

Variations in Surgeon Treatment Preferences and  
The Impact on the Cost-Utility of Surgery for Soft Tissue Sarcoma

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**Abstract**

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*Background*

The primary treatment for soft tissue sarcoma (STS) is surgical excision of the tumor. There are variations in the surgical strategies used to excise the tumor. It is unknown which surgical strategy is more cost-effective in treating STS and whether the perspectives of surgeons compared to patients and the general public about the health states following these surgical strategies leads to inefficient allocation of surgical resources to treat STS.

## *Objectives*

To quantify surgeons' health state utility preferences for sarcoma health states and if their preferences predict their choices for surgical treatment strategies of STS. To calculate the economic consequences of variations in surgeon treatment strategies and surgeon health state preferences on patient health outcomes, societal costs, and cost-effectiveness.

## *Methods*

A review of the STS health state literature was conducted and health states for STS were developed. An online questionnaire and standard gamble (SG) exercise was administered to orthopaedic and surgical oncologists to elicit health state utility values from a surgeon's perspective. A cost-utility model was used to compare the projected cost-utility of alternative surgical strategies based on the surgeon preferences about health states as compared to those of either patients or the general population.

## *Results*

This study found that there is significant variation among surgeons in their valuations of LE-STS-related health states. Acceptable function following primary excision of STS has significant impact on perceived quality of life with the median utility decrement ranging from -0.20 to -0.26 depending on margin status, but local recurrence has a somewhat higher median utility decrement of close to -0.30. For the patient and societal perspectives, over both a 10-year and lifetime time horizon, the surgical strategy of AM with an adverse functional outcome (AM-F) dominates—i.e., lower cost and better outcomes—the surgical strategy of IM with an acceptable functional outcome (IM+F). For surgeons, the incremental cost-effectiveness ratio

(ICER) of IM+F compared with AM-F was \$8,284 per QALY gained over a 10-year time horizon, but the AM-F strategy was dominant in the lifetime horizon.

### *Conclusions*

The results generally supported the hypothesis that surgeons' utility for LE-STs-related health states influence their choice of surgical treatment strategy for STS. If the average surgical strategy followed the preferences of surgeons, it would produce lower health gains (i.e., QALYs) for a typical patient as compared to a strategy reflecting community or patient's valuation of health states. From the standpoint of cost-utility from a health system perspective, therefore, there will be a welfare loss if the default strategy is based on surgeons' preferences.

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## **DEDICATION**

To Alan, Nora, and Luke Cizik I love you most.

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## Chapter I. Introduction

### I.A Rationale

Soft tissue sarcomas (STS) are rare cancers, with 11,410 new cases diagnosed and an estimated 4,390 deaths reported in the United States in 2013 with the majority of these tumors found in the extremities.<sup>(1, 2)</sup> First line treatment for lower extremity (LE) STS is surgical resection of the tumor.<sup>(3, 4)</sup> However, due to variability in surgical treatment patterns, in part due to the controversy about the appropriate margin width and the trade-off with functional outcome used during surgical excision (surgical strategy) of STS, there is continued debate by surgeons on how to best treat this disease.<sup>(3, 5-7)</sup> Surgical resection of these tumors is completed with a curative intent by planning for a sufficient margin of healthy tissue surrounding the tumor for complete excision, while maximizing functionality of the extremity by removing as little healthy tissue as possible.<sup>(6-9)</sup> The basis for these differences in surgical treatment preferences among surgeons is not well understood. Surgeons may believe that: 1) narrow margin surgery is preferred because it can increase the function of the limb or 2) the probability of a local recurrence is generally low; or 3) the patient prefers functionality at an increased risk of local recurrence.<sup>(10-12)</sup>

The rationale for considering the surgeon's perspective by using cost-utility methods is two-fold: 1) Surgeons have conflicting roles as they must both represent their patient that they took an oath to care for and 2) to consider societal preferences for allocating the limited resource of surgical care. Using a cost-utility modeling framework can provide a method for assessing the consequences of surgeons' choices for different surgical strategies.<sup>(13, 14)</sup> Empirical data have not been collected to assess whether the STS surgeon, the ostensible agent of the patient, is

substituting their own health state preferences for those of patients or if they are a true agent and are representing the patient's health state preferences.

## I.B Objectives

This study aims to understand the following objectives:

1. Quantify surgeons' health state utility preferences for sarcoma health states.
2. Quantitatively assess the role, if any, that these preferences predict surgeons' choices for surgical treatment strategies of LE STS.
3. Calculate the economic consequences of variations in surgeon treatment strategies and surgeon health state preferences on patient health outcomes, societal costs, and cost-effectiveness.

## I.C Specific Aims

### I.C.i Specific Aim 1

To assess surgeon's self-reported stated preferences for STS surgical strategies and, in particular, whether surgeons' preferences about health states influence their choice of surgical strategy.

*Hypothesis:* Differences in surgeons' stated health state preferences about function and margin status will be a significant predictor of treatment variations in surgical treatment strategies holding other covariates constant.

*Approach:* A convenience sample of STS surgeons attending a major professional meeting will be surveyed about their training, the surgical strategies they employ, perceptions of risk factors

and the clinical epidemiology of post-surgical STS, and their health state preferences for STS-related health states using an online standard gamble (SG) exercise.<sup>(19)</sup>

#### I.C.ii Specific Aim 2

To assess the consequences of any divergence between surgeons' valuations of health state utilities and those of the general public in terms of the cost-effectiveness of the surgical strategies used for LE STS, comparing the strategy of adequate margin surgery to inadequate functional-preservation surgery.

*Hypothesis:* If surgeons base their STS treatment recommendations on their own health state preferences rather than those of the general public, then the ratio of the expected value of utility for patients experiencing recurrence will be smaller in relation to the expected utility of the function health state, compared to the same ratio based on the preferences of the general public.

*Approach:* To achieve this aim, a cost-utility model using a lifetime time horizon will be used.<sup>(20)</sup> Costs and utilities for the societal perspective will be obtained from the literature. The positive or behavioral economic analysis of surgeon preferences for LE STS surgical strategies will be compared with a normative economic analysis by modeling the economic and health outcomes using a literature based cost-utility analysis. This will provide an estimate of aggregate social cost of misaligned preferences.



## Chapter II. Developing Health State Vignettes for Estimating Health State Utility Values in Soft Tissue Sarcoma: Methods, Lessons, and Implications

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Health state utilities; standard gamble; clinical vignettes; soft tissue sarcoma;

Running Title: Health Statue Vignettes in Sarcoma

## II.A Abstract

There is substantial methodological literature on how to conduct direct preference elicitation via various techniques, such as the standard gamble (SG) or time trade-off (TTO) methods, but the literature is lacking a cohesive text focused on how to develop and implement these health states into preference elicitation methods. The aim of this review is to develop and test a methodology for writing health state descriptions that are used for preference elicitation methods with a particular focus in how to employ these methods in the future when using computer and internet technology. The strengths and weaknesses of health state descriptions will be reviewed, along with methods for how to format, display, and present health state descriptions within a selected preference elicitation exercise. A case study in soft tissue sarcoma is used to demonstrate how these methods can be applied.

This review identifies four types of health state descriptions used in preference elicitation exercises: 1) clinical vignettes, 2) attribute-based health state descriptions, including the use of multi-attribute utility instrument (MAUI) descriptions, and 3) a combination of these first two types. Computer methods for presenting health states are emerging via new software technology, but still lack the ability to mimic the “gold standard” of the probability wheel for SG or the sliding time scale for TTO. We describe how to overcome these key requirements using computer software. The selection of health state descriptions always depends on the primary research question, the education of the participants, and the method of presentation being used.

## II.B Introduction

The health state utility (HSU) literature has many well-referenced papers on methods for measuring HSU preferences using technique such as standard gamble (SG), time trade-off (TTO), or multi-attribute utility scales.<sup>1, 2</sup> There are, however, few publications that describe how to develop the clinical vignettes, also known as health state descriptions or scenarios.<sup>1</sup> Also, these methods were designed before the widespread use of personal computers and the internet. The original methods of health state description development can be found from the early 1970s where descriptions ranged from single-word or single-phrase descriptions, such as “well-being” or “feeling weak and tired”<sup>3, 4</sup>, to more narrative descriptions of what it is like to have dialysis in the hospital<sup>5</sup>, or even more in-depth descriptions that use audio, video, or photographs to provide more context.<sup>6-9</sup>

As the field has matured, more health state descriptions have focused on measurable attributes (that can be grouped into “domains”) associated with health, such as pain, physical function, mental health, and social function. These attributes have then been distilled further into sub-attributes, such as depression and anxiety within the domain of mental health. This has led the field to move away from time-consuming and thus costly direct methods of measurement (such as the SG or TTO), which thus reduces the need for clinical vignettes. Instead, the field seems to be moving to more efficient, indirect methods of measurement, comprised primarily of generic multi-attribute utility instruments (MAUIs), such as the Health Utilities Index (HUI)<sup>10</sup>, EQ-5D<sup>11</sup>, and the SF-6D<sup>12</sup>. These measures are generic because they can measure health status across a variety of health conditions or medical interventions, as compared to disease-specific measures that can only be used for specific diseases, conditions, or treatments.<sup>13</sup> However, many studies have found that using MAUIs for preference elicitation does not yield that same HSU

values or richness of data compared to the more in-depth direct methods of elicitation.<sup>14, 15</sup> For the studies that continue to use these gold-standards of direct measurement methods, there has been a trend toward using attributes to create health states that are very specific to a particular disease, for example developing pain attributes very specific to pain, numbness and tingling only experienced by those with diabetic peripheral neuropathy.<sup>6</sup> Other studies have used attributes directly from a MAUI and combined them to form vignette-styled health state descriptions.<sup>16</sup>

The aim of this review is to describe the development and pilot implementation of a methodology for writing health state descriptions to be used in direct methods of preference elicitation (SG or TTO) that rely on the use of web-based software technology. The strengths and weaknesses of the style of health state descriptions will be reviewed along with methods for how to format, display, and present health state descriptions within a selected preference elicitation exercise. A case study in soft tissue sarcoma is used to demonstrate how these methods can be applied.

