurance coverage, individuals and households may still face significant out-of-pocket costs for healthcare services. Regardless of the Vietnamese government’s efforts to alleviate financial strain on patients, out-of-pocket expenditure remains the primary means of financing healthcare in Vietnam. Between 2000 and 2016 out-of-pocket expenditure accounted for 35–45% of total healthcare spending; 20–25% was paid by the SHI fund, 10–20% by the state budget, and the rest by external funding sources such as donations and official development assistance (20).

Between 2002 and 2012, the proportion of out-of-pocket expenditure as a share of current health expenditure remained relatively stable, at 37.1–37.4%. However, in 2017 it increased significantly to 45.09% due to increases in the prices of healthcare services between 2014 and 2017 (6, 21). In the 2000s healthcare-service prices covered only a limited range of direct medical costs, including drugs, medical supplies, equipment
maintenance, and staff intervention allowances; operational costs were added to the pricing structure in 2013 (21). By 2017 healthcare-service prices had been increased to cover full personnel costs, including salary, allowances, and outsourcing costs (21). Since 2018, the prices for healthcare services have included both direct medical costs, such as drugs, medical supplies, equipment maintenance, personnel, operational costs, and equipment depreciation, and indirect costs, such as related training and administrative costs (21). However, the increase in prices for healthcare services was not matched by an increase in reimbursement rates, resulting in an increase in the out-of-pocket rate in 2017 (22). In 2018 the MOH released an updated reimbursement drug list and reimbursement rates for healthcare services (16, 17). This policy change helped to reduce the out-of-pocket rate (as a share of current health expenditure) by 2% in 2018 (6).

1.2.3 Provision of essential services in Vietnam

The provision of essential healthcare services is a crucial element of attaining UHC. The adequacy of such services can be assessed by examining the list of drugs and healthcare services offered in the Vietnamese context, within the SHI benefit package. Currently the SHI benefit package provides a wide array of services, including expensive medications (14). From its inception, the SHI benefit package has comprised inpatient and outpatient services as its core components (19). However, it has since expanded to also incorporate pregnancy check-ups (from 2005), treatment of squints, short-sightedness, refractive defects for children under six, physical and self-inflicted injuries, mental-health conditions (from 2014), and HIV/AIDS and tuberculosis treatment (from 2015) (14). The current SHI benefit package encompasses an assortment of services, such as hospital beds, diagnostic imaging, traditional medicine, rehabilitation, testing, emergency resuscitation and antidote, internal medicine, dermatology, endocrinology, surgery, obstetrics and gynaecology, ophthalmology, otolaryngology, oral and maxillofacial surgery, burn treatment, oncology, anaesthesia, and haematology (16). Nevertheless, the SHI benefit package falls short of covering preventive and palliative healthcare services (16, 19), which are critical in light of Vietnam’s ageing population.

An essential drugs list was initially introduced in 2005; by 2014 it contained 1064 types of modern medication and 57 types of radiopharmaceutical (23). The 2014 SHI drugs list includes mono-therapy, combination therapies, and expensive drugs that are not in the World Health Organization’s essential drug list. The SHI essential drugs list has undergone modification every five years since 2014; in 2018 it contained 1030 types of modern medication and 59 types of radiopharmaceutical (17). It was expected that by 2023 the SHI essential drugs list will cover 1037 types of modern medication and 59 types
of radiopharmaceutical (24). Given the SHI essential drugs list is anticipated to undergo updates, it is imperative that greater attention is devoted to guaranteeing the inclusion of crucial medications, while simultaneously maintaining the financial resources necessary for reimbursing such drugs.

1.2.4 Health technology assessments in Vietnam

Given the constraints of limited resources, Vietnamese decision-makers undertake careful consideration of which technologies, such as medical services and drugs, should be incorporated into the SHI, and subsequently determine appropriate reimbursement levels for these. This is done in order to ensure the long-term sustainability of healthcare spending from the SHI fund. In order to support decision-making processes, an evidence-based approach is adopted when developing SHI benefit packages.

In 2018, the MOH issued a decree that established a set of principles and criteria for the development of the SHI essential drugs list, including reimbursement rates and conditions for reimbursement for modern drugs (25). The decree requires evidence of budget impact analysis for the inclusion of any new drug in the SHI drugs list. Furthermore, if a drug is included in the World Health Organization essential drugs list, it will be considered for inclusion in the SHI only if it is affordable for the SHI fund. If a drug is not part of the World Health Organization essential drugs list, additional evidence in the form of a health technology assessment (HTA) must be provided before the drug can be considered for inclusion in the SHI (25). The criteria include: (1) the drug being the first-line indication for the relevant treatment, with clinical effectiveness having been confirmed by national or international treatment guidelines, and there should be no substitutes (or comparators) in the active SHI drugs list; (2) if the drug is not a first-line indication, or is a first-line indication and has been confirmed to be effective but has comparators in the active SHI drugs list, evidence on cost-effectiveness and budget impact analysis must be provided (25).

The application of HTA goes beyond drugs, and includes healthcare interventions such as therapy, machines, and healthcare programmes. Economic evaluations are a critical component of HTA and can take various forms, including but not limited to cost-benefit analyses, cost-effectiveness analyses, and cost-utility analyses (CUA).

A cost-benefit analysis compares the monetary value of the benefits and costs of an intervention to determine whether a specific goal is worth pursuing, and what quantity of resources should be allocated to achieving that goal (26). The decision rule for cost-
benefit analyses is based on the principle that health interventions should only be provided if the monetary value of additional benefits exceeds the costs required to provide the intervention (26). Although cost-benefit analyses are effective decision-making tools, it is challenging to identify the additional benefits of each intervention and convert them into monetary terms (2, 26).

The primary goal of a cost-effectiveness analysis is to identify interventions that can provide greater health benefits at the same cost, or similar benefits at a lower cost (26). This analysis measures health outcomes in natural units, including final outcomes such as life years gained and intermediate outcomes such as reduction in blood pressure (2, 26). For an outcome to be valid, it must have a consistent value that can be compared across individuals, and the value of each change in the outcome should only depend on its size (26). Despite their relative ease of execution, cost-effectiveness analyses only take into account a single outcome, and cannot incorporate other aspects of quality of life into the analysis. Moreover, a standard cost-effectiveness analysis may not facilitate comparison of interventions with differing health effects or across different diseases (2, 26), limiting its usefulness to decision-makers.

The CUA is regarded as a more advanced form of cost-effectiveness analysis because of the way in which outcomes are measured. Unlike cost-effectiveness analyses, CUAs measure effect in terms of “healthy years”, which is a multidimensional utility-based measure that combines life years gained with quality-of-life assessments (26). This includes measures of final health gain outcomes, such as quality-adjusted life years (QALYs) (2, 26). If the quality-of-life assessment is based on a generic measure, a CUA can be used to compare across interventions and diseases. However, if the quality-of-life assessment is based on a condition-specific measure, the analysis can only compare across interventions of the same disease/condition.

1.2.5 The application of HRQOL in health science

As the Vietnamese healthcare system moves towards achieving UHC, it is crucial to enhance its capacity to meet the healthcare needs of the community. The application of HRQOL measures can play a significant role in this regard, as they can be employed in various ways in clinical and epidemiological research to support this purpose.

A primary rationale for HRQOL assessments is that they allow treatments to be compared, which involves identifying the aspects of HRQOL that may be impacted by the interventions or nature of the disease. A crucial aspect of utilising HRQOL is its
applicability as a final health outcome in situations where complete cure or guaranteed survival are challenging to ascertain, as is the case for chronic diseases, HIV/AIDS, and cancers. In such instances, the influence of healthcare interventions on a patient's HRQOL appears to be more readily discernible than relying on natural indicators. Historically, medicine has focused on symptom relief based on professional assessment; HRQOL outcomes reported by patients, in contrast, can uncover issues that are equally or more important to them, and this has led to their widespread use today (1).

In economic evaluations, HRQOL is not typically used directly as a final health outcome. The primary objective of economic evaluation is to facilitate decision-making regarding the allocation of healthcare resources. Therefore, decision-makers need to consider the impact of treatments on both survival and quality of life. Despite this, HRQOL outcomes continue to play a crucial role in measuring the universal general health-gain outcome in terms of QALYs, which are frequently used in economic evaluations. The advantage of QALYs is that they capture both gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) in a single measure (2). Therefore, decision-makers are able to consider the impact of treatments on both survival and quality of life.

Operationalising the QALYs concept requires quality of life weights that are often presented as health-state values. Thus, HRQOL outcomes that are designed using preference-based measures are well-suited as HRQOL weight estimations for QALYs. However, it is more typical to include a profile-based measure, such as SF-36, or a disease-specific instrument for the health condition of interest in clinical trials (2). This poses a challenge for economic analysis because QALY estimates for relevant health states relating to the diseases of interest may not be available (2). Mapping, or cross-walking, is one potential solution to this problem, as it facilitates the prediction of health-state preference values when no preference-based measures have been included in the available dataset or literature (27).

### 1.3 Research gaps

In the context of Vietnam, there exist certain deficiencies that limit the potential benefits of HRQOL measures – notably a paucity of validated HRQOL measurement tools specific to the Vietnamese population.
1.3.1 Availability of HRQOL measurement tools in Vietnam

The utilisation of HRQOL measurement remains limited in Vietnam. A search of the PubMed database using the Boolean operators "health related quality of life" and "Vietnam" yielded 62 publications that made use of HRQOL outcomes. Among these, one study employed a single global measure (28), seven studies used condition-specific measures (29-35), 16 studies used generic profile-based measures (36-51), and 38 studies used generic preference-based measures (52-89).

The SF-36 and shorter SF-12 were frequently utilised in studies that employed a profile-based measure for HRQOL, as both have been validated for Vietnamese since 2000 (90). Meanwhile, another profile-based measure, the WHOQOL-BREF – a quality of life measurement tool proposed by the World Health Organization – was less commonly employed, as it was only validated for use in Vietnam in 2022 (91). Among studies that employed generic preference-based HRQOL measurement, the EQ-5D – an HRQOL measure tool produced by the EuroQol Research Foundation – was the most commonly utilised, with 36 publications between 2010 and 2018 found via Pubmed (52-87). Among the others, one study utilised a single global question, asking participants to rate their HRQOL on the day of the study (28), and the others employed condition-specific HRQOL measurement tools (30-35). It is important to note, however, that none of these tools have been validated for use with the Vietnamese population.

In general, there is an increasing demand for a generic preference-based measurement tool to assess HRQOL. Despite the evidence of validity of the SF-36, a generic profile-based measurement tool, for use in Vietnam in 2000, its utilisation has only recently gained greater attention, specifically since 2020. This can be attributed to the fact that generic preference-based instruments for HRQOL are generally shorter in length than generic profile-based measurements (1, 2).