## II.C Developing Health State Descriptions

The design and development of health state descriptions is based on some basic design conventions.<sup>17-19</sup> First, health state descriptions can be categorized—depending on duration—as either chronic or temporary. Prognosis is a very important aspect of the description, and the previous literature is clear in how to define this part of the health state description. Prognosis introduces the concept of time or how health changes over time. It is recommended, for example, that for health states describing a chronic condition, the prognosis description should remain unchanged until the person dies at a specified age, and for those describing a temporary condition, the prognosis is unchanged until the temporary condition has ended and then the

patient (or potential patient) returns to “perfect” health.<sup>8, 17, 20</sup> Thus, the prognosis is not to be a part of the description itself, but to be part of the measurement process, such as how the health state is anchored in the SG (perfect health, death, or next worst health state) or the time spent in the state for the TTO method.

In order to distinguish between impacts on morbidity versus mortality, health state descriptions are developed so as not to depend on other prior or future health states, as then the value placed on that health state could be confounded by the any interdependency over time. Another convention is that the descriptions should be understood by the participant population required to value them and should not be so specific that they include actual names of the diagnosis or disease, or test results. Lastly, when measuring their values using preference elicitation methods, the duration for each health state presented should be either temporary or chronic, and not vacillate between the two.

This review identifies three types of health state descriptions used in preference elicitation exercises: 1) clinical vignettes<sup>5</sup>, 2) attribute-based health state descriptions, which includes the use of multi-attribute utility instrument (MAUI) descriptions<sup>16</sup>, and 3) a combination of these first three types.<sup>21</sup> Selection of the type of health state descriptions to use depends on the following: 1) the primary research question, 2) the education and perspective of the participants, and 3) the method of presentation being selected.

### II.C.i Clinical Vignettes

A clinical vignette is a description that provides detail about a patient experiencing a specific clinical condition or diagnosis. It aims to evoke an image or scenario of a health state that “anchors” respondents to a situation for which they are then asked to make a decision or a

measurement. Vignettes are a way to harmonize complex, multi-domain descriptions of health.<sup>22,</sup>

<sup>23</sup> Clinical vignettes can be broad and describe a diagnosis or symptomology of a condition, such as chronic kidney disease, or they can be robust and specific, describing not only the health condition and symptomology, but also the type of treatment the person in the described health state is undergoing. Clinical vignettes can range from a few brief bulleted items to several paragraphs that provide a more cohesive narrative (Figure 1).<sup>4, 15</sup>

Early examples of clinical vignettes can be found describing in detail a scenario of a patient experiencing in-hospital dialysis for chronic renal failure or gallstone disease.<sup>5, 24</sup> These descriptions can provide great detail for any respondent—whether clinician, patient, or general public – on average, what a patient would experience in a health state. Nonetheless it would be difficult to know which part of the description might affect a particular respondent’s valuation of this health state. For example, the descriptor “feeling tired and sluggish” may have more (or less) value to some, while for others, “there is no severe pain” in this health state may have more (or less) significance in their valuation and preference for a particular health state. Also, clinical vignettes can be inconsistent from state to state with some descriptions describing the patient’s pain and/or nausea, while other descriptions in the same preference elicitation study might fail to mention either concept.

As noted above, when using clinical vignettes, one should be careful in adding in any hint of prognosis as a part of the health state description. If prognosis is important to the health state description, then a health state description should be written for each prognosis scenario. For example, the prognosis of remaining alive with disease could be written as “you have had a life-threatening illness which has responded to treatment”. As the prognosis worsens the phrase could change to “you have a life-threatening illness and your condition is getting worse despite

undergoing rounds of treatment”. In both of these statements there is no mention of the time to death.

Disadvantages to using clinical vignettes as the base HSU description are that they are the most time-consuming and costly method in terms of both development and presentation. Qualitative methods, such as focus groups and in-depth interviews are typically conducted prior to developing and writing a health state description. These are complex qualitative studies in and of themselves and not including the preparation time, it can require several hours to run a focus group or 1 to 2 hours per participant interviewed.<sup>6, 21, 25</sup> After development is completed, and the vignettes are deployed for use in the preference elicitation study, depending on the number of health states being valued, the time for health state presentation can range from 20 minutes (via telephone), 33 minutes (via in-person), up to 60 minutes (via computer) to several hours.<sup>6, 26, 27</sup>

#### II.C.ii Attribute-Based

In terms of the history of measurement in this field, because vignettes can be time-consuming, complex, and inconsistently measure different attributes across various health states, the approach of domain-based health state descriptions was developed as an alternative to clinical vignettes, to elicit utility values.<sup>8, 28</sup> Attributes are classifications that make up dimensions of quality of life, and when combined together these attributes are known as domains. One early study stated that there six main domains that should be included in every health state description: physical function, emotional function, sensory function, cognitive function, self-care function, and pain.<sup>28</sup> While these six domains could arguably encompass an overall description of a person’s quality of life regardless of disease,

another study recommended that due to cognitive burden, a maximum of five attributes should be evaluated in any one health state.<sup>20</sup>

Nonetheless, the number of proposed “key” domains has increased over the years. These include the additions of: general health, quality of life, and role- and social-functioning to name a few.<sup>29, 30</sup> Along with emerging domains that only define one key attribute or concept, there are also sub-domains or sub-attributes of a domain that are also available for health state descriptions. As the literature often uses the words, “domain” and “attribute” interchangeably it is important to use them correctly.<sup>31</sup> An example is the domain of pain, which can then be further sub-classified into the sub-domains of pain-catastrophizing, pain-interference, and pain intensity.<sup>32</sup> Attributes can be general or they can be disease-specific and both kinds can and have been used in health state descriptions. In the pain example, an attribute can be how pain is different at home or work. Another example is that physical health as a domain can have many attributes that contribute to how someone values their physical health. For example, attributes, such as ability to perform at work, in the home, or in social activities all could be valued differently within the domain for physical function.

The additional benefit in using attribute-based methods to create health states is that the levels of these attributes can be varied or adjusted across health states being compared and can help the researcher understand conceptually and measure how the level of the domain is influencing the value assigned and why preference is given to one health state over another. Level adjustment can be comparable to measuring the severity and/or the presence or absence of a particular domain. For example, to designate a level of an attribute, phrases are used that typically mimic a Likert scale: “never”, “sometimes”, “often”, “and always”. Or



words like, “limited”, “with difficulty”, “very”, “none” and “some” can be used to show the degree to which the attribute contributes to the health state.<sup>4, 30</sup>

#### II.C.ii.a Disease-specific attributes

Disease-specific attributes focus on attributes that are related to a specific disease, and thus the preferences weights or utility values elicited would not be generalizable to a different type of disease. Typically, these attributes are developed after qualitative interviews with patients who are currently experiencing or have experienced the disease of interest.

This type of preference elicitation with disease-specific attributes has been done in disease areas such as diabetic peripheral neuropathy, prostate cancer, and chronic obstructive pulmonary disease (COPD).<sup>6, 25, 33</sup> For example, for diabetic peripheral neuropathy, the authors varied the attribute of numbness of the extremities which ranged from “sometimes numb” to “often numb”. This study also included photographs of the condition.<sup>6</sup> For prostate cancer, the attributes of sexual, urinary, and bowel function were varied to “never experiencing a problem” to “always experiencing a problem”.<sup>25</sup>

Even though the symptoms are disease-specific, in some studies, health state descriptions were written in such a way that they could possibly be generalizable across other diseases for patients experiencing health state dysfunction across all the domains. For example, the health states in a prostate cancer study may be generalizable to a condition, such as spinal cord injury or other diseases or injuries affecting the pelvic nerves. For COPD, the disease-specific domains focused on dyspnea, sleep, and medication efficacy, which could be applied to other airway obstructive disease, such as obstructive sleep apnea or asthma.<sup>33</sup>

Disease-specific attributes are appropriate for use in describing complex diseases or disorders and can be used when eliciting patient or clinician preferences. They would not be recommended for use in the general population as they may be too specific and difficult for anyone who does not have experience with the disease.