1.3.2 Demand for the EQ-5D-5L

In the context of the development of national HTA with a focus on achieving UHC in Vietnam, there is a growing demand for a generic preference-based HRQOL measurement that can be used to calculate QALYs. Since the multi-attribute health status classification system with preferences is often employed in practice, existing literature suggests that the Health Utility Index (HUI), the EQ-5D, and the Short Form 6D (SF-6D) are the three most commonly used instruments (2). However, in Vietnam the EQ-5D tools are the most well-known and frequently utilised instruments. Despite the lack of a Vietnamese preference value set for the EQ-5D, its application has been reported since 2010. To overcome the lack of value set, researchers have utilised value sets from
countries that share similar cultural factors with Vietnam, including China, Thailand, and Korea (54-68). Additionally, the EQ-5D is a recommended method of deriving HRQOL weights, which are integral to QALYs, in numerous countries, including Australia, the United Kingdom, and several European countries (92-94). While the use of value sets from other countries may be acceptable in situations where no national value set is available, the development of country-specific EQ-5D value sets should be considered best practice (95).

The EQ-5D instrument consists of a descriptive system and a visual analogue scale known as EQ-VAS (96). The descriptive system identifies five critical dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents are asked to assess their current health by selecting three or five levels of severity within each dimension (96). As a result, two versions of the EQ-5D – the EQ-5D-3L and EQ-5D-5L – are generated based on the severity levels chosen. EQ-VAS, which is integrated into both versions, is a hash-marked scale ranging from 0 to 100, with 0 representing the worst imaginable health and 100 the best imaginable health (96). EQ-5D value sets comprise preference weights of health states generated by either the three or five-level versions. The EQ-5D-5L version is argued to provide more precise measurement at individual and group levels in terms of descriptive system data and utilities (97), while the increased sensitivity and precision of the EQ-5D-5L makes results achieved using it generalisable to longitudinal studies such as intervention designs (97). Therefore, the adoption of the five-level version is recommended in various applications, including economic evaluations, clinical research, and public-health research (97).

Image 2. The author met supervisors in Hanoi for doctoral project in 2018.
2 Study aim

**Overall aim:** To increase knowledge of health-related quality of life in Vietnam in order to support scientific research and decision-making processes.

2.1 Specific objectives

1. To develop and establish an EQ-5D-5L value set for measuring HRQOL in Vietnam.
2. To validate a HRQOL measurement tool that was specifically designed for patients with hypertension in Vietnam.
3. To utilise the validated HRQOL measurement tool in a CUA of consolidation durvalumab as a treatment for inoperable stage III non-small cell lung cancer (NSCLC) in Vietnam.
4. To explore the acceptability and feasibility of utilising HRQOL outcomes and the EQ-5D-5L as tools for decision-making in healthcare practices in Vietnam.

2.2 Structure of the doctoral project

This doctoral project was undertaken in response to the need for a HRQOL measurement tool to support HTA in relation to approaching UHC in Vietnam. The study was conceptualised with the aim of developing a HRQOL measurement tool for the Vietnamese population ([Error! Reference source not found.](#)).

The project first developed and published the EQ-5D-5L value set based on the preferences of the Vietnamese general public (98). In early 2020, during preparations for Paper 2, the COVID-19 pandemic had a significant impact on people's health and wellbeing. Consequently, we conducted a study to investigate how COVID-19 affected people's HRQOL, and how this had changed compared to pre-COVID-19 levels (82). This investigation led us to recognise the need for reference data on the HRQOL of the general public, which could serve as a basis for future scientific comparisons. Therefore, we incorporated the development of the HRQOL reference data and construct validity testing for the EQ-5D-5L into Paper 2. We selected a hypertensive population to test the validity of the EQ-5D-5L tool, on the basis that high blood pressure is one of the most burdensome risk factors for NCDs in Vietnam (8). It was thought that adding evidence on validity of the tool using this population would help to establish a better scientific environment for further studies on healthcare for the hypertensive group.

Figure 2. Structure of the doctoral project.
3 Theoretical framework

At the outset of this research, we found that EQ-5D-5L has been commonly used in Vietnam, however, further efforts has been required in order for it to be considered to be a credible tool to support decision-making processes via HTA. This requires the development of EQ-5D-5L health-state preference scores, along with more evidence regarding the tool's psychometric properties, which include reliability, validity, sensitivity, and responsiveness. Finally, a significant factor to consider is the willingness of stakeholders to incorporate the EQ-5D-5L into their practice.

3.1 Health-state preference measurements

The health-state preference measurement process has two critical components. The first is the choice of method by which subjects are prompted to respond – either using a scale or based on choices. The second is a decision must be made as to whether to utilise certain or uncertain assumptions in the formulation of the questions (2).

The scale-based approach is a straightforward method of gauging preferences using rating scales, category scaling, or visual analogue scales (VAS). Typically, a rating scale employs a numerical range from 0 to 100, whereas category scaling entails a smaller number of categories, often 10 or 11, which the subjects are evenly spaced. A VAS consists of a line on a page, usually 10 cm in length, with clearly defined endpoints. The subject is asked to assume they are permanently residing in a specific health state at a given time, and their preference with regard to that state is shown by where they place a mark on the line.

The choice-based approach is another method of measuring preferences; here, subjects are asked to choose between two options and their preferences for one health state are determined via a series of choice-based questions. The standard gamble and time trade-off (TTO) methods are common types of choice-based approach.

The standard gamble offers subjects a choice of two options, let say option A and B. Option A allows subject to live in full health for a certain time (t) at a probability P, or they may die immediately at a probability (1-P). Option B allows subject to live in a healthy state for a certain time (t). Preference of health state is determined by varying the probability - P in option A until the subject perceives the two options to be equally desirable. Hence the uncertainty assumptions are formulated in the descriptions for option A, which are presented as the set of probabilities P.
The TTO method is designed similarly to the standard gamble but questions are formulated with certain assumptions. Subjects have to choose between option A is to live at full health for a proposed time ($t_a$); option B is to live in a health state for a certain time ($t_b$), which are followed by immediate death at both options. The TTO preference is determined by varying the time lived at full health - ($t_a$), until the subject perceives the two options to be equally desirable.

The scale-based and choice-based methods both provide a preference range from 0 to 1, with death typically assigned a value of zero and full health a value of 1. However, if death is not considered the worst state, the preference measurement can adjust to negative values to capture values of worse-than-death states (2).

The measurement of health-state preference is an essential aspect of health-economics research. The use of different methods to obtain these measures has been the subject of ongoing debate in the field. The scaling methods are straightforward which can provide the preferences directly to the researchers and not time-consuming for respondents. However, sometimes respondents may find it is difficult to estimate a value for a health state and they often provide ordinal responses rather than interval values, which can introduce measurement bias (99-101). In contrast, choice-based methods are user-friendly as everyone can easily make their choice between option A or B, however it is time-consuming for the respondents as they have to answer several questions to identify preference for one health state (101). Despite the lack of a gold standard for measuring preference, many researchers prefer choice-based methods (2).

When comparing choice-based approaches, the standard gamble incorporates risk attitude by including uncertainty assumptions in its questions. Risk attitude can significantly impact the preference measurement process as it depends on the individual’s propensity for risk-taking (100). However, the impact of risk attitude are only valid for individual decision-making and when preferences are aggregated for societal decision-making, such impact is no longer applies (102). Therefore, it can be concluded that any choice-based measurement approach would be appropriate for developing preference score sets for EQ-5D-5L health states, which were intended to inform societal decision-making in Vietnam. The EuroQol Research Foundation has established a global standard valuation protocol; they use the TTO method combined with a pair comparison method - a choice-based method, to measure EQ-5D-5L health-state preferences (103). Following this approach for developing the preference score sets for EQ-5D-5L health states in Vietnam was felt to be appropriate and reasonable.
The question of whose values should be employed when evaluating health states is a critical matter. The debate centres on whether to utilise values from patients or from the general public when assessing health states. Advocates of the use of patient values argue that patients are the intended recipients of the treatments being evaluated. Conversely, proponents of using general public values argue that this group should be employed as they provide the majority of funding for healthcare through taxes, particularly in countries with publicly funded national-health services or health-insurance schemes. Nonetheless, one of the challenges associated with using preference measurements derived from the general public is that the public generally lack direct experience with the health states being evaluated, making it difficult for them to comprehend how an unfamiliar health state might impact their quality of life (2). On the other hand, patient preference measurements may be biased, as patients may be willing to pay a substantial amount to resolve their health issues (104, 105). Because Vietnam requires the use of a HRQOL measurement tool that can aid decision-making from a societal standpoint, a preference elicitation from the general public was felt to be more persuasive.

In summary, in order to facilitate the development of a HRQOL measurement tool that supports decision-making in relation to HTA from a societal perspective, it was concluded that using preference measurements from the general public and choice-based measurement approaches, such as the TTO, was the optimal way to elicit the valuation of EQ-5D-5L health states in Vietnam.

### 3.2 Validity

The framework for testing psychometric properties followed a classification proposed by Peter M. Fayers (1). In order to establish credibility, any measurement must meet certain fundamental criteria, such as validity, reliability, sensitivity, and responsiveness. These properties are interconnected, but each one is important in its own right.

- Validity is to test whether the instrument accurately measures what it is intended to measure, and whether it is useful for its intended purpose.
- Reliability and repeatability pertain to the random variation associated with measurements.
- Sensitivity refers to the ability of measurements to facilitate differences between patients or groups being identified.
- Responsiveness is similar to sensitivity, but pertains to ability to detect changes in a patient's condition over time.
For this project, which aimed to develop a tool for measuring HRQOL from a societal perspective rather than targeting specific diseases or populations, the most critical aspects of the psychometric property testing were the validity and reliability of the instrument. It is worth noting that, due to resource constraints, the focus of the doctoral project was solely on validity assessment.

Validity assessment is an essential aspect of determining the accuracy and usefulness of an instrument, and is typically divided into three key areas: content validity, criterion validity, and construct validity.

- **Content validity** evaluates the appropriateness of an instrument in terms of the number and scope of questions.
- **Criterion validity** involves comparing an instrument’s results against an established standard or known truth.
- **Construct validity** is widely regarded as the most critical aspect of validity assessment, as it examines the theoretical relationship between the items and their proposed scales.

In practice, assessing validity is a complex and ongoing task, and this process involves accumulating more and more evidence to demonstrate that a scale is appropriate and behaves as expected.

Construct validity has three commonly used forms: known-groups validation, convergent validity, and discriminant validity.

- **Known-groups validation** is a relatively straightforward form of construct validation that is based on the premise that certain groups of individuals are expected to score differently from others, and the instrument should be able to detect these differences.
- **Convergent validity** is another crucial aspect of construct validity that involves demonstrating that a hypothesised quality of life dimension is significantly correlated with other dimensions that are theoretically related to it.
- **Discriminant validity**, on the other hand, recognises that some dimensions of quality of life are expected to be less related to others, and thus, their correlations should be low.

Due to resource constraints, the doctoral project focused on known-groups validation.

### 3.3 Acceptability

In the development of health-states preferences measurement and assessment of the psychometric properties of HRQOL measurement tools, such as validity, reliability, and
sensitivity, it is important to also consider the acceptability of these tools to stakeholders. However, the acceptability of HRQOL measurement tools is often overlooked and inadequately conceptualised. Although some studies have attempted to assess acceptability in healthcare (106-110), these efforts have been limited. To address this gap, Sekhon and colleagues propose a definition and theoretical framework of acceptability that can inform evaluations of the acceptability of healthcare interventions (111). Specifically, they define acceptability as a “multi-faceted construct that reflects the extent to which people delivering or receiving a health outcome measure consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention” (111). This study adapted Sekhon et al.’s theoretical framework of acceptability to assess the acceptability of HRQOL measurement tools in supporting the decision-making processes in relation to HTA in Vietnam.