#### II.C.ii.b Generic Attributes or Multi-Attribute Utility Instruments

Generic attributes for health state descriptions are widely accepted attributes of health, described previously, that can be measured across different types of diseases or disorders and do not focus on specific symptomology of a disease. Generic attributes are most often measured using multi-attribute utility instruments, such as the EQ-5D, HUI, and SF-6D (using data from the SF-36 and SF-12 instruments).<sup>11, 12, 34</sup> The generic domains used in these instruments are found in Table 1 and can be used together to form health state descriptions. An example of using this type of description can be found in a study that elicited preferences from people who have insurance for health care utilization given a health state vignette based on the EQ-5D.<sup>16</sup> One vignette was as follows:

*“I have no problems in walking about. I have no problems with self-care. I have some problems with performing my usual activities (e.g. work, study, and housework, family, or leisure activities). I have no pain or discomfort. I am moderately anxious or depressed.”*

Using MAUIs to write health state descriptions when conducting SG and TTO provides standardization and supports validity by relying on health states already well-described in the literature. An added benefit to using MAUIs domain descriptions to create health state descriptions is the results become more generalizable when using them in a disease-specific

study. Using the vignette above, we know that this condition is generalizable to a health state equal to the value of 11212 in the EQ-5D. These type of health state descriptions would be highly recommended when eliciting preferences from the general population as they are more generic and do not require specific knowledge about a disease or disorder. As some of these instruments are proprietary, caution should be used to ensure that appropriate citations and licensing agreements have been adjudicated before use, especially in commercial and clinical trial studies. Also, while this type of health state description provides standardization to the presentation of health states, its rigidity may not properly elicit the dynamic differences within a person's preferences and between people's preferences across various health states.<sup>14</sup>

### II.C.iii Combination

Finally, another way to write health state descriptions is using a combination of the two types of methods described previously. Clinical vignettes can be supplemented or formed using attribute-based methods to describe a specific clinical condition.<sup>35</sup> It has been found that “enriching” a scenario with more personalized information did not change the health state value when compared to a standard health state description. An example of this method is in a study that conducted preference elicitation in the general population for the disease of soft tissue sarcoma.<sup>21</sup> This study used clinical vignettes, such as “You have a life-threatening illness which due to your treatment is not getting any worse. You have undergone an operation which has left you with some unsightly scarring. You have lost some weight.” Additionally across all the health state descriptions in the study, there were several attribute-based descriptions that described attributes for the domains of physical function, mental health, usual-care, and social-functioning. An example of the physical function attribute was described as follows: “You experience

difficulty in moving around and are unable to walk long distances. You feel a constant need to rest”.<sup>21</sup>.

By using this combined method the authors were able to be specific to the disease and have the ability to understand the disutility of disease-specific attributes while holding other general attributes constant. The benefit in using this method is it can be used to elicit preferences across all perspectives from the general population, patient, and clinician. This method is also useful for understanding utility decrements between health states.

## II.D Methods of Health State Presentation

Regardless of the type of health state description chosen to present a health state the following approaches to assessing the health state by eliciting a value requires thoughtful selection of the scaling method chosen, including SG, TTO, and VAS; how the question is framed, from a prompt or using a top anchor or bottom anchor approach; and how the “search” for the value is achieved – these are described in the following section.

### II.D.i Traditional Modes of Administration

Traditional modes of administration for presenting health state descriptions for preference elicitation include the use of props, in-person interviews, and less-used participant-initiated, paper-based methods. These methods have long been considered the standard by which SG and TTO techniques are conducted.<sup>36</sup> Typically, when conducting SG and TTO researchers interview the participants using a guide with the health states printed out on index cards or paper and guide the participant through each health state. Health states presented during these in-person interviews have ranged from 5 to 12 across studies and, on average, take about 60 to 70

minutes with a ranges as short as 23 minutes and as long as 140 minutes (Table 3), which depends primarily on the number of health states presented during a session.

#### II.D.i.a Use of Visual Aids

Visual aids or props have long been used to help participants visualize the task being asked of them. The props change depending on the method used to elicit HSU values. For the SG method, there is a probability wheel, and for the TTO method there is a board that shows a sliding scale or bar that adjusts time spent in good health.<sup>2, 36</sup> Even the rating scale method, while a direct preference elicitation method, but not choice-based preference measure uses a “feeling thermometer”, typically in healthcare this is the visual analogue scale (VAS).<sup>37</sup>

There are also “search” methods by which the props are used to elicit the participants HSU value.<sup>38</sup> Within these search methods, also known as titration, there are three ways to elicit a person’s probability or time preference for a health state depending on which end of the scale you begin with. The first way is to start at the low-end of a scale (i.e., 0%, 1 year) and incrementally work your way up to the top of the scale (i.e., 100%, 10 years) using a certain interval (i.e., 5%, 10% 5 years): this method is “bottom-up” titration. The second is the reverse, starting at the high-end of the scale and working downwards to the bottom of the scale, known as “top-down” titration. The third method is a less commonly used method called, “internal division”, that uses the formula of internal division of a line segment (e.g., 1 year, 5 years, 7.5 years, 8.75 years). The other method is “ping-pong”, which as it sounds, “ping-pongs” between the high and low end of the scales and alternates until the person is indifferent (unable to choose) to the value presented (i.e., 0%, 100%, 10%, 90%, 95%, 5%, 80%, etc.). The ping-pong method

is the most commonly used titration method to elicit HSU values used when measuring health states.<sup>14, 25, 39</sup>

One other prop that is not widely used and is not necessary to aid in the measurement process is the use of media in the form of images presented via photos or video; it helps the respondent to better visual the actual health state.<sup>7, 40, 41</sup> Videos showing people in the actual health states or photos showing a condition have been used infrequently in studies. One criticism in using this type of visual aid for health state descriptions is the patient is now rating the health state of the person they are seeing instead of placing their value on how they would experience the health state. One publication gave the suggestion of having the patient simulate the experience, for example give them a walking aid, such as a crutch or cane to demonstrate physical function limitations.<sup>7</sup>

#### II.D.i.b Use of Paper-based Questionnaire or Guides for Self-Completion

Handing participants a paper-based guidebook for both TTO and SG has been used. With this method, an interviewer still provides guidance with an example before handing over a booklet or guidebook for self-completion.<sup>36</sup> This method is usually supervised, although physicians in one study completed it on their own, and in another study patients were mailed the paper-based questionnaire prior to receiving a phone call where the interviewer walked them through the paper-based questionnaire.<sup>27, 42, 43</sup> However, paper versions of these studies can be 19 – 20 pages per health state ascertained and as previously shown the length of time to complete these can be long.<sup>25, 44</sup> With the invention of the personal computer and Internet the use of paper-based questionnaires are not recommended. Paper should only be used when creating and

reading from guides for in-person interviews so that there is consistency when administering the SG and TTO to participants.

#### II.D.ii Technology-based Methods

Computer-based or web-based methods of presenting health states are emerging with new software technology, but their ability to mimic the “gold standard” of the probability wheel for SG or to change time for TTO is still limited. Computers are sometimes used as a visual aid with an interviewer still being present to demonstrate the iterative and complex method of searching for the elicited value.<sup>45</sup> Proprietary packages, such as U-titer, U-Maker, iMPACT, and Gambler exist as online preference elicitation software, but these have not been made widely available and have been designed for disease-specific studies.<sup>41, 46</sup> Lenert and colleagues have well-established that computer-based methods for utility assessment can be used for direct preference elicitation.<sup>41, 47-49</sup> With more robust data visualization tools, such as Tableau (Tableau Software; Seattle, WA) or Power BI (Microsoft; Redmond, WA), it is only a matter of time until we see direct preference elicitation studies moving to more automated processes. Automated processes can aid in the search methodology (i.e. titration or ping-pong) used to find the indifference point and thereby eliciting the HSU value.<sup>38</sup> Another benefit of computer-based health state descriptions is that visual aids, such as photos and video describing the health states can be used in conjunction with graphical props, such as a probability wheels and time slider scales.

Another computer-based opportunity for preference elicitation studies is how we recruit the general population for societal-based perspectives. The tool Amazon Mechanical Turk (Amazon; Bellevue, WA) is a place where this could become a reality and tasks, such as completing an online standard gamble are posted and within minutes thousands from the

“general population” could complete the task that can range from no pay to pay based on time spent on the task. (<http://mturk.com>)

## II.E Summary: Methods of Health State Description and Presentations

In this review we described how to write and develop health state descriptions for direct preference elicitation studies. We identified three ways to describe a health state: 1) clinical vignettes, 2) attribute-based methods, either disease-specific or general health attributes, and 3) a combination of both methods. We further described how to then present these health state descriptions through the use of visual aids, in-person descriptions, and paper-based questionnaires to encouraging the use of online software products to use both visual aids and automation to search for elicitation values. Also, we describe how computer technology-based methods can help us better recruit specific populations, in particular, the general population, to participate in these types of studies.

## II.F A Case Study: Development of Soft Tissue Sarcoma Health State Vignettes

The following case study develops health state descriptions for a health outcomes study to elicit HSU preferences from surgeons who treat soft tissue sarcoma. This study was inspired by two prior works—a paper by Shingler et al. that developed population HS preferences in sarcoma; and the U.S. Public Health Service Panel on Cost-Effectiveness seminal methods volume, which states: , “the best articulation of society’s preferences for particular health states would be gathered from a representative sample of fully informed members of the community” and that “a person experiencing the health state is in the best place to assess the value of that health state”.<sup>21, 50</sup> This led to the question of how this applies to the field of surgery and whether



the most fully informed member about the health state is the surgeon who can alter the health state by the type of surgical treatment they provide. Surgeon's HS valuation in this field have not been explored or documented. In order to assess a surgeon's preference for a particular health state, the health state must reflect the result of surgical intervention. In other words, how does the patient's health state change after surgical intervention?

Since surgery is the primary treatment for soft tissue sarcoma (STS) it is important that health state descriptions used in STS health-related quality of life (HRQoL) research reflect the implication of surgical decision-making that involves weighing limb preservation with the trade-off of tumor control for local recurrence. Several HRQoL studies in the breast and lung surgery have shown that surgical decision-making can be examined using HSU valuation.<sup>51-54</sup> To understand quality of life in the range of health states associated with a diagnosis of STS, this study conducted a review of the HRQoL literature to assess the current state of values, ranges, and perspectives for which STS health state valuations exist. Secondly, it was important to understand if the existing clinical vignettes or health state descriptions designed to elicit health state preferences for STS appropriately recognized the likely tradeoff between functional status and tumor margin that is inherent in the treatment of STS.

#### II.F.i Literature Review of Utility Studies for Soft Tissue Sarcoma

Soft tissue sarcomas (STS) are rare cancers, with 11,410 new cases diagnosed and an estimated 4,390 deaths reported in the United States in 2013 and with the majority of these tumors found in the extremities.<sup>55, 56</sup> First-line treatment for lower extremity (LE) STS is surgical resection of the tumor.<sup>57, 58</sup> There is continued debate by surgeons on how to best treat this disease and hence variability in surgical treatment patterns. This is likely due in part to the

controversy about the appropriate margin width given a likely trade-off of poor functional outcome with the risk of recurrence. Following surgical excision of STS.<sup>57, 59-61</sup>

A systematic literature search found six published studies reporting existing health states valuations for sarcoma patients (Tables 3 & 4). Of the six, 2 studies had a surgical perspective<sup>62, 63</sup>, and the remaining 4 were from an oncology perspective, of which 3 focused on advanced or metastatic STS.<sup>21, 64-66</sup> Four of the studies used indirect MAUIs, such as EQ-5D™, Health Utilities Index (HUI®), and SF-6D, to value health states and the remaining 2 studies used the direct methods of SG and TTO for STS-specific health states. The majority of the studies elicited patient preferences (n=4) from multiple countries across North America and Europe, and only two elicited societal preferences, of which both were from the general population in the United Kingdom. The number of health states represented in the six studies ranged from 5 to 15 (Table 2).<sup>14, 15, 21, 42, 67</sup>

Of the two directly measuring STS-specific health states, one was chosen as the reference health states for this study because the health states: 1) closely paired with the SF-6D domains, 2) included specific physical function domains, and 3) were developed to encompass health states for both local and advanced STS populations.<sup>21</sup> This study presents health states from a side-effect profile for patients experiencing other forms of cancer treatment, such as chemotherapy and radiation, but it did not necessarily address the health state from a surgical perspective that would reveal the result of a tradeoff between limb preservation and local control outcome. Mean utility decrements for side effects, that included pain, dyspnea, fatigue, diarrhea, nausea and vomiting, and progressive disease were calculated compared to the base health state of stable disease, along with the mean utility values for each health state. In order to elicit the

trade-off between losing function or increasing the risk of local recurrence, new health states were created to reflect this question.

## II.F.ii Health State Descriptions for Surgeons Treating STS

Using the methods described above, the combination method of writing a clinical vignette that was supplemented with an attribute-based description was used to describe disease-specific health states following the surgical treatment of a lower extremity soft tissue sarcoma. . To understand the trade-off of local recurrence specific language about “responded to treatment” and “worry about dying” and for functional loss, “a lot of difficulty in walking” or “little difficulty in running long distances”, both clinical descriptions were used. As for the attribute of pain and domain of mental health, these descriptions more closely matched the attribute-based descriptions from the SF-6D(Figure 3).<sup>12</sup>

These states were written as if reflecting chronic duration and were based on the health states developed by Shingler and colleagues.<sup>21</sup> However, in order to eventually map the health states to the SF-6D a “vitality” domain was added to the health state states.<sup>68, 69</sup> Also, to more accurately portray the deterioration of health states across the clinical continuum, a set of rules were developed in collaboration with an expert in the surgical treatment of STS to more precisely weigh how different surgeries and disease progressions affected the levels of the attributes (Figure 2).

From the reference health state of perfect health, 16 health states were created to meet the objective of this study. There are five “main” health states: Disease-Free Survival (DFS), Alive with Disease (AWD), Local Recurrence (LR), Metastatic (MET), and Re-excision (REEX). Within the DFS, AWD, LR, MET and REEX state, attribute levels were varied depending on

original margin status (Adequate (AM) vs. Inadequate (IM)) and functional status (Acceptable (+F) vs. Adverse (-A)) pathways (Table 5). A selected full description of these health states can be found in Figure 3, and all 16 health states are described in Appendix 5.

### II.F.iii Online Standard Gamble exercise and Questionnaire Development

Using Qualtrics, an online survey software product (Qualtrics, Provo, UT), an online SG exercise was developed. This platform was chosen because it had the following features: 1) there was no monetary cost, 2) easily programmable with the ability to use skip logic, 3) allowed for randomization of questions and participants, and 4) ability for participants to engage online using multiple modalities, including web-based interface, tablet, or other mobile devices. The SG task mimicked the use of the standard SG prop by presenting “virtual health state cards”, but there was no ability to program a probability wheel.<sup>1</sup> Similar to other types of computer adaptive testing, questions were presented using display and skip logic to limit the number of questions that need to be answered. The display and skip logic allowed for the “ping-pong” effect that aided in decreasing “anchor point bias”.<sup>14, 70</sup> Additionally, a rating exercise using a visual analog scale (VAS) for the same health states presented in the SG task were used to establish construct validity with the SG.<sup>14, 50, 71, 72</sup> Surgeons completed the VAS and performed SG exercises to elicit their preferences for 8 health states selected from the table described previously. In order to obtain more values for more health states, while not wanting to cognitively overwhelm the participants, we randomized the health states descriptions given to participants. Additionally, we randomized the presentation order of the preference elicitation methods: thus, not all participants had the same survey. Each had a 1 in 4 chance of receiving the same health states with the same order of questions (VAS then SG vs. SG then VAS). Surgeons were also surveyed about their

demographics, post-graduate training, medical practice variation, surgical treatment strategies they employ, and the clinical epidemiology of post-surgical STS. A human subjects' consent was also presented online via the secure Qualtrics website.

This also required the decision of how many health states to present, the search procedure for finding the values and how to frame question. In choosing how many health states to present, the decision to present 7 – 8 was made based on a suggestion that between 6 – 10 health states could be valued at any one time.<sup>67</sup> However, it was only after this study had been completed that another study was found demonstrating that physicians validating clinical vignettes could only complete 4 vignettes in a 60 – 70 minute session.<sup>26</sup> The traditional “ping-pong” search methods was used to elicit the values and the questions were framed using a prompt and a top-anchor approach by starting all exercises with the best health state and working down to the worst health state. Standard gambles were presented in the format of a chronic health state preferred to death and some were presented as a chronic health state considered worse than death to use for chaining in a later study.<sup>18</sup> Training questions were also given at the beginning of each series of tasks: one for the VAS and two for the SG that “forced” participants to answer correctly before they could engage in the “true” preference elicitation exercises.

#### II.F.iv Survey Administration Results

A convenience sample of STS surgeons who are members of the Connective Tissue Oncology Society (CTOS) and/or the Musculoskeletal Tumor Society (MSTS) were recruited and enrolled in this study. Additionally emails were sent to former tumor fellows and colleagues of tumor surgeons in the Department of Orthopaedics and Sports Medicine at the University of Washington. An announcement was also placed in the MSTS/CTOS newsletter encouraging

survey participation. No additional incentives were given to encourage participation, other than the promise to share results at meetings and in manuscripts. Only orthopaedic oncologic surgeons were eligible for statistical analysis (presented in Chapter 2).

There were 67 total survey participants who self-completed the online SG, VAS and survey questionnaire. Of those almost two-thirds ( $N=43/67$ , 64%) were orthopaedic and surgical oncologists and the remaining 36% of participants were medical oncologist, pathologist or were unknown ( $N=24/67$ ). The completion rate of the entire survey (all SG and VAS and other questions answered) was only 37% ( $N=25/67$ ). For surgeon participants, the VAS completion rate ranged from 32% ( $N=14/43$ ) to 63% ( $N=27/43$ ) and for the SG there was a drop-off with the range of completion to as low as 21% ( $N=9/43$ ) to as high as 42% ( $N=18/43$ ). The average time to complete the survey was approximately 46 minutes (range 15 minutes – 114 minutes). No one completed the survey between 2 – 3 hours, but there were 4 participants who completed the survey in > 3 hours (range 3 hours – 29 hours). It is known that these participants “took a break” and completed the survey at a later time.