Following Sekhon et al.’s theoretical framework, this doctoral project explored the acceptability of the use of HRQOL measurements and the EQ-5D-5L in healthcare decision-making in relation to seven aspects: affective attitude, burden, ethicality, coherence, cost, perceived effectiveness, and self-efficacy (Figure 3). Affective attitude refers to the perception of stakeholders regarding the HRQOL measurement tool. Burden represents the perceived effort required to use or implement the HRQOL measurement tool. Ethicality captures the degree to which the use of the HRQOL measurement tool aligns with the value systems of stakeholders. Coherence indicates the extent to which participants understand the measurement tool and its functioning. The original framework proposed opportunity cost as a means of assessing the acceptability of healthcare interventions, but the definition of this term was imprecise (111). Therefore, we adapted this component to assess the cost of accessing the HRQOL measurement tool, and considered whether stakeholders were willing to pay for it. Perceived effectiveness relates to stakeholder opinions regarding the psychometric properties of the HRQOL measurement tool. Finally, self-efficacy reflects stakeholder confidence in using or implementing the HRQOL measurement tool.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affective attitude</td>
<td>• The perception of the participant during the use of HRQOL outcomes and the EQ-5D-5L during healthcare decision-making processes.</td>
</tr>
<tr>
<td>Burden</td>
<td>• The perceived level of effort required to use or apply HRQOL outcomes and the EQ-5D-5L in healthcare decision-making.</td>
</tr>
<tr>
<td>Ethicality</td>
<td>• The extent to which the use of HRQOL outcomes and the EQ-5D-5L in decision-making processes aligns with the participant’s values.</td>
</tr>
<tr>
<td>Coherence</td>
<td>• The extent to which the participant understands HRQOL outcomes, the EQ-5D-5L, and their functioning.</td>
</tr>
<tr>
<td>Cost</td>
<td>• The extent to which benefits, profits, or values must be given to engage with HRQOL and the EQ-5D-5L in healthcare decision-making.</td>
</tr>
<tr>
<td>Perceived effectiveness</td>
<td>• The perceived likelihood of HRQOL outcomes and the EQ-5D-5L achieving their intended purpose.</td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>• The participant’s confidence in their ability to perform or use HRQOL outcomes and the EQ-5D-5L in healthcare decision-making.</td>
</tr>
</tbody>
</table>

**Figure 3. The framework on assessing acceptability.**
4 Methodology

The doctoral project comprised four sub-studies: (1) the EQ-5D-5L valuation study, (2) the validity assessment study, (3) the CUA study, and (4) the acceptability study. Sub-studies (1) and (4) involved the collection of primary data, while (2) and (3) utilised secondary data. A summary of the methods used in the four sub-studies is presented in Table 1.

4.1 Study population

Sub-study (1), which focused on the EQ-5D-5L valuation, enrolled a total of 1200 Vietnamese adults who possessed the ability to comprehend and respond to the research inquiry. The participants were selected from the general populations of six distinct geographical regions of Vietnam through a multi-stage stratified cluster quota-based sampling method. Households were identified for recruitment purposes, and a door-to-door approach was employed. Further elaboration of the sampling procedure can be found in Paper 1 (98). The sample in this sub-study was chosen to develop reference data for the EQ-5D-5L, as discussed in Paper 2 (112).

Sub-study (2), which focused on known-groups validity assessment, employed secondary data obtained from a post-evaluation community survey of a project called ‘Evaluation of the Ho Chi Minh City Communities for Healthy Hearts - CH2’. The CH2 sample comprised 1296 adults aged 40 and above residing in eight districts of Ho Chi Minh City, which is the largest megacity in southern Vietnam (113). Blood-pressure measurements and medical history of hypertension for each individual were used to create three groups: one of 577 non-hypertensive adults, one of 477 adults diagnosed with hypertension by a physician, and one of 242 hypertensive adults without a physician diagnosis (who their blood pressure indexes were equal or above the hypertension’s threshold). The detail method used to creat the three groups is described in Paper 2 (112).

Sub-study (3) involved a CUA that investigated the use of durvalumab as a treatment option for inoperable stage III NSCLC that had not progressed. The assessed intervention was standard of care and consolidation treatment with durvalumab, and the assessed comparator was standard of care and placebo. The CUA was conducted using a modelling approach, and the study population was restricted to patients with inoperable stage III NSCLC. The eligible patients were those who had not progressed following concurrent chemotherapy and radiotherapy. To adjust for patient characteristics in the CUA model, data on average age, weight, and height in Vietnam were utilised (Paper 3).
**Sub-study (4)** qualitatively assessed the acceptability of the use of HRQOL outcomes and the EQ-5D-5L in decision-making processes, with the ultimate goal of supporting HTA in Vietnam. Relevant stakeholders were identified based on the structure of the Vietnamese pharmacoeconomic council, including specialists in health economics, healthcare financing, healthcare policy and strategy, pharmacists with pharmacoeconomic expertise, and health insurance specialists from the MOH (114). While clinical experts and specialists from the SHI participate in the council, their primary responsibilities are evaluating effectiveness of drugs and considering the affordability of the SHI fund for the proposed drugs to be included in the SHI’s drug list (114), and as such were not identified as relevant stakeholders. Given the widespread use of HRQOL outcomes and the EQ-5D-5L in public-health research in Vietnam, stakeholders with public-health expertise were included in the study. A purposive sampling method was used to recruit participants: in total, eleven individuals participated in this qualitative study (Paper 4).

### 4.2 Data collection

It should be noted that secondary data were utilised for Sub-studies (2) and (3), obviating the need for any data collection procedures. This section outlines the data-collection process employed for Sub-studies (1) and (4).

**Sub-study (1)**, which evaluated the EQ-5D-5L, was conducted in accordance with a standardised protocol developed by the EuroQol Group (EQ-VT 2.1 in Vietnamese). Fieldwork was carried out between 20 November and 25 December, 2017, and interviews were conducted face-to-face by trained interviewers. We used a web-based platform of the EQ-VT to record the data, which was designed by the EuroQol Group. To ensure the reliability and validity of the data, daily uploads and quality-control measures were implemented. The data-collection form consisted of four main sections, starting with the collection of background demographic information from the respondents. The participants were asked to report their current health status using the EQ-5D-5L descriptive system. They then responded to 10 TTO questions to elicit values for 10 random health states. The 10 random health states were actually a block of health states over ten different blocks in the EQ-VT design. The lead-time TTO approach allowed us to collect values for both better- and worse-than-death health states. Finally, discrete choice experiment (DCE) technique was employed; the participants selected their preferred health state in a pairs. Respondents were asked to answer seven DCE questions, which is one block of from a total of 28 blocks of DCE questions (115).
Data collection for Sub-study (4) was conducted between June 2021 and June 2022. Data was collected via Zoom by interviewing relevant stakeholders. The interviewees were selected and interviewed by the author. Potential participants were provided with information about the study and verbally asked to give their consent to participate and for their interview to be recorded. Following receipt of consent, the interview commenced with a warm-up discussion during which the interviewees shared details about their current work related to HTA and experience of using HRQOL outcomes and the EQ-5D-5L. The interviewees were then asked to provide their views on the seven aspects outlined in Figure 3. The seven questions are listed in detail in Paper 4. Each interview concluded with an invitation to provide any additional comments. The audio was recorded and subsequently transcribed by a public-health Bachelor's student. The transcribed data was then cross-checked by the author.

Image 3. A public-health student interviewing a woman for Sub-study (1).
4.3 Variables

The primary objective of Sub-study (1) was to estimate values for all EQ-5D-5L health states using a mathematical regression equation. The independent variables were a subset of 20 variables with five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and four severity levels (ranging from slight problems to extreme problems). The dependent variable was the original observed health state value obtained from the lead-time TTO tasks. In addition, the DCE tasks did not directly generate values for health states, but rather provided information regarding respondents’ preferences between pairs of health states. These choices were then used as binary dependent variables. Various estimation models were employed using the aforementioned two dependent variables (TTO value and DCE binary). Paper 1 contains a comprehensive description of the variables that were used in Sub-study (1) (98).

For the estimation of reference data, which was part of Paper 2, we followed the standardised method recommended by the EuroQol Group to develop the EQ-5D-5L population norms (3). The dependent variables for this analysis were the descriptive statistics for the five dimensions: the five levels, the EQ-VAS, and the EQ-5D-5L values. The suggested independent variables were age group and sex. To broaden the use of the reference data, we included other socioeconomic characteristics as independent variables in the final model, including education, geographical location, marital status, place of residence, ethnicity, religion, occupation, and SHI usage. A detailed account of the variables that were used for the development of the EQ-5D-5L reference data is provided in Paper 2 (112).

Sub-study (2) focused on the validation of known groups for the EQ-5D-5L among hypertensive groups; we utilised HRQOL outcomes, namely the EQ-VAS and EQ-5D-5L values, as dependent variables. The hypotheses tested in this study were that the presence of hypertension and comorbidities is associated with lower HRQOL metrics, and that patients who are aware of their hypertensive status report a poorer quality of life (116-120). To investigate this hypothesis, three groups were selected as independent variables: non-hypertensive, diagnosed hypertensive, and undiagnosed hypertensive. This study aimed to test the hypothesis that HRQOL among hypertensive individuals is typically lower among females and individuals with more comorbidities, lower levels of education, older ages, and higher body mass index (BMI) (121, 122). These factors were therefore included as independent variables. The specifics of the variables included in the sub-study are outlined in Paper 2 (112).
Sub-study (3) employed a partitioned survival model to compare the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) of two treatment arms. The first arm was standard of care and consolidation treatment with durvalumab, while the second arm was standard of care and placebo. The CUA model required three main inputs for its estimations: clinical outcomes, cost, and utility. The clinical inputs consisted of published survival data (123), including five-year overall and progression-free survival, as well as the probabilities of experiencing adverse events due to treatment. The utility inputs were obtained from a cross-sectional survey of NSCLC patients conducted by Ha, Hoang (124) in 2018, which provided patient characteristics, EQ-5D-5L values, and disease-stage information. Utility decrement due to adverse events was extracted from the literature (125-127). Cost inputs were estimated from a healthcare-system perspective. The study only considered financial costs, including direct medical costs of drugs and services covered by the SHI and patient out-of-pocket costs. A microcosting approach was used to estimate costs for inoperable stage III NSCLC in Vietnam, including durvalumab acquisition and administration costs, monitoring costs, subsequent treatment costs for those who progressed, and adverse-event treatment costs (16, 17, 128). The cost of medical services was estimated using SHI reimbursement prices and rates, while drug costs were estimated using SHI reimbursement rates and average prices from centralised drug procurement (16, 17, 128). The patient out-of-pocket costs were extracted from the above-mentioned study by Ha, Hoang (124). Paper 3 presents the full details of the inputs that were used.