## II.G Discussion

This review is important in synthesizing the literature describing how health state descriptions are developed and implemented into direct preference elicitation exercises. While many papers in the healthcare decision science literature focus on the methods of preference elicitation, whether to use VAS, TTO or SG, there is a gap of literature that describes in-depth and step by step how to prepare and implement health state descriptions into these methods.<sup>2, 36, 37</sup> Some key papers do exist though on the processes by which to write these descriptions, but they are either outdated or do not contain all the information.<sup>15, 35, 41</sup> This reviews attempts to

bring all this information together and provide a case study to demonstrate the rigorous methodology that is required to develop and implement a well-designed health state description. The other critical evidence gap that the development of these STS health states fulfills is the need for health states to describe the attribute of local recurrence. From a surgical perspective, local recurrence or the need to decrease its risk through proper surgical margins is the key driver of decision-making in the surgical treatment of STS.

Reviewing the literature, and developing and writing new health state description is its own scientific aim and requires its own methodology which was described in this review. It was found that in the STS literature review that only 2 of 6 total health state preference studies had a surgical perspective. Both of these studies used MAUI instruments and did not conduct direct preference elicitation. Of the other four non-surgical sarcoma HS preference studies, only two conducted preference elicitation methods, using SG and TTO. However, both of these studies focused on advanced STS health states and neither sought to understand the surgical concept of local recurrence. Thus this study focused on properly executing health state descriptions to assess a surgeon's preference for a particular health state that was a result of surgical treatment for STS. The education of the surgeon participants was indubitably high and it was strongly desired to use an online survey platform to present the health states. For the case study of STS health states we chose to use the combination method for two reasons, the first was to understand the nuances between local recurrence and functional loss and the second was the ability to crosswalk the health states with the SF-6D. Health state presentation summarized in this case study included the choices of using an online survey platform, Qualtrics; with the scaling methods of both VAS and SG; using chronic forms of the health states; framing these questions

with both prompts and a top-anchor approach, while using a ping-pong search procedure for eliciting the HSU values.

The pilot study to implement a SG online was limited in its ability to enroll participants and once enrolled to have participants complete the survey. This is most likely due to the participant population and the length of the survey - surgeons do not have the time to take a 45 – 1 hour survey. Also, because there was no in-person interaction it was unclear if the variation in the resulting HSU values was due to surgeon variation in how they value STS health states or if it was due to a lack of understanding of the survey questions or using probabilities. There was missing data and more automated forced answers should have been programmed into the survey to increase survey completeness.

## II.H Lessons and Implications

There are three ways to write health state descriptions that have been described in this review: 1) clinical vignettes, 2) attribute-based methods, either disease-specific or general health attributes, and 3) a combination of both methods. There are many methodological considerations on how to present them. Approaches for how the description will be presented include the method of administration, the type of scaling method, the framing of the question, the search procedure for eliciting the values, to training the subject. However, dependent on the primary research question, the education and perspective of the participants, and the method of presentation being selected one should think of the various ways to present health state descriptions as tools that are selected to best accomplish the task.

Cost and time to design, recruit and administer the survey should also be considered. Based on the experience of the authors and review of the literature it is recommend that only 4 health



state descriptions be given for evaluation at any one sitting especially when conducting these assessments online this will reduce time spent on the task and thus increase completion rates. Once the data was analyzed there was much variation in the HSU values elicited. It is highly suspected that even highly-educated surgeons did not understand probability as has been well-documented as a limitation of using the standard gamble.<sup>73</sup> It is recommended that when no interaction between study staff and study participants will occur that a a Numercy test or some other mean to rate participant's ability to understand probabilities be given as part of the training questions.<sup>74</sup> The methods and experience described in this paper is a means by which to standardize health state descriptions for direct methods of preference elicitation. Standardization can improve the consistency and responsiveness of participants when measuring preference utility weights used in healthcare decision science.

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## II.J Tables

Table 1. Multi-Attribute Utility Instruments

| <b>EQ-5D</b>       | <b>SF-6D</b>         | <b>HUI2 &amp; HUI3</b> |
|--------------------|----------------------|------------------------|
| Mobility           | Physical Functioning | Mobility               |
| Usual Activities   | Role Limitations     | Ambulation             |
| Self-Care          | Social Functioning   | Self-Care              |
| Pain/Discomfort    | Pain                 | Pain                   |
| Anxiety/Depression | Mental Health        | Emotion                |
|                    | Vitality             | Cognition              |
|                    |                      | Dexterity              |
|                    |                      | Sensation              |
|                    |                      | Fertility              |
|                    |                      | Vision                 |
|                    |                      | Hearing                |
|                    |                      | Speech                 |

Table 2. Recommendations for Health State Descriptions

| Health State Description Methods                                     | Primary Research Question                                                | Participant Type               | Preference Elicitation Method | Crosswalk   | Generalizable |
|----------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------|-------------------------------|-------------|---------------|
| 1. Clinical Vignettes                                                | Disease Specific Treatment Specific                                      | Clinician, Patient             | TTO, SG, VAS                  | No          | No            |
| 2. Attribute -Based                                                  |                                                                          |                                |                               |             |               |
| a. Disease-Specific Attributes                                       | Disease Specific                                                         | Clinician, Patient             | TTO, SG, VAS                  | No          | No            |
| b. Generic Attributes or Multi-Attribute Utility Instruments (MAUIs) | Population Health Treatment Specific Condition Specific                  | Population, Clinician, Patient | TTO, SG, VAS                  | Yes         | Yes           |
| 3. Combinations                                                      | Disease Specific Treatment Specific Population Health Condition Specific | Population, Clinician, Patient | SG, VAS                       | Potentially | Potentially   |



Table 3. Health States Presentations in Selected Studies

| Author                           | Year | N of Participants          | Number of Health States         | Time (Mean or Median)                        | Population                                            | Type of HS presentation             | Elicitation Method | Method of Presentation        | Disease Area                   |
|----------------------------------|------|----------------------------|---------------------------------|----------------------------------------------|-------------------------------------------------------|-------------------------------------|--------------------|-------------------------------|--------------------------------|
| Dolan <sup>(50)</sup>            | 1996 | 335 (test)<br>110 (retest) | 8                               | NR                                           | general population                                    | MAUI                                | SG<br>TTO          | Props<br>Booklet<br>Interview | General Health                 |
| Brazier & Dolan <sup>(28)</sup>  | 2005 | 58                         | 7                               | NR                                           | staff and students at University                      | MAUI                                | SF-6D<br>SG        | Props<br>Paper<br>Interview   | General Health                 |
| Llewellyn-Thomas <sup>(29)</sup> | 1982 | 64                         | 5                               | NR                                           | patients                                              | Domain<br>Vignette or<br>“Scenario” | SG                 | Paper<br>Interview            | General Health                 |
| Brazier <sup>(56)</sup>          | 1998 | 165                        | 8 = patient<br>12 = non-patient | NR                                           | patients, health professionals, managers and students | MAUI                                | SG<br>VAS<br>SF-6D | Paper Booklet                 | General Health                 |
| Shingler <sup>(35)</sup>         | 2013 | 100                        | 8                               | NR                                           | general population                                    | Domain<br>Vignette                  | VAS<br>TTO         | Interview                     | Advanced Soft Tissue Sarcoma   |
| Sullivan <sup>(20)</sup>         | 2002 | 52                         | 7                               | <60 minutes                                  | patients                                              | Domain<br>Vignette                  | VAS<br>SG          | Computer                      | Diabetic Peripheral Neuropathy |
| Sun <sup>(84)</sup>              | 2014 | 36                         | 9                               | 46 minutes                                   | patients                                              | MAUI                                | SG<br>DCE          | Computer with Graphical Props | Breast Reconstructive Surgery  |
| van Wijck                        | 1998 | 65                         | N/R                             | 20 minutes (phone)<br>33 minutes (in-person) | patients                                              | current health                      | TTO                | Interview<br>Phone            | Peripheral Arterial Occlusive  |

NR=not reported; Average Health States  $\approx 7 - 8$ ; SG=standard gamble; MAUI=multi-attribute utility instrument; VAS=visual analogue scale; TTO=Time Trade-Off

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2. Brazier J, Dolan P. Evidence of preference construction in a comparison of variants of the standard gamble method. *HEDS Discussion Paper 05/042005.*
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Table 4. STS Health Utility Values by Multi-Attribute Utility Instruments (MAUIs)

| Author    | Year | Country               | Population                                                                           | Type of Health State                                                                                 | 15D  | SF-6D | EQ-5D | HUI  |
|-----------|------|-----------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------|-------|-------|------|
| Soini     | 2011 | Europe                | Used values from another paper out of Spain (Poveda, N=28) all types of advanced STS | disease-specific EORTC QLQ-C30 mapped to 15D, SF-6D and EQ-5D (stable disease = progressive disease) | 0.74 | 0.67  | 0.65  |      |
| Gundle    | 2014 | US                    | N=63 Bone & STS LE                                                                   |                                                                                                      |      | 0.59  |       |      |
| Barrera   | 2011 | Canada                | N=28 LE bone sarcoma survivors                                                       |                                                                                                      |      |       |       | 0.75 |
| Reichardt | 2012 | Europe, North America | N=120 metastatic bone & STS SABINE study (N=12 - 35 per HS)                          | disease-specific EORTC QLQ-C30 and EQ-5D                                                             |      |       |       |      |
|           |      |                       |                                                                                      | <b>HS 1 - 1st line CXT preprogressive</b>                                                            |      |       | 0.72  |      |
|           |      |                       |                                                                                      | <b>HS 2 - 2nd line CXT preprogressive</b>                                                            |      |       | 0.64  |      |
|           |      |                       |                                                                                      | <b>HS 3 - <math>\geq</math> 3rd line CXT preprogressive</b>                                          |      |       | 0.77  |      |
|           |      |                       |                                                                                      | <b>HS 4 - progressive</b>                                                                            |      |       | 0.56  |      |
|           |      |                       |                                                                                      | <b>HS 5 - after CXT pre progressive</b>                                                              |      |       | 0.77  |      |

Table 5. Mean (or Median) STS Health State Utilities by Health State Descriptions

| Author    | Year | Country                | Population                                     | Type of Health State                                    | 1st line CXT pre-progressive | 2nd line CXT pre-progressive | ≥ 3rd line CXT pre-progressive | progressive                          | after CXT pre-progressive                         |
|-----------|------|------------------------|------------------------------------------------|---------------------------------------------------------|------------------------------|------------------------------|--------------------------------|--------------------------------------|---------------------------------------------------|
| Reichardt | 2012 | Europe & North America | N=120 bone & STS SABINE study (12 - 35 per HS) | disease-specific EORTC QLQ-C30 and EQ-5D (EQ-5D values) | 0.72                         | 0.64                         | 0.77                           | 0.56                                 | 0.77                                              |
|           |      |                        |                                                |                                                         | Stable disease               | Complete Response            | Treatment Response             | Stable disease with SAEs (Mean of 5) | Partial Response (similar HS description to SAEs) |
| Guest     | 2013 | UK                     | N=207 general population                       | Advanced STS based on NSCLC proxy (SG)                  | 0.31                         | 0.51                         |                                |                                      | 0.43                                              |
|           |      |                        |                                                | (TTO)                                                   | 0.43                         | 0.60                         |                                |                                      | 0.51                                              |
| Shingler  | 2013 | UK                     | N=100 general population                       | General STS (TTO)                                       | 0.74                         |                              | 0.79                           | 0.45                                 |                                                   |

Table 6. Health State Matrix for Soft Tissue Sarcoma

| Health State Number | Acronym  | Margin     | Function   | Disease State | Type of Disease  | Surgical State  | Abbreviation |
|---------------------|----------|------------|------------|---------------|------------------|-----------------|--------------|
| HS1                 | AM+F     | Adequate   | Acceptable | No Disease    | None             | Post Index      | DFS          |
| HS2                 | AM-F     | Adequate   | Adverse    | No Disease    | None             | Post Index      | DFS          |
| HS3                 | IM+F     | Inadequate | Acceptable | Disease       | Marginal         | Post Index      | AWD          |
| HS4                 | IM-F     | Inadequate | Adverse    | Disease       | Marginal         | Post Index      | AWD          |
| HS5                 | AM+F+M   | Adequate   | Acceptable | Disease       | Metastatic       | Post Index      | MET          |
| HS6                 | AM-F+M   | Adequate   | Adverse    | Disease       | Metastatic       | Post Index      | MET          |
| HS7                 | IM+F+M   | Inadequate | Acceptable | Disease       | Metastatic       | Post Index      | MET          |
| HS8                 | IM-F+M   | Inadequate | Adverse    | Disease       | Metastatic       | Post Index      | MET          |
| HS9                 | AM+F+LRx | Adequate   | Acceptable | No Disease    | None             | Post Reexcision | REEX/DFS     |
| HS10                | AM-F+LRx | Adequate   | Adverse    | No Disease    | None             | Post Reexcision | REES/DFS     |
| HS11                | AM+F+LR  | Adequate   | Acceptable | Disease       | Local Recurrence | Post Index      | LR           |
| HS12                | AM-F+LR  | Adequate   | Adverse    | Disease       | Local Recurrence | Post Index      | LR           |
| HS13                | IM+F+LRx | Inadequate | Acceptable | Disease       | Marginal         | Post Reexcision | REEX         |
| HS14                | IM-F+LRx | Inadequate | Adverse    | Disease       | Marginal         | Post Reexcision | REEX         |
| HS15                | IM+F+LR  | Inadequate | Acceptable | Disease       | Local Recurrence | Post Index      | LR/AD        |
| HS16                | IM-F+LR  | Inadequate | Adverse    | Disease       | Local Recurrence | Post Index      | LR/AD        |



## II.K Figures

Figure 1. Bulleted-Form versus Paragraph Form of a Health State Description (excerpted from Llewellyn-Thomas' 1982 paper: "The measurement of patients' values in medicine.")

| <b>Case B</b>                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Style 1</b>                                                             | <b>Style 2</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>AGE:</b> 40–64 employee/housekeeper                                     | I am in the age range 40–64 years.                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>MOBILITY:</b> in hospital                                               | Although I worked until recently, I am presently hospitalized and on complete bed rest. A nurse bathes, dresses, and feeds me. I am confused about time and place and have some memory loss. I have vomited and am only able to take clear fluids by mouth. I am dehydrated (lack water) and receive fluids by vein (IV therapy). I am incontinent (unable to control my bowels and bladder) and presently have a catheter (tube into the bladder). I have low back pain. |
| <b>PHYSICAL ACTIVITY:</b> in bed                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>SOCIAL ACTIVITY:</b> required assistance with self care                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>SYMPTOM/PROBLEM:</b> trouble learning, remembering, or thinking clearly |                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

Figure 2. Domain Rules for Soft Tissue Sarcoma Health States

#### Physical Function (PF)

- Adequate Margin starts at level 3
- Inadequate Margin starts at level 2
- Any additional surgery (such as REEX) adds 1 level (+1)
- Reexcision add 1 more level (+1)
- Poor Function is 1 level more than Good Function (+1)

#### Role Limitation (RL)

- Everyone starts at level 1
- Poor Function adds an additional level (+1)
- Metastatic Disease and Good Function at level 3 (+2)
- Metastatic Disease and Poor Function at level 4 (+3)
- Reexcision add 1 more level (+1)

#### Social Functioning (SF)

- Everyone starts at level 1
- Presence of cancer (such as LR) add 2 more levels (+2)
- Poor Function add 1 more level (+1)

#### Pain (PN)

- Everyone starts at level 2
- Add 1 level for each surgery (+1)
- Presence of cancer (such as LR) add 1 more level (+1)
- Poor Function is 1 level more than Good Function (+1)

#### Mental Health (MH)

- Rule assumption is based on margin status and whether cancer is in situ
- Everyone starts at level 2
- Inadequate Margin add 1 level (+1)
- In Situ Cancer (LR or MET) add 1 level (+1)
- Excision of Tumor subtract 1 level (-1)
- Poor Function add 1 level (+1)

#### Vitality (VT)

- Everyone starts at level 2
- For each additional surgery (REEX) add 1 level (+1)
- In Situ Cancer (LR or MET) add 1 level (+1)

|



Figure 3. Selected Health State Descriptions for Soft Tissue Sarcoma

**HS - 2 Adequate Margin and Adverse Function (Disease Free State)**

- You had a life-threatening illness which has responded to treatment.
- You have undergone an operation which has left you with some unsightly scarring.
- You have lost some weight.
- You have a lot of difficulty in walking long distances.
- You are able to wash and dress yourself, but limited in jobs around the home due to physical health.
- You are limited in your ability to shop and perform other daily activities due to your physical health.
- You are able to socialize with friends and family and a little of the time have to cut it short due to your illness.
- You have a little pain that interferes with activities listed above.
- You experience some anxiety but you are pleased that you are responding to treatment.
- You some of the time feel worried about dying and how your loved ones will manage without you.
- You have a lot of energy most of the time.

**HS - 10 Adequate Margin and Adverse Function with Local Recurrence that was Re-excised (Disease Free State)**

- You had a life-threatening illness which did not respond to first treatment and required a second treatment.
- You have undergone operations which has left you with unsightly scarring.
- You have lost some weight.
- You have a little difficulty in washing and dressing yourself and are limited in jobs around the home due to physical health.
- You are able to socialize with friends and family and a little of the time have to cut it short due to illness.
- You have some pain that interferes with activities listed above.
- You experience a little anxiety about not initially responding to treatment.
- You feel a little worried about dying and how your loved ones will manage without you.
- You have a lot of energy some of the time.