Sub-study (4) was a qualitative study, and as such no quantitative variables were used. It was designed to explore the acceptability of using HRQOL outcomes and the EQ-5D-5L as a tool in healthcare decision-making using seven questions.

4.4 Data analysis

In Sub-study (1), three sets of regression models were tested in order to find the most accurate model for estimating EQ-5D-5L health-state values. The three sets of models used data from TTO and DCE tasks either separately or in combination. TTO data was used to estimate an original Tobit, a heteroscedastic Tobit, and a panel Tobit model, and DCE data was used to estimate a Logit model. Whether it was reasonable to combine the C-TTO and DCE data was then checked by comparing their predictions using scatter plots and testing the correlation between them. After it had been confirmed that the data could be combined, hybrid models that included both types of data were estimated. The best-performing model was chosen based on its consistency and accuracy (see Paper 1). In relation to the EQ-5D-5L reference data, a descriptive analysis was conducted that
encompassed various measures such as frequency, mean, standard deviation, and inter-quartiles of both the EQ-VAS and EQ-5D-5L across various age-sex groups (see Paper 2). An additional age-sex stratified analysis was performed to describe the EQ-5D-5L reference data.

**Sub-study (2)** utilised non-parametric statistical testing to assess the differences in the EQ-VAS and EQ-5D-5L indices across sub-groups, taking into account the impact of the ceiling effect. Specifically, Mann-Whitney tests were used for two-group categorical variables, while Kruskal Wallis H Tests were applied for more-than-two-group categorical variables. Additionally, post-hoc analyses were performed to investigate any differences among multiple pairwise comparisons. Finally, a multivariate linear regression model was used to determine the associations between the mentioned known groups and the EQ-VAS and EQ-5D-5L values (see Paper 2).

**Sub-study (3)** undertook a base-case analysis to estimate ICER and NMB of durvalumab in the treatment for stage III unresectable NSCLC, with specific assumptions having been made. Firstly, all patients were assumed to enter the model at the progression-free stage and move forwards. Secondly, durvalumab was included in the SHI, and there was no discount on its acquisition cost. Thirdly, copayment between the health insurance and the patient was not applied. Fourthly, the cost and disutility of related adverse events were incorporated into the analysis. Fifthly, a discount of 3% was applied to both costs and outcomes. Lastly, a lifetime model of 15 years was used to calculate the costs and outcomes of both the durvalumab and placebo arms. The acceptability threshold for calculating NMB was 258 million VND, based on the three-times-GDP threshold suggested by the World Health Organization for cost-effectiveness analysis (129, 130). The outcomes were presented as both incremental cost per LY gained and incremental cost per QALYs gained, ICER, and NMB. Deterministic sensitivity analysis, one-way sensitivity analysis, and probability sensitivity analysis were conducted; a detailed account of the methods employed is presented in Paper 3. An additional analysis was performed using the PACIFIC utility inputs to observe the change of final conclusion on the intervention.

In **Sub-study (4)** the author employed NVIVO software for coding and analysing data. To maintain its authenticity, the data was coded in the native language. The transcribed interviews underwent analysis using a theoretical thematic approach (131). The analytical process followed a deductive methodology. Initially, the author reviewed the transcripts, conducted coding of the transcripts, and generated preliminary themes and accompanying analytical notes. The preliminary themes (sub-themes) and overarching
themes were agreed among all of the co-authors. The analysis adopted a latent approach, aimed at identifying and analysing underlying ideas and meanings within the empirical data (131).

4.5 Ethical approvals

Prior to their involvement in the studies, all of the participants in Sub-studies (1) and (4) were duly informed about the study and provided their consent to participate. The study designs for all four sub-studies were reviewed and approved by the Ethical Review Board for Biomedical Research at Hanoi University of Public Health, with the identification numbers 374/2017/YTCC-HD3; 300/2019/YTCC-HD3; 403/2008/YTCC-HD3; and 359/2021/YTCC-HD3, respectively.
<table>
<thead>
<tr>
<th>Paper 1 (Sub-study (1))</th>
<th>Paper 2</th>
<th>Paper 3 (Sub-study (3))</th>
<th>Paper 4 (Sub-study (4))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference data</strong> (Sub-study (1))</td>
<td>Known-groups validation (Sub-study (2))</td>
<td><strong>Cost inputs</strong></td>
<td><strong>Utility inputs</strong></td>
</tr>
<tr>
<td>Overall objective no.</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Study population and sample size</td>
<td>1200 adults from general population</td>
<td>Adults aged 40+ Non-hypertensive: 577 Diagnosed hypertensive: 477 Undiagnosed hypertensive: 242</td>
<td>Inoperable stage III NSCLC</td>
</tr>
<tr>
<td>Sampling method</td>
<td>Multi-stage stratified cluster quota-based approach; face-to-face interviews</td>
<td>Secondary data from a community survey of CH2 project</td>
<td>Microcosting and secondary data from a patient-based survey (N=400)</td>
</tr>
<tr>
<td>Source of data</td>
<td>Primary data from a cross sectional survey</td>
<td>Secondary data from a patient-based survey (N=400) and literature review</td>
<td>Literature review</td>
</tr>
<tr>
<td>Source of data</td>
<td>Primary data from a cross sectional survey</td>
<td>Secondary data from a patient-based survey (N=400) and literature review</td>
<td>Literature review</td>
</tr>
<tr>
<td>Dependent variable(s)</td>
<td>TTO observed value and binary DCE variable</td>
<td>Self-reported EQ-VAS and EQ-5D-5L values</td>
<td>NMB between: Comparator: standard of care Intervention: Standard of care and durvalumab consolidation Acceptability threshold: 301,347,998 VND – mean willingness to pay among NSCLC patients</td>
</tr>
<tr>
<td></td>
<td><strong>Paper 1</strong> (Sub-study (1))</td>
<td><strong>Paper 2</strong></td>
<td><strong>Paper 3</strong> (Sub-study (3))</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Independent variables</strong></td>
<td>A subset of 20 variables from four severity levels and five dimensions</td>
<td>Main factors: age-sex groups</td>
<td>SHI cost: direct medical cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other factors: socioeconomic characteristics</td>
<td>OOP cost: direct medical and non-medical cost</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>A best-fit model was selected among TTO models, different Tobit DCE models, Logit TTO and DCE models, and different Tobit and Logit models</td>
<td>Descriptive analysis. Non-parametric statistical testing. Post-hoc analysis.</td>
<td>ICER and NMB values from base-case and sensitivity analyses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Additional analysis: age-sex stratified analysis for the EQ-5D-5L reference data</td>
<td>Additional analysis: NMB of the model compared using Vietnamese and international utility inputs</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>A regression equation to estimate values for all EQ-5D-5L health state.</td>
<td>EQ-5D-5L reference data for the general population</td>
<td>Feasibility of using the EQ-5D-5L to generate evidence on CUA for HTA in Vietnam shown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Validity of the EQ-5D-5L among hypertensive population shown</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Mapping of the sub-studies of the doctoral project.**
5 Results

5.1 The Vietnam EQ-5D-5L value set

A Vietnamese value set for the EQ-5D-5L was created by analysing data from 1200 valid participants. Given the cultural norms in Vietnam, some adjustments to the standard EQ-VT protocol were made. Specifically, during the pilot study, it was recognised that asking individuals direct questions about illness or death can be perceived to be insensitive. To address this, a third party who was generally of the same age, sex, and socio-economic status, was the subject when the TTO questions were asled. Another adjustment related to the inclusion of study participants aged 70 and above; the pilot study showed that these respondents had difficulty comparing the two health states presented in the DCE tasks, potentially due to lack of visual acuity or difficulty imagining the health states. To alleviate this, a visual aid in the form of a coloured card was provided, and the original visualisation of the DCE task was shown on a computer screen. The visual aid consisted of five rectangular pieces of paper, each printed in a different shade of yellow, representing the five levels of severity. These adjustments aimed to enhance the cultural appropriateness of the value set.

In this study, we utilised the regular censored hybrid model to determine 3125 EQ-5D-5L health state values for the Vietnamese population. The values generated ranged from -0.5115, which represented the worst state, to 1, which represented full health. We observed that disutility weights for the mobility dimension were the largest, with disutility values of 0.0692 for “slight problems” and 0.3761 for “unable to walk”. On the other hand, we found that the smallest disutility weights were observed in self-care, with disutility values of 0.0428 for “slight problems” and 0.2311 for “unable to”. A detailed discussion is presented in Paper 1.

5.2 The Vietnam EQ-5D-5L reference data

In the Vietnamese general population, the average EQ-VAS and EQ-5D-5L scores were 81.10 (SD: 13.35) and 0.94 (SD: 0.09), respectively. The percentages of people with full health was reported at 8.92% via EQ-VAS and 54.42% via the descriptive system (EQ-5D-5L score). Based on feedback received during the midterm seminar of this doctoral study, the reference data was improved by presenting EQ-VAS and EQ-5D-5L values by age-sex combinations. Therefore, we extended the analysis accordingly (Table 2); detail regarding age-sex stratified EQ-VAS and EQ-5D-5L by socioeconomic characteristics is presented in Supplementary Table 1 and Supplementary table 2.

The examination of the unstratified data showed that younger individuals had considerably greater average HRQOL scores, for both EQ-VAS and EQ-5D-5L. However, the analysis of the age-sex stratified data showed showed a correlation between lower age and better HRQOL. Results showed that younger females may possess significantly better HRQOL than females who were at least 10 years older than them. For example, the HRQOL scores for females between 18 and 44 were higher than those of females between 55 and 64 (Table 2).

On the other hand, among males there was a 30-year gap, with better HRQOL scores among those between the ages of 18 and 34 compared to those over the age of 65 (Table 2). The examination of the unstratified data suggested that males may have a higher HRQOL than females. Further analysis revealed that there was no significant disparity in HRQOL between males and females of the same age, but that males in younger age groups may have significantly higher HRQOL scores than females in older age groups (Table 2). The findings of this study suggest distinct differences as regards HRQOL between socio-economic groups. Specifically, the results of the stratified analysis indicate notable variations compared to those obtained through unstratified analysis.