**HS - 3 Inadequate Margin and Acceptable Function (Alive With Disease State)**

- You had a life-threatening illness which has responded to treatment.
- You have undergone an operation which has left you with some unsightly scarring.
- You have lost some weight.
- You have a little difficulty in running long distances.
- You are able to wash and dress yourself and do jobs around the home.
- You have no problems in your ability to shop and perform other daily activities.
- You are able to socialize with friends and family and never have to cut it short due to your illness.
- You have pain, but it does not interfere with activities listed above.
- You experience some anxiety but you are pleased that you are responding to treatment.
- You some of the time feel worried about dying and how your loved ones will manage without you.
- You have a lot of energy most of the time.

**HS - 16 Inadequate Margin and Adverse Function with Local Recurrence (Advanced Diseased State)**

- You have a life-threatening illness which did not respond to first treatment.
- You have undergone an operation which has left you with some unsightly scarring.
- You have lost some weight.
- You have a little difficulty in walking long distances.
- You are able to wash and dress yourself, but limited in jobs around the home due to physical health.
- You are limited in your ability to shop and perform other daily activities due to your physical health.
- You are often too tired to enjoy spending time with friends and family and most of the time have to cut it short due to your illness.
- You have some pain that interferes with activities listed above.
- You are depressed about not responding to first treatment and often think about dying.
- You always feel worried about dying and how your loved ones will manage without you.
- You have a lot of energy some of the time.

Figure 4. Study Population and Respondents by Health States

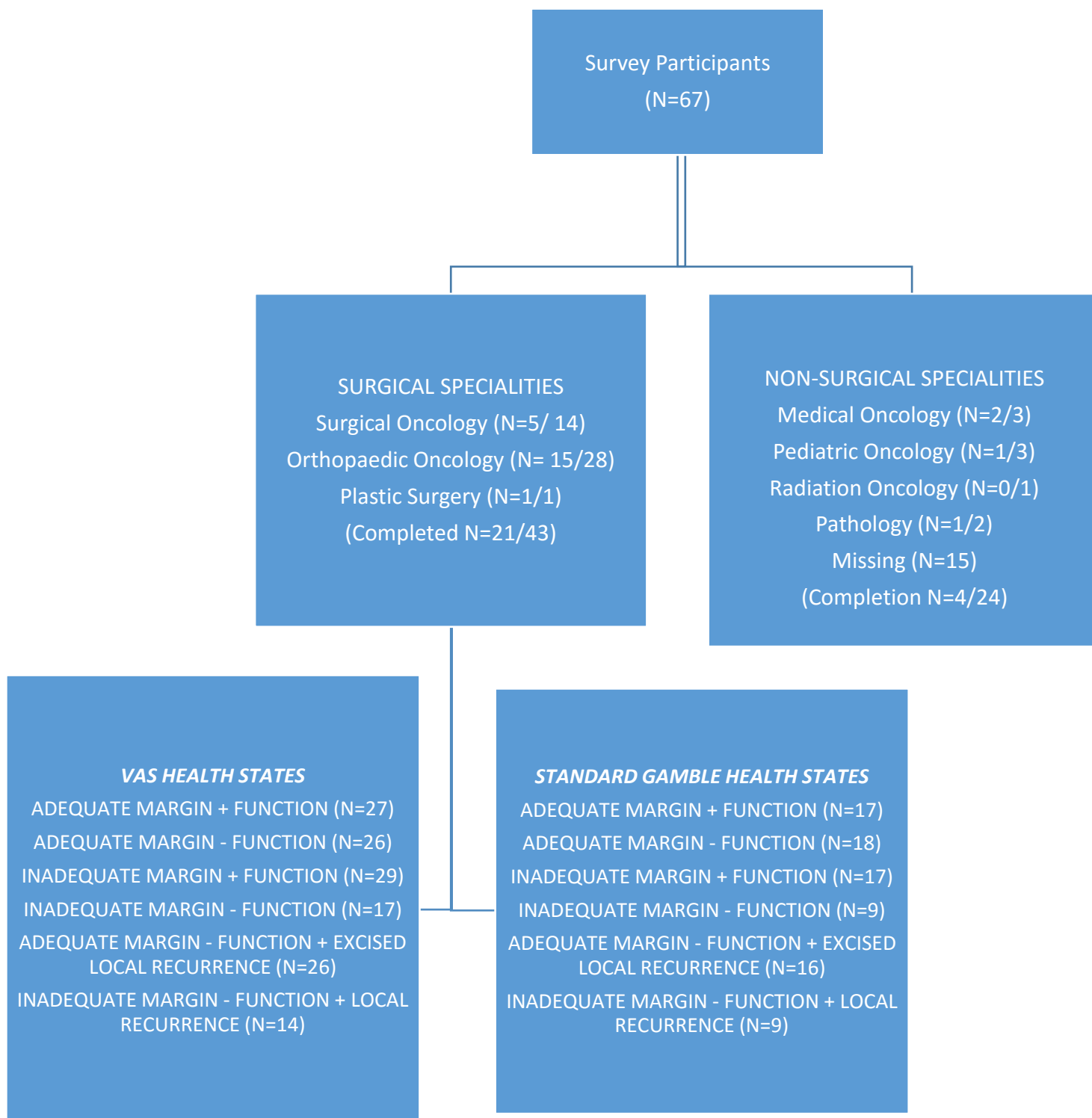


Figure 5. Screenshot of VAS “feeling thermometer” Question

Read the health state description below, imagine living in this state for the rest of your life, and then slide the bar along the thermometer according to your preference. Remember, the distances between the slider should represent how much more preferable or less preferable you feel about this health state when compared to other health states you will see. More than one health state can reflect the same value on the “thermometer” if you want, and you can move the bars around for each health state you are presented to “order” the health states.

Please read each health state carefully as they are all different.

**HS - 1**

- You had a life-threatening illness which has responded to treatment.
- You have undergone an operation which has left you with some unsightly scarring.
- You have lost some weight.
- You have a little difficulty in walking long distances.
- You are able to wash and dress yourself and do jobs around the home.
- You have no problems in your ability to shop and perform other daily activities.
- You are able to socialize with friends and family and never have to cut it short due to your illness.
- You have pain, but it does not interfere with activities listed above.
- You experience a little anxiety but you are pleased that you are responding to treatment.
- You feel a little worried about dying and how your loved ones will manage without you.
- You have a lot of energy most of the time.

0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Health State 1  77

Figure 6. Screenshot of Standard Gamble Question

Please continue to the next set of health states. Again, ***please read each choice carefully and note the changes in probability*** in each series of questions. There are no right or wrong answers, make a choice based on what you prefer.

Choice "A"

100%

HS - 01

- You are healthy. You do not have a life-threatening illness.
- You do not have dysfunction that limits you physically. You do have difficulty in running long distances.
- You are able to wash and dress yourself and do jobs around the home.
- You have no problems in your ability to shop and perform other daily activities.
- You are able to socialize with friends and family.
- You have no pain.
- You feel calm and happy and experience no worry related to your health.
- You have a lot of energy all of the time.

and

0%

Death

- Imagine that sometime within the next month you will die, without pain and discomfort.

Choice "B"

100%

HS - 1

- You had a life-threatening illness which has responded to treatment.
- You have undergone an operation which has left you with some unsightly scarring.
- You have lost some weight.
- You have a little difficulty in walking long distances.
- You are able to wash and dress yourself and do jobs around the home.
- You have no problems in your ability to shop and perform other daily activities.
- You are able to socialize with friends and family and never have to cut it short due to your illness.
- You have pain, but it does not interfere with activities listed above.
- You experience a little anxiety but you are pleased that you are responding to treatment.
- You feel a little worried about dying and how your loved ones will manage without you.
- You have a lot of energy most of the time.

In Choice "A" - You have a 100% chance of living in HS-01 for the rest of your life with a 0% chance of immediate death.

In Choice "B" - You have a 100% chance of being in HS-1 for the rest of your life.

Would you prefer Choice "A" or Choice "B" or are the two choices equal and you cannot decide?

Choice "A"                      Choice "B"                      Can't Decide

☐                                      ☐                                      ☐

**>>**

### Chapter III. Surgeons' Ratings of Health State Utilities Related to the Treatment of Soft Tissue Sarcoma

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Health state utilities; soft tissue sarcoma; quality of life; local control; surgeon decision-making

Running Title: Surgeon Health Statue Utilities in Sarcoma

### III.A Abstract

#### Background and Objectives

How a surgeon perceives the utility of health states related to lower extremity soft-tissue sarcoma (LE-STS) may influence their decision in choosing or recommending a particular surgical treatment strategy. This study estimates self-reported utilities from a surgeon's perspective for LE-STS health states and assesses whether they influence self-reported surgical treatment strategies.

#### Methods

Using an online survey software product, surgeons who treat LE-STS were surveyed about their demographics, post-graduate training, medical practice variation, surgical treatment strategies they employ, the clinical epidemiology of post-surgical STS, and their health state utilities (HSU) for LE-STS-related health states using an online standard gamble (SG) task. Additionally, a rating exercise using a visual analog scale (VAS) for the health state presented in the SG task was conducted to establish construct validity with the SG.