5.3 Known-groups validity for the EQ-5D-5L in Vietnam

As is discussed above, it is crucial to assess the validity and reliability of the EQ-5D-5L for the Vietnamese population. However, this project faced limitations in terms of resources and data, thereby restricting its ability to perform any validation beyond known-groups validation. The results of this sub-study (2) indicate that the EQ-5D-5L has been validated for the hypertensive population in Vietnam through known-groups validation testing. Specifically, the mean EQ-VAS and EQ-5D-5L values of individuals in the diagnosed hypertensive group (71.48 and 0.94, respectively) were significantly lower than those in the other two groups (p value < 0.05). The EQ-VAS and EQ-5D-5L values were comparable for individuals in the non-hypertensive and undiagnosed hypertensive groups (76.65 and 0.97; 76.95 and 0.96, respectively). Details are presented in Paper 2.
<table>
<thead>
<tr>
<th></th>
<th>Unstratified analysis (Paper 2)</th>
<th>Additional age-sex stratified analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EQ-VAS</td>
<td>EQ-5D-5L value</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Significantly higher among younger people than older people</td>
<td>Significantly higher among females:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- aged 18–44 vs. 55–64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- aged 25–34 vs. 65+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significantly higher among males aged 18–34 vs. 65+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant difference</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Significantly higher among males than females</td>
<td>Significantly higher among males aged 18–44 than females aged 55–64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant difference</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td>Significantly higher among those who completed high school or have a higher-education degree</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant difference</td>
</tr>
<tr>
<td><strong>Occupation status</strong></td>
<td>Significantly higher among the employed than the unemployed</td>
<td>Significantly higher among males aged 35–44 or 65+ who are employed than males who were at the same age and unemployed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant difference</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td>Significantly higher among single people</td>
<td>Significantly higher among males aged 65+ and married than males aged 65+ who are divorced/separated/widowed</td>
</tr>
<tr>
<td><strong>Geographical region</strong></td>
<td>Significantly lower among people in the Central Coast area</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significantly lower among females aged 18–24 in the Mekong River area than those a same age in the Southeast area</td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td></td>
<td>Significantly higher among males aged 45–54 in urban areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significantly higher among females:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- aged 18–24 in rural areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- aged 45–54 in urban areas</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td>Significantly higher among females aged 45–54 from the Kinh community</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significantly higher among females aged 45–54 and from the Kinh community</td>
</tr>
<tr>
<td><strong>Religion</strong></td>
<td></td>
<td>Significantly higher among females aged 45–54 with religious beliefs</td>
</tr>
</tbody>
</table>

Table 2. Summary of additional analysis on the stratified age-sex EQ-5D-5L reference data
5.4 Feasibility of the EQ-5D-5L in HTA in Vietnam

Sub-study (3) aimed to examine the feasibility of using the EQ-5D-5L tool within an HTA to establish the cost-effectiveness of a modern medicine in Vietnam. Utility, which is an essential component of a CUA, is required to calculate QALYs. Typically, HTA submissions in Vietnam utilise utility inputs directly from published literature, which may originate from randomised controlled trials or systematic reviews. Nevertheless, such international utility evidence may not accurately reflect Vietnamese utility levels due to cultural and social welfare differences. The utility of the Vietnamese NSCLC patients investigated in this sub-study (3) (0.76 during the progression-free stage and 0.68 during the progressed disease stage) was considerably lower than the reported utility for NSCLC patients in the PACIFIC trial (0.86 during the progression-free stage and 0.83 during the progressed disease stage). As Paper 3 presents the results related to the cost-effectiveness of the intervention (durvalumab) in detail, this section provides a summary and additional analysis.

This analysis focused on the differences in the NMB between the Vietnamese utility data (EQ-5D-5L data on Vietnamese NSCLC patients) and data from published trials (Note: Data was extracted from a model with a 15-year lifetime. Data was presented as discounted NMB and in million VND. Bold results present the cost-effectiveness conclusion. Table 3). In summary, the calculation of the NMB involved estimating the incremental QALYs multiplied by the acceptability threshold, and then subtracting the incremental cost between durvalumab and placebo. A positive NMB value indicates that the intervention is cost-effective, provided the monetary value of the incremental QALYs does not exceed the incremental cost.

In general, the total QALYs gained would have been higher if PACIFIC utility inputs had been recruited, however this would not have significantly affected the overall tendency of the final conclusion regarding the cost-effectiveness of the drug (Note: Data was extracted from a model with a 15-year lifetime. Data was presented as discounted NMB and in million VND. Bold results present the cost-effectiveness conclusion. Table 3). The use of PACIFIC utility inputs would have resulted in a higher monetary value of the incremental QALYs, which impacted the NMB. The final conclusion regarding the cost-effectiveness of the intervention was similar for various scenarios; however, the NMB using the international utility inputs was much lower than the original analysis, for example in Scenario 2 (Note: Data was extracted from a model with a 15-year lifetime. Data was presented as discounted NMB and in million VND. Bold results present the cost-effectiveness conclusion.)
Table 3. This indicates the importance of taking into account the Vietnamese utility value when preparing HTA evidence in Vietnam. It also demonstrates the practicability of utilising the EQ-5D-5L in the HTA context in Vietnam.

<table>
<thead>
<tr>
<th>Total QALYs gained</th>
<th>Vietnamese utility</th>
<th>PACIFIC trial utility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Partial societal perspective</td>
<td>Healthcare system perspective</td>
</tr>
<tr>
<td>Full durvalumab acquisition cost and no copayment (base-case)</td>
<td>-662.90</td>
<td>-618.96</td>
</tr>
<tr>
<td>durvalumab acquisition cost cut by 50% (Scenario 1)</td>
<td>-217.39</td>
<td>-173.44</td>
</tr>
<tr>
<td>durvalumab acquisition cost cut by 70% (Scenario 2)</td>
<td>-39.18</td>
<td>4.77</td>
</tr>
</tbody>
</table>

Note: Data was extracted from a model with a 15-year lifetime. Data was presented as discounted NMB and in million VND. Bold results present the cost-effectiveness conclusion.

Table 3. Summary of additional analysis regarding discounted NMB in CUA.

5.5 Acceptability of HRQOL outcomes and the EQ-5D-5L in Vietnam

This study aimed to assess the acceptability of related stakeholders in using HRQOL outcomes and their willingness to use the EQ-5D-5L in decision-making processes in Vietnam. Two main themes emerged: (1) HRQOL measurements are crucial for healthcare decision-making, and (2) HRQOL measurements face challenges in Vietnam.

HRQOL measurements play a vital role in healthcare sciences, particularly in HTA. The widely accepted EQ-5D-5L is a valuable tool, offering brevity and sensitivity in assessing HRQOL variations. The outcomes support well-informed decision-making, aiding the assessment of healthcare technology benefits, calculation of QALYs, and drug inclusion on the SHI reimbursement list in Vietnam. Despite global acceptance, challenges persist in Vietnam, including ambiguity in the theoretical framework of HRQOL, limited recognition in clinical and public-health studies, and inadequate understanding of how to interpret results, particularly for the EQ-5D-5L. Standardisation issues lead to varied data-collection practices, potential publication bias, and insufficient result interpretation. Initiatives to improve HRQOL measurement education and integrate HRQOL measurements into policy require increased attention and investment. Vietnamese
stakeholders express a desire for an open-source HRQOL database to alleviate costs and improve standardisation.

The results collectively highlight both the importance of and challenges associated with HRQOL measurements in Vietnam, emphasising the need for education, standardisation, and policy integration in order to improve usage of HRQOL measurements.

6 Discussion

Vietnam is currently striving to achieve UHC, and various initiatives have been implemented to enhance the scope of health insurance, safeguard patients’ financial interests, and provide crucial healthcare services to the Vietnamese populace. Given the constraints of limited resources, the MOH has adopted a judicious approach to determining which healthcare technologies, including medical services and drugs, should be included in the SHI and at what reimbursement levels. This has been undertaken to ensure the long-term sustainability of essential healthcare services and financial protection for patients. Therefore, the application of HTA has become increasingly important for the Vietnamese MOH, as well as other stakeholders such as SHI managers and researchers. Since HTA have become more common in decision-making processes in relation to SHI in Vietnam, the demand for HTA inputs, such as instruments for estimating the costs, health gains, and effectiveness of technologies, has increased.

This doctoral project was initiated in response to the necessity of measuring health gains, specifically HRQOL, in order to facilitate HTA for the broader purpose of achieving UHC in Vietnam. The overarching objective of this project was to advance knowledge related to HRQOL in Vietnam, thereby providing support for scientific research and decision-making processes. The specific aims of this project were: (1) to develop a general public preference-based multi-attribute health-status classification system by conducting the EQ-5D-5L health states preferences from the perspective of Vietnamese, (2) to assess the validity of the EQ-5D-5L tool for the Vietnamese population, (3) to use the Vietnamese EQ-5D-5L tool in a CUA to evaluate its suitability for use in HTA, and (4) to explore the acceptability of HRQOL outcomes to stakeholders, and the use of the EQ-5D-5L in HTA.

The doctoral project was developed with a mixed-method approach, which comprised a health preference elicitation study utilising a standardised TTO and DCE method recommended by the EuroQol Group that employed empirical data (to achieved Objective 1). Furthermore, the research design incorporated a validity study utilising secondary data (to achieved Objective 2), a CUA that used both secondary data and normative costing data (to achieved Objective 3), and a qualitative study that used empirical data (to
achieved Objective 4). Moreover, the doctoral project proposed a reference dataset for HRQOL pertaining to the general population of Vietnam by utilising the EQ-5D-5L instrument.

6.1 The use of the EQ-5D-5L in Vietnam

6.1.1 EQ-5D-5L usage

This project resulted in a value set based on societal preferences for the EQ-5D-5L health states in Vietnam. The values were derived from a nationally representative sample, and can be used to calculate QALYs based on the EQ-5D-5L descriptive system. This value set is expected to be a valuable resource for HTA and healthcare science in Vietnam.

The dissemination of the EQ-5D-5L valuation study was completed in late 2018, and the final EQ-5D-5L value set was published in early 2020. Since the dissemination of the doctoral project that developed the Vietnamese preference-based EQ-5D-5L values on November 27, 2018 (Image 4), 19 studies utilising the EQ-5D-5L have been published on Pubmed (69-87), and 39 Vietnamese publications have been added to the Research Gate database as of 2023. The Vietnamese EQ-5D-5L value set has been recommended in the national guidelines for HTA since 2021. The successful completion of the EQ-5D-5L valuation study, which focused on providing health-state preferences among adults, enabled the author to participate in the development of an EQ-5D-3L value set for the younger population in 2022. A summary of the development of EQ-5D instruments is presented in Figure 4.

![Figure 4. A summary of the development of EQ-5D instruments in Vietnam.](image)

The importance of reference data on the HRQOL of the general public cannot be overstated. Such data can serve as a foundation for future scientific comparisons. The reference data can serve as a basis for HRQOL comparisons across sub-populations or interventions. To this end, an EQ-5D-5L reference dataset was developed and published, which presents data on age and gender for the descriptive part of the EQ-5D-5L, EQ-VAS, and EQ-5D-5L values. While this doctoral project attempted to capture the associations of
HRQOL with individual socioeconomic characteristics, further research is necessary for reference data relating to e.g. comorbidity.

6.1.2 Validity of the EQ-5D-5L in Vietnam

The psychometric properties, including validity, reliability, sensitivity, and responsiveness, of the EQ-5D-5L have been tested in numerous countries and for various disease areas (132). In 2012, Tran et al. conducted a study assessing the convergent validity, discriminative validity, and internal consistency (reliability) of the EQ-5D-5L among HIV/AIDS patients. The findings indicated that the EQ-5D-5L has good validity and reliability within the studied population (133). Subsequently, there has been no further examination of additional psychometric properties in Vietnam.

In this doctoral project, the focus was on developing a generic HRQOL measurement tool that does not target any specific disease or population; thus, ensuring the validity and reliability of the instrument was crucial. However, due to resource limitations we were only able to test the known-groups validity of the EQ-5D-5L in this project. Assessing validity is a continuous and multifaceted process that involves accumulating evidence to demonstrate that an instrument is appropriate and behaves as anticipated. Therefore, the known-groups validity testing undertaken in this project adds evidence that supplements the existing literature.

In light of Vietnam’s efforts to improve non-communicable disease prevention and elderly care with the end goal of UHC, this study chose the hypertensive population to evaluate the validity of the EQ-5D-5L tool. The validity of the instrument among this group could establish a better scientific framework for future studies on healthcare for the hypertensive group, contributing to the healthcare system’s progress towards UHC. The author conducted studies beyond the scope of this doctoral project to investigate the sensitivity of the EQ-5D-5L in diverse contexts, such as estimating HRQOL variations among various quarantined groups during the COVID-19 pandemic and groups with varying degrees of disability (82, 134). Overall, the EQ-5D-5L demonstrated satisfactory performance among these populations.

6.1.3 An example on the use of EQ-5D-5L in HTA in Vietnam

CUAs rely on the inclusion of HRQOL outcomes (as utility). In Vietnam, HTA submissions typically rely on utility inputs obtained from published literature, which are
often sourced from randomised controlled trials or systematic reviews. However, it is important to note that such utility evidence, which is based on a global perspective, may not accurately capture the utility levels prevalent in Vietnamese society, due to cultural and social welfare differences.

The findings of Sub-study (3) revealed that when the utility inputs from international reference is used in comparison to the inputs from Vietnamese, the final conclusion on a drug’s cost-effectiveness can undergo significant changes. This suggests that, although researchers may encounter challenges in collecting Vietnamese inputs for their economic evaluations, it is possible to adjust these evaluations by incorporating cost and utility data (derived from the EQ-5D-5L) in Vietnam. However, it is imperative to acknowledge that operationalising the collection of local inputs corresponding to the different stages of the model in economic evaluations could pose practical challenges. Therefore, establishing standardised protocols for integrating the EQ-5D-5L into the healthcare system (as proposed in Sub-study (4)) would be advantageous for research in such scenarios.

6.1.4 Low recognition of the EQ-5D-5L in Vietnam

The use of the EQ-5D-5L extends beyond the scope of HTA (135). Among publications using HRQOL outcome in Vietnam, the HRQOL measurements, including EQ-5D-5L, are primarily applied in approximately 80% of publications which are designed for non-economic evaluation purposes (28-91). Most studies employ HRQOL outcomes as a final measure to assess the health status of particular population (e.g. people with diseases, elderly, etc.) reflecting the emphasis on public-health research. Although the EQ-5D-5L has recently received considerable attention, we found that only a few names (or research groups) consistently worked on the topic (28-91). This suggests that the recognition and understanding of the usage of HRQOL outcomes and the EQ-5D-5L for public-health purposes among Vietnamese researchers is generally low, consistent with the findings of Sub-study (4).

6.2 Considerations relating to the EQ-5D-5L

6.2.1 Who should elicit health states values?

As is discussed in Section 3.1, the question of who should value health states remains a pivotal concern. There exist two core methods of producing health-state valuations: deriving values from the experiences of individuals (patient values) with the health state, and obtaining values based on a description of the health state (social/hypothetical values). Discrepancies exist between patients and the general public in how they interpret
health-state descriptions, however: patients, given their direct experience of illnesses, find health-state descriptions to be more accurate than the public (136). However, the reference point effects may lead patients to emphasise the effects and distortions of health states more than the general public (137).

The role of experience in health-state valuation appears to be significant. However, a clear distinction regarding the impact of experience between patients and social values is not well-defined. The process of health-state valuation often entails presenting a series of health states for respondents to value. Consequently, patients typically value their own current health state and other health states described to them, which they might not have experienced. On the other hand, general-public respondents may, by chance, be currently undergoing or have experienced the health states being evaluated (137-139).

Neither patient values nor social values are without flaws (138). The question of who should value health states is answered differently according to the preferences of countries, policy-makers, and researchers. This question parallels the challenges associated with deciding which perspectives to consider in economic evaluations. It is important to note that there is no universally right or wrong answer, as the choice of perspective is inherently contextual (140). The Vietnamese guidelines for HTA emphasise a healthcare-system perspective, with a focus on the SHI reimbursement aspect. The guidelines also suggest the need for a broader perspective, including societal considerations, in line with practices in other countries (92). Therefore, the social values developed in Sub-study (1) would be suitable for current HTA purposes in Vietnam.

6.2.2 Ceiling effects

Ceiling effects suggest a limitation as regards an instrument's range, and are evident when a significant proportion (suggested cutoff of 15% by Terwee, Bot (141)) of study participants consistently select the highest response on the scale. The previous version of the EQ-5D descriptive system – the EQ-5D-3L – faced criticism due to a noticeable ceiling effect, especially among studies capturing the HRQOL of the general population (142). The updated EQ-5D-5L has been shown to be effective in mitigating this ceiling effect compared to the previous version (142, 143). In the context of this doctoral project, the ceiling effect persists in the HRQOL reference data among the Vietnamese general population (Sub-study (2)). Notably, 54.42% of respondents reported full health (EQ-5D-5L value = 1), while only 8.92% indicated being at the best health they could imagine (EQ-VAS = 100). The prevalence of the ceiling effect for the EQ-5D-5L is consistently observed, and remains a noteworthy issue (144).
The ceiling effect not only impacts the summary of the health profile but has significant implications for HTA. Given the primary application of the EQ-5D-5L in economic evaluations is to calculate utility for QALYs, the ceiling effect may result in an overestimation of QALYs gained, potentially influencing final decisions in such evaluations. However, insights from Germany suggest that the ceiling effect of the EQ-5D-5L may diminish with an increase in the morbidity of the studied population (at least four or more diseases) (144). This finding should be taken into consideration when contemplating the use of the EQ-5D-5L in HTA in Vietnam. It is recommended that factors associated with the ceiling effect of the tool be explored in the Vietnamese context. Additionally, careful consideration is advised when making economic evaluations for populations with lower morbidity.

6.2.3 Recall period issues

The EQ-5D-5L instrument employs "your health today" as a recall period to capture the HRQOL of respondents. This approach may not precisely reflect the health status of patients with diseases that show frequent fluctuations, such as dementia and multiple sclerosis (145, 146). One study underscored this difficulty of the EQ-5D-5L in responding to fluctuations in a patient's health status (147).

Vietnamese researchers and HTA bodies should take note of this limitation. A recommendation is to consider a combined approach, integrating other HRQOL measurements alongside the EQ-5D-5L for cases involving conditions with significant health-status variability. This would provide a more comprehensive and accurate depiction of HRQOL in situations where the EQ-5D-5L alone may prove insufficient.

6.2.4 Limited responsiveness in disease-specific contexts

The suitability of a generic preference-based measure such as the EQ-5D-5L for evaluating health outcomes in disease-specific populations was a point of discussion in Sub-study (4), and is more generally in the international research community. In 2016, a systematic review of the responsiveness of the EQ-5D was conducted, encompassing both the three- and five-level versions across 56 conditions. The findings revealed that the tool showed responsiveness in only 25 conditions and had no responsiveness observed for alcohol dependency, schizophrenia, limb reconstruction, and hearing impairment (148). In 2018, a study conducted a study highlighting the potential shortcomings of the EQ-5D-5L in capturing essential aspects of a patient's HRQOL, such as fatigue and medication side-effects (147). Furthermore, a systematic review by You-shan et al. in 2021 focused on
the psychometric properties of the EQ-5D-5L, demonstrating moderate responsiveness when applied to specific subgroups with observed improvements in health (132). Efforts have been made to improve the responsiveness of EQ-5D-5L to disease-specific conditions (149, 150).

Consequently, while we work to bolster the validity of the EQ-5D-5L in Vietnam, HTA stakeholders are advised to explore other HRQOL disease-specific measurement tools in the context of Vietnam. However, it is important to note that generic preference-based HRQOL measures hold significance in HTA, as they can support policy-makers in comparing outcomes across diseases and interventions. Hence, a suggestion is to combine a disease-specific HRQOL measurement with a generic one such as the EQ-5D-5L, aligning with existing international evidence (148).

6.3 Recommendations for enhancing EQ-5D-5L usage

Given the low recognition of HRQOL measurements in Vietnam, the first recommendation is to incorporate HRQOL measurement into the official training programmes for medical and public-health students that encompass HRQOL measurements, covering both measurement methods and outcome classifications. Furthermore, disseminating knowledge related to HRQOL through national conferences and publications can significantly contribute to increasing the understanding and practice of such measure in Vietnam. The results of Sub-study (4) reveal that Vietnamese researchers encounter challenges in interpreting EQ-5D-5L results, indicating a knowledge gap. To address this, the development of a comprehensive guideline on the application of the EQ-5D-5L in Vietnamese is recommended, encompassing aspects from design to reporting. This would be a valuable resource for bridging existing knowledge gaps and ensuring effective application of the EQ-5D-5L in healthcare research and decision-making processes.

In Sub-study (4), concerns were raised about the responsiveness of the EQ-5D-5L in disease-specific contexts. The validity of the EQ-5D-5L was also scrutinised, particularly regarding differences between EQ-VAS and EQ-5D-5L values. Furthermore, the reliability of the EQ-5D-5L was investigated in relation to substantial variations in values for the same subjects at different times. It is crucial to acknowledge that the EQ-VAS and EQ-5D-5L represent distinct methods, and potentially yield different responses. While evidence supporting the psychometric properties of the EQ-5D-5L is available for several countries (132), such evidence is currently lacking for Vietnam. Therefore, additional efforts are
needed in order to conduct further research on the validity, reliability, sensitivity, and responsiveness of the EQ-5D-5L in relation to the Vietnamese context.

The subject of standardisation as regards the implementation of HRQOL measurements has been a recurring topic of discussion among Vietnamese HTA bodies (Sub-study (4)). A potential means of addressing this involves creating a comprehensive national database on HRQOL. To this end, it is recommended to regularly update HRQOL reference data for the Vietnamese general population by integrating the EQ-5D-5L into the national census, which is conducted on a five-year basis. Moreover, it would be advantageous for all stakeholders to establish standardised protocols for the integration of the EQ-5D-5L as a patient-reported outcome into the national hospital information system. Valuable lessons can be drawn from the successful implementation of the EQ-5D as a routine patient-reported outcome measure in healthcare in countries such as Canada and Sweden (151, 152).

6.4 Project limitations

The limitations of each of the four sub-studies have been discussed in the relevant papers. In this section, the limitations of the doctoral study as a whole are discussed.

Firstly, modifications were made to the EuroQol Group's standardised protocol for valuing EQ-5D-5L health states during Sub-study (1). Specifically, we employed a third party to ask the questions during the TTO tasks in order to reduce the sensitivity of the issue of death for the respondents. Additionally, the use of cards for differentiating the health states for the DCE tasks was a departure from the standardised protocol. These modifications were necessary in order to culturally adapt the study. However, with regard to standardisation in valuation studies across countries, these changes may have implications that require careful consideration before comparisons between countries are made.

Secondly, although the sample of 1200 individuals was considered to be of sufficient size to facilitate the elicitation of preferences for the EQ-5D-5L health states, this would perhaps be questionable for developing EQ-5D-5L reference data. To address this, several sampling techniques were employed to ensure that the sample characteristics were similar to those of the national population.

Thirdly, while the project provides evidence on known-groups validation for the EQ-5D-5L, several aspects of the psychometric properties were not assessed, including other
types of validity, reliability, sensitivity, and responsiveness. Therefore, more efforts are needed to establish the instrument's credibility.

Fourthly, as the selection of perspectives in economic evaluations is always context-dependent, results from both healthcare and societal perspectives are presented in Sub-study (2). However, due to the scarcity of data on costs, utilities, and epidemiology specific to the studied population, the CUA was conducted from a partial societal perspective, which did not fully capture the opportunity costs (such as productivity loss/gain from patients if their diseases do not progress) or differences in non-medical costs between the intervention and comparator. This underscores the need for further research when more data become available for these inputs. It also highlights the need for public data sources, encompassing cost, health outcomes, and epidemiological data for HTA in Vietnam.

Finally, as was discussed in relation to Sub-study (4), the use of the EQ-5D-5L as a patient-reported outcome measure in the healthcare system would have several benefits for health science in Vietnam. However, this would require action from hospitals, clinicians, and other management units, such as information systems and data storage, which were not included in our qualitative study. Therefore, a crucial piece of the puzzle in assessing the acceptability of using HRQOL outcomes and the EQ-5D-5L in healthcare decision-making has not been investigated.
7 Conclusion and recommendations

7.1 Conclusion

The MOH in Vietnam has implemented an evidence-based strategy to determine which healthcare technologies, medical services, and drugs should be included in the national SHI programme, and at what reimbursement rates. This approach aims to ensure the long-term sustainability of essential healthcare services and financial protection for patients. Consequently, the integration of HTA in decision-making processes for SHI has become increasingly important. HTA require that cost and clinical outcome estimations be input, which together provide an estimation of cost-effectiveness. In light of this, the focus of this doctoral project was developing a health-related quality of life measurement to be used in HTA in Vietnam.

Specifically, a generic preference-based HRQOL measurement has been developed for the Vietnamese population using the EQ-5D-5L instrument. The EQ-5D-5L can be utilised not only as a measure of effectiveness for HTA, but across other health-science disciplines. This instrument comprises a descriptive system with five questions, a visual analogue scale (EQ-VAS), and a value set that facilitates the assignment of health-state values for the EQ-5D-5L. The value set was developed based on the preferences of the general public in Vietnam. Furthermore, the doctoral project developed EQ-5D-5L reference data that is proposed as a foundation for comparing HRQOL across different diseases and interventions. The credibility of the EQ-5D-5L has been demonstrated for the Vietnamese population through a known-groups validation conducted on individuals with hypertension. This validity evidence has facilitated the establishing of a favourable environment for the implementation of this tool in Vietnam. Additionally, the EQ-5D-5L has exhibited satisfactory performance in producing data that is appropriate for utilisation in HTA in Vietnam. Despite some concerns regarding its precision as regards disease-specific populations, the EQ-5D-5L is generally well accepted in Vietnam.

In conclusion, this doctoral project has contributed to the UHC in Vietnam by developing HRQOL measurement in the form of the EQ-5D-5L. The credibility and satisfactory performance of the instrument has been demonstrated through the production of data suitable for use in HTA in Vietnam. The outcomes of the doctoral project are a favourable HTA environment and enhancements for evidence-based decision-making, which will ultimately contribute to achieving UHC in Vietnam.
7.2 Recommendations

Based on the findings of the study, the following recommendations are made:

- HRQOL reference data for the Vietnamese general population should be regularly updated by integrating the EQ-5D-5L into the national census, which is conducted on a five-year basis.

- Further assessment of the psychometric properties of the EQ-5D-5L across the Vietnamese populations is needed.

- Official training should be provided to medical and public-health students to improve their knowledge of HRQOL outcomes and the use of the EQ-5D-5L. Dissemination of HRQOL-related knowledge through local channels is also necessary.

- A Vietnamese guideline on the application of the EQ-5D-5L should be developed to bridge the knowledge gap in interpreting EQ-5D-5L results.

- All stakeholders should establish standardised protocols for the integration of the EQ-5D-5L as a patient-reported outcome in the national hospital information system.
Acknowledgements

I wish to convey my profound gratitude to the Erling Persson Foundation, the Department of Epidemiology and Global Health at Umeå University (EpiGH), and the Center for Population Health Sciences (CPHS) at Hanoi University of Public Health, for their steadfast financial, academic, and administrative support. This invaluable assistance has been instrumental in making this PhD project a reality. Additionally, I extend my sincere appreciation to the EuroQol Research Foundation for their generous financial support in facilitating the data collection for this PhD project (EuroQol project 20170220). Without the support of them, this project would not have been possible.

I am deeply indebted to my principal supervisor, Prof. Klas-Göran Sahlen, and my home-country supervisor, Prof. Hoàng Văn Minh; both of you are my super mentors. Thank you for affording me the invaluable opportunity to undertake this PhD training. To my co-supervisors, Prof. Lars Lindholm, Assoc. Prof. Sun Sun, and Assoc. Prof. Kim Bảo Giang, I express immense gratitude for your expert guidance, unwavering support, and enduring patience from the very inception of my PhD journey. The knowledge and skills I have gained under your mentorship are truly priceless.

I wish to express my sincere gratitude to Prof. Anna-Karin Hurtig for her invaluable guidance as my examiner. I am deeply appreciative of the insightful comments and suggestions provided by Prof. Curt Löfgren, Prof. Bo Burström, Assoc. Prof. Nguyễn Xuân Thanh, Prof. Magnus Zingmark, and Prof. Britt-Marie Lindgren during my PhD training. Their contributions have been instrumental in shaping and refining my work.

I wish to extend my heartfelt thanks to Prof. Nan Luo and Dr. Juan Manuel Ramos-Goñi for their invaluable academic support in the first sub-study of this PhD project. My gratitude extends deeply to my research assistant, Thắng, and my dedicated interviewers, Phượng, Trang Trần, Như, Ngân, Hòa, Minh Trang, Linh, Hương, and Quỳnh, who stood by me during the extensive 60-day data collection journey across Vietnam. Their commitment and contributions were indispensable to the success of this research.

I express my gratitude to all my colleagues at EpiGH for their warm welcome and steadfast support. Special acknowledgment goes to Ulrika Harju and Ulrika Järnholm for their assistance with various administrative matters. Additionally, I want to extend my thanks to my CPHS colleagues — Ngọc, Văn, Ngân, Thảo, Tuấn Anh, Phượng, and Trang — for their time and support during the challenging days of my PhD training.
I extend my heartfelt appreciation to my fellow PhD sisters and brothers, Carla, Nu Anh, Puthy, Chama, Nia, Alieu, Ester, Edwinah, Catrine, Adam, Huzeifa, Kapuya, Chavula, Rodrigo, Kaspar, Hanah and other PhD colleagues. Together, we've navigated the diverse challenges and triumphs of this academic journey. Without your invaluable companionship, my PhD life would have been considerably dull. I am genuinely grateful for every shared moment.

Shoutout to my beloved besties – em Phương CPHS, Hà Xanh, Na, Pio, bông Cúc, bông Lan, bông Phương, em Change, tô hữu Lan và các chị em HAT bát ồn! Big thanks for always cheering me on and encouraging me to keep my head held high.

Finally, I want to send my deep gratitude to my wonderful parents, mẹ Vườn and bố Tài, for their consistent encouragement and unwavering belief in my capacity to undertake and successfully complete this PhD training. To my sibling and his family, anh Tuấn, chị Trang, cháu Nhím, cháu Bin, thank you for consistently lifting my spirits.
References

23. Circular 40/2014/TB-TBY on promulgation of list of modern medicines, biologicals, radiopharmaceuticals and tracers covered by Health Insurance, reimbursement ratio and payment conditions. [Expired], (2014).
24. Circular 20/2022/TB-TBY on promulgation of list of modern medicines, biologicals, radiopharmaceuticals and tracers covered by Health Insurance, reimbursement ratio and payment conditions. [Active], (2022).


Vu MQ VT, Nguyen MV, Khuc HH, Hoang VM, Banks M., editor. Difference in Health-Related Quality of Life Among People With and Without Disabilities. ISPOR Europe 2022; 2022 December 2022; Vienna, Austria: Value in Health.

EQ-5D has uses outside of clinical trials and HTA. Pharmacoeconomics & Outcomes News. 2017 2017/04/01/775(1):4-.


## Supplementary results

<table>
<thead>
<tr>
<th>Highest education level attained**</th>
<th>Female</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Male</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary and lower</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>91.75 (3.5)</td>
<td>84.682 (15.22)</td>
<td>80.303 (17.045)</td>
<td>80.682 (14.499)</td>
<td>68.174 (15.678)</td>
<td>72.292 (15.035)</td>
<td>86.75 (13.21)</td>
<td>83.077 (14.511)</td>
<td>79.433 (13.367)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>83.969 (10.971)</td>
<td>83.389 (9.892)</td>
<td>82.722 (12.072)</td>
<td>82.111 (10.729)</td>
<td>73 (18.288)</td>
<td>78 (14.405)</td>
<td>83.96 (9.723)</td>
<td>85.104 (10.541)</td>
<td>88.269 (10.835)</td>
</tr>
<tr>
<td><strong>High school</strong></td>
<td>88.929 (7.888)</td>
<td>79.5 (10.501)</td>
<td>75.417 (11.598)</td>
<td>78.188 (10.355)</td>
<td>67.5 (29.58)</td>
<td>75.625 (15.91)</td>
<td>83.636 (9.244)</td>
<td>81.778 (11.814)</td>
<td>84.692 (12.632)</td>
</tr>
<tr>
<td><strong>Undergraduate and higher</strong></td>
<td>82.895 (6.732)</td>
<td>82.957 (8.062)</td>
<td>82.84 (12.747)</td>
<td>80.44 (12.597)</td>
<td>80.769 (11.152)</td>
<td>77.083 (16.02)</td>
<td>82.565 (10.387)</td>
<td>83.525 (11.112)</td>
<td>87.84 (11.459)</td>
</tr>
<tr>
<td><strong>Geographical regions</strong>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Northern mountains</strong></td>
<td>88.929 (7.888)</td>
<td>79.5 (10.501)</td>
<td>75.417 (11.598)</td>
<td>78.188 (10.355)</td>
<td>67.5 (29.58)</td>
<td>75.625 (15.91)</td>
<td>83.636 (9.244)</td>
<td>81.778 (11.814)</td>
<td>84.692 (12.632)</td>
</tr>
<tr>
<td><strong>Red River Delta</strong></td>
<td>82.895 (6.732)</td>
<td>82.957 (8.062)</td>
<td>82.84 (12.747)</td>
<td>80.44 (12.597)</td>
<td>80.769 (11.152)</td>
<td>77.083 (16.02)</td>
<td>82.565 (10.387)</td>
<td>83.525 (11.112)</td>
<td>87.84 (11.459)</td>
</tr>
<tr>
<td><strong>Highlands</strong></td>
<td>77.857 (15.774)</td>
<td>82.5 (10.516)</td>
<td>89 (18.944)</td>
<td>77.5 (13.222)</td>
<td>73.333 (14.124)</td>
<td>60 (14.142)</td>
<td>80.714 (15.924)</td>
<td>83.571 (9.288)</td>
<td>75 (16.33)</td>
</tr>
<tr>
<td><strong>Central Coast</strong></td>
<td>85 (10)</td>
<td>83.31 (12.879)</td>
<td>74.038 (17.437)</td>
<td>72.3 (15.39)</td>
<td>66.471 (14.005)</td>
<td>66.444 (21.995)</td>
<td>81.913 (12.435)</td>
<td>84.472 (10.495)</td>
<td>79.484 (16.81)</td>
</tr>
<tr>
<td><strong>South-East</strong></td>
<td>81 (10.455)</td>
<td>86.647 (7.937)</td>
<td>83.769 (11.212)</td>
<td>86.765 (13.456)</td>
<td>70 (12.91)</td>
<td>84.252 (8.425)</td>
<td>85.914 (9.856)</td>
<td>83.105 (14.271)</td>
<td>82.105 (12.523)</td>
</tr>
<tr>
<td><strong>Mekong River Delta</strong></td>
<td>85.5 (9.263)</td>
<td>89.171 (13.082)</td>
<td>83.481 (12.948)</td>
<td>77.095 (14.805)</td>
<td>71.8 (26.774)</td>
<td>80 (5.774)</td>
<td>87.81 (7.434)</td>
<td>89.667 (7.303)</td>
<td>82.609 (12.235)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.16</td>
<td><strong>0.00</strong></td>
<td>0.07</td>
<td><strong>0.03</strong></td>
<td>0.26</td>
<td>0.43</td>
<td>0.44</td>
<td>0.16</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
<td>------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>83.557</td>
<td>84.487</td>
<td>80.184</td>
<td>77</td>
<td>72.513</td>
<td>72.742</td>
<td>84.304</td>
<td>84.463</td>
<td>82.964</td>
</tr>
<tr>
<td>Urban</td>
<td>83.57</td>
<td>83.655</td>
<td>81.867</td>
<td>82.171</td>
<td>70.741</td>
<td>75.867</td>
<td>84.24</td>
<td>84.603</td>
<td>82.094</td>
</tr>
<tr>
<td>p-value</td>
<td>0.96</td>
<td>0.49</td>
<td>0.52</td>
<td>0.10</td>
<td>0.95</td>
<td>0.68</td>
<td>0.53</td>
<td>0.56</td>
<td>0.59</td>
</tr>
<tr>
<td>Ethnicity*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinh (as majority)</td>
<td>83.484</td>
<td>85.043</td>
<td>80.853</td>
<td>79.253</td>
<td>71.5</td>
<td>74.2</td>
<td>84.18</td>
<td>84.513</td>
<td>82.8</td>
</tr>
<tr>
<td>Others</td>
<td>84</td>
<td>73.846</td>
<td>80.417</td>
<td>75</td>
<td>76.25</td>
<td>70.833</td>
<td>85.625</td>
<td>84.5</td>
<td>81.333</td>
</tr>
<tr>
<td>p-value</td>
<td>0.91</td>
<td>0.00</td>
<td>0.70</td>
<td>0.21</td>
<td>0.59</td>
<td>0.55</td>
<td>0.55</td>
<td>0.97</td>
<td>0.85</td>
</tr>
<tr>
<td>Religion*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No religion</td>
<td>83.978</td>
<td>84.355</td>
<td>80.438</td>
<td>78.549</td>
<td>72.085</td>
<td>73.933</td>
<td>84.16</td>
<td>84.248</td>
<td>83.078</td>
</tr>
<tr>
<td>Religion</td>
<td>79.5</td>
<td>83.261</td>
<td>81.844</td>
<td>79.219</td>
<td>71.053</td>
<td>73.438</td>
<td>84.895</td>
<td>86</td>
<td>81.5</td>
</tr>
<tr>
<td>p-value</td>
<td>0.13</td>
<td>0.70</td>
<td>0.95</td>
<td>0.53</td>
<td>0.69</td>
<td>0.80</td>
<td>0.81</td>
<td>0.41</td>
<td>0.46</td>
</tr>
<tr>
<td>Marital status**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>83.047</td>
<td>83.75</td>
<td>66.667</td>
<td>90</td>
<td>65</td>
<td>84.065</td>
<td>84.417</td>
<td>85.5</td>
<td>79.167</td>
</tr>
<tr>
<td>Married</td>
<td>84.222</td>
<td>84.086</td>
<td>81.098</td>
<td>78.045</td>
<td>70.717</td>
<td>74.267</td>
<td>86.167</td>
<td>84.64</td>
<td>82.5</td>
</tr>
<tr>
<td>Separated/widowed/divorced</td>
<td>90 ()</td>
<td>89</td>
<td>82.5</td>
<td>82.167</td>
<td>75.278</td>
<td>72.813</td>
<td>83.333</td>
<td>87.5 (5)</td>
<td>70 (10)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.75</td>
<td>0.63</td>
<td>0.19</td>
<td>0.41</td>
<td>0.52</td>
<td>0.69</td>
<td>0.78</td>
<td>0.92</td>
<td>0.80</td>
</tr>
<tr>
<td>Occupation**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

58
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>84.762</td>
<td>84.014</td>
<td>80.731</td>
<td>79.099</td>
<td>68.875</td>
<td>70.714</td>
<td>83.984</td>
<td>84.534</td>
<td>83.504</td>
<td>78.889</td>
<td>77.383</td>
<td>81.667</td>
</tr>
<tr>
<td>Student/retired/housewife</td>
<td>82.661</td>
<td>85.029</td>
<td>81.462</td>
<td>77.5</td>
<td>73.452</td>
<td>74.794</td>
<td>85.037</td>
<td>83.333</td>
<td>40</td>
<td>75</td>
<td>77.75</td>
<td>79.25</td>
</tr>
<tr>
<td>Unemployed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71</td>
<td>76.667</td>
<td>86</td>
<td>()</td>
<td>70</td>
<td>()</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(18.841)</td>
<td>(5.774)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(8.165)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.22</td>
<td>0.59</td>
<td>0.99</td>
<td>0.73</td>
<td>0.20</td>
<td>0.75</td>
<td>0.27</td>
<td>0.65</td>
<td><strong>0.05</strong></td>
<td>0.66</td>
<td>0.99</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td><strong>Health insurance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>85</td>
<td>84.765</td>
<td>79.857</td>
<td>77.571</td>
<td>75.625</td>
<td>60</td>
<td>80.152</td>
<td>82.151</td>
<td>78.45</td>
<td>72.75</td>
<td>79.429</td>
<td>72.774</td>
</tr>
<tr>
<td>Yes</td>
<td>83.173</td>
<td>83.984</td>
<td>81.198</td>
<td>79.061</td>
<td>71.259</td>
<td>74.386</td>
<td>85.86</td>
<td>85.619</td>
<td>84.974</td>
<td>80.547</td>
<td>77.438</td>
<td>72.774</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.25</td>
<td>0.51</td>
<td>0.39</td>
<td>0.77</td>
<td>0.68</td>
<td>0.14</td>
<td><strong>0.02</strong></td>
<td>0.06</td>
<td><strong>0.04</strong></td>
<td>0.05</td>
<td>0.53</td>
<td></td>
</tr>
</tbody>
</table>

Notes: * Difference were tested using the Mann Whitney test. ** Difference were tested using the Kruskal Wallis test.

**Supplementary Table 1. Age-sex stratified for EQ-VAS among the Vietnamese general population.**
<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest education level attained</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary and lower</td>
<td>0.984 (0.032)</td>
<td>0.966 (0.058)</td>
</tr>
<tr>
<td>Secondary</td>
<td>0.969 (0.056)</td>
<td>0.955 (0.073)</td>
</tr>
<tr>
<td>High school</td>
<td>0.942 (0.067)</td>
<td>0.971 (0.05)</td>
</tr>
<tr>
<td>Undergraduate and higher</td>
<td>0.968 (0.039)</td>
<td>0.959 (0.054)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.26</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Geographical regions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern mountains</td>
<td>0.968 (0.056)</td>
<td>0.945 (0.058)</td>
</tr>
<tr>
<td>Red River Delta</td>
<td>0.956 (0.067)</td>
<td>0.967 (0.048)</td>
</tr>
<tr>
<td>Highlands</td>
<td>0.963 (0.048)</td>
<td>0.947 (0.064)</td>
</tr>
<tr>
<td>Central Coast</td>
<td>0.966 (0.037)</td>
<td>0.958 (0.076)</td>
</tr>
<tr>
<td>South-East</td>
<td>0.921 (0.057)</td>
<td>0.973 (0.052)</td>
</tr>
<tr>
<td>Mekong River Delta</td>
<td>0.985 (0.032)</td>
<td>0.963 (0.075)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td><strong>0.04</strong></td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>0.969 (0.045)</td>
<td>0.965 (0.058)</td>
</tr>
<tr>
<td></td>
<td>Female 18–24</td>
<td>Female 25–34</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Urban</td>
<td>0.93 (0.072)</td>
<td>0.953 (0.061)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Ethnicity *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinh (as majority)</td>
<td>0.953 (0.06)</td>
<td>0.962 (0.058)</td>
</tr>
<tr>
<td>Others</td>
<td>0.956 (0.062)</td>
<td>0.944 (0.071)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.85</td>
<td>0.36</td>
</tr>
<tr>
<td>Religion*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No religion</td>
<td>0.956 (0.058)</td>
<td>0.96 (0.06)</td>
</tr>
<tr>
<td>Religion</td>
<td>0.935 (0.077)</td>
<td>0.965 (0.051)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.45</td>
<td>0.92</td>
</tr>
<tr>
<td>Marital status**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0.947 (0.062)</td>
<td>0.933 (0.109)</td>
</tr>
<tr>
<td>Married</td>
<td>0.964 (0.056)</td>
<td>0.961 (0.056)</td>
</tr>
<tr>
<td>Separated/widowed/divorced</td>
<td>1 ( )</td>
<td>0.987 (0.029)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.27</td>
<td>0.58</td>
</tr>
<tr>
<td>Occupation**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>0.967 (0.045)</td>
<td>0.962 (0.059)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>--------</td>
<td>------------------</td>
</tr>
<tr>
<td>Student/retired/housewife</td>
<td>0.944 (0.067)</td>
<td>0.957 (0.059)</td>
</tr>
<tr>
<td>unemployed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.15</td>
<td>0.72</td>
</tr>
<tr>
<td>Health insurance*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.969 (0.047)</td>
<td>0.964 (0.066)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.95 (0.063)</td>
<td>0.959 (0.057)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.23</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Notes: * Difference were tested using the Mann Whitney test. ** Difference were tested using the Kruskal Wallis test.

Supplementary table 2. Age-sex stratified for EQ-5D-5L values among the Vietnamese general population.