#### Results

Of the 43 surgeon participants (N=43/67, 64%) almost 50% completed the survey (N=21/43, 49%). The utility decrement between health states for functional loss due to LE-STS ranged between -0.20 (95% CI:-0.25, - 0.15) with an adequate margin and -0.26 (95% CI:-0.34, - 0.15) with an inadequate margin. For local recurrence, the utility decrement was -0.29 (95% CI:-0.42, -0.19). In valuing surgical strategy choices, surgeons expressed a willingness to accept a higher probability of loss of function ( $p=0.68$ , range: 0.18, 1.00), compared to a much lower probability of willingness to accept a local recurrence ( $p=0.28$ , range: 0.01, 1.00).

#### Conclusions

This study found that there is significant variation among surgeons in the ratings of LE-STs-related health states. Surgeons value acceptable function following surgery, implying that over a 10-year time horizon, a loss of function could decrease quality of life the equivalent of between 2.0 and 2.6 quality-adjusted life years (QALYs). However, while local recurrence is perceived by surgeons to have a larger disutility value, very few patients would remain in this health state for more than 1 year, which implies a lower QALY loss of about 0.29 for one year. In general, these surgeons favor local control and are more willing to accept a more substantial loss of physical function.

### III.B Background

In the context of the surgical excision of cancers, “local control” can be defined as the ability to cure cancer by “controlling” the primary (localized) tumor site.<sup>1</sup> Evidence indicates the best way to “cure” most cancer is to remove the entirety of the tumor—in other words, primary surgical excision. In the past, this has included mastectomy for breast cancer, lobectomy for lung cancer, and amputation for soft tissue sarcoma (STS) of the extremities.<sup>2,3</sup> However, as technology (imaging, pathology, and surgical techniques), chemotherapeutic options, and radiation therapy have improved, the surgical treatment for cancer has moved away from these functionally debilitating surgeries to tissue-conserving surgical procedures.<sup>4</sup> Limb-sparing surgery is then correspondingly considered functionally-improving and, thus, would be expected to result in an increase in patient quality of life (QoL). In moving primary surgical treatment to favor tissue-conserving techniques, a trade-off occurs: by preserving tissue that may contain microscopic or undetectable forms of the tumor, the probability of tumor recurrence increases and thus local control decreases.

The lower extremity (LE) STS literature contains several studies that report survival and hazard function statistics for tumor recurrence adjusted for the status of the surgical tumor margin.<sup>5-10</sup> For example, O’Donnell and colleagues found that those with unexpected positive margins have a 5-year local recurrence-free survival (LRFS) of 63.4% and a cause-specific survival (CSS) (i.e., deaths due to STS) of only 59.2%. Comparatively, those with negative margins, but whose procedure sacrificed critical structures had the highest LRFS at 91.2% ( $p=0.8$ ) and CSS 63.6% ( $p=.9$ ) at 5 years. However, resecting the critical structure in other patients did not statistically significantly improve LRFS and CSS (LRFS=85.4%, CSS=59.2%) when compared to those whose critical structure was preserved even with a planned close or



positive margin. These findings, while extremely helpful in illustrating the trade-off between function and margin, are difficult to interpret, especially when using them to counsel patients and surgeons in making informed, “shared decisions” without understanding the impact on patient QoL following the surgery.

Since all studies seem to agree negative margins are the most desirable and lead to the lowest risk of local recurrence, one might wonder why margin status is debatable.<sup>11</sup> The deliberation lies in the anatomic setting where these tumors arise and their impact on functional outcome and overall patient QoL. Because of the inherent nature of LE-STs, as the name suggests, these tumors often are found abutting critical skeletal and neurovascular structures.<sup>5, 11</sup> This can present surgeons with an clinical and ethical dilemma: (a) sacrifice these structures, which can lead to adverse functional status and QoL, in order to gain more confidence about removal of the tumor and thus a lower risk of local recurrence; or (b) leave these structures intact to improve function and QoL, but with a higher risk of tumor recurrence.<sup>12-14</sup> Even the National Comprehensive Cancer Network (NCCN) Guidelines for STS provide an equivocal reference as to what is an adequate margin.<sup>15</sup> The guidelines state that surgical resection should “resect the tumor with oncologically appropriate margins . . . and close margins may be necessary to preserve critical neurovascular structures, bones, joints, etc.” Other recommendations propose that margins should be >1.0 cm and should “minimize surgical morbidity” for certain STS subtypes.<sup>11</sup>

Because surgical margin definitions vary for what is “appropriate” or “adequate”, and because individual surgeons may apply these definitions differently, this results in practice variation among LE-STs surgeons. Some surgeons choose a surgical strategy that favors the functional aspect of QoL at the risk of increasing local recurrence, while others choose a

different surgical strategy that favors the mental or emotional aspect of QoL by reducing the risk of local recurrence and decreasing the worry that can be associated with tumor recurrence at the expense of decreasing function. Practice variation in margin definitions and margin status has been documented not only in the sarcoma literature, but in the breast cancer literature as well.<sup>11, 16, 17</sup> It is unclear what influences a surgeon to choose one surgical strategy over another. It has been suggested that surgeon specialty, age, years in practice, or post-graduate training may affect choices in the strategies approached for the treatment and follow-up of sarcoma patients.<sup>18-20</sup> Surgeons may believe that: 1) the additional benefit of a narrow margin surgery increases the function of the limb or QoL; 2) that the risk of local recurrence is not as high as the literature suggests for narrow margin surgery; or 3) that the patient, if adequately informed, might be willing to trade an increased risk of local recurrence for better function or QoL.<sup>11, 21</sup> Given these uncertainties from the surgical community regarding the best LE-STS surgical strategy, it is important to try to understand this practice variation from the surgeons' perspective to better understand what motivates the surgeon's choice of margin.

To better understand the role of surgeons' perceptions in influencing practice variations, it can be useful to measure their personal assessment of health state utilities (HSU) by presenting health state descriptions using preference elicitation methods such as time trade-off (TTO) or standard gamble (SG).<sup>22</sup> How a surgeon perceives the value of an LE-STS-related health state from their own perspective may influence their decision in choosing or recommending a particular surgical treatment strategy which can, in turn, influence a patient's decision about surgical treatment for STS. Therefore, this study aims to assess self-reported utilities from a surgeon's perspective for health states that are a result of LE-STS surgical treatment strategies. We hypothesized that surgeons' utility estimates for LE-STS-related health states would

influence their choice of surgical treatment strategy for LE-STS. As a secondary aim, we hypothesized that a surgeon's specialty training would influence their valuation of the LE-STS-related health states.

### III.C Materials and Methods

#### III.C.i Data Source

Through primary data collection using Qualtrics (Qualtrics, LLC, Provo, Utah), an online survey software product, surgeons who treat LE-STS were surveyed about their demographics, post-graduate training, medical practice variation, surgical treatment strategies they employ, the clinical epidemiology of post-surgical STS, and their HSU for LE STS-related health states using an online standard gamble (SG) task.<sup>23</sup> Additionally, a rating exercise using a visual analog scale (VAS) for the health state presented in the SG task was conducted to establish construct validity with the SG.<sup>24-27</sup> The sampled surgeons completed the VAS and performed 6 - 8 SG exercises to elicit their utilities for the health states described below.

In order to understand what surgeons' believe is the clinical epidemiology of post-surgical STS, we asked surgeons to provide answers for the transition probabilities for local recurrence and metastatic disease.<sup>28</sup> Surgeons' preferences for surgical treatment strategies were measured in two ways: 1) using questions about acceptable levels of local recurrence and physical function using a question similar to a VAS rating scale (see Appendix X), and 2) by self-reporting higher utilities for health states that have adequate margins, but lower function, versus those have inadequate margins, but higher function.

A convenience sample of LE-STS surgeons who are members of the Connective Tissue Oncology Society (CTOS) and/or the Musculoskeletal Tumor Society (MSTS) were recruited

and enrolled in this study via in-person recruitment at society meetings, and through newsletter and direct email announcements. Members were recruited at the 2014 CTOS Annual Meeting, the 2015 MSTS Specialty Day at the American Academy of Orthopaedic Surgeons (AAOS), and the 2015 International Society for Limb Salvage Surgery (ISOLS) and MSTS combined meeting. Only surgeons were eligible for statistical analysis (Figure 1) using STATA 13.1 (StataCorp, College Station, TX) for statistical analysis. Human subjects' consents and data collection were approved by the University of Washington Human Subjects Review Board and were presented online via the secure Qualtrics website.

### III.C.ii Health State Development

LE-STs health states were developed and modified using those already published in the literature. A review of the extant literature found six studies with existing health states for sarcoma patients. Of those six, two studies had a surgical perspective<sup>29, 30</sup>, and the remaining 4 were from an oncology perspective, of which three focused on advanced or metastatic STs.<sup>31-34</sup> Four of the studies used indirect multi-attribute utility instruments (MAUIs), such as EQ-5D<sup>TM</sup>, Health Utilities Index (HUI<sup>®</sup>), and SF-6D, to value health states and the remaining 2 studies used direct methods of SG and TTO for LE-STs-specific health states. Of the two direct LE-STs-specific health states, one was chosen as the reference health states for this study because the health states: 1) were closely paired with the SF-6D domains, 2) included specific physical function domains, and 3) were developed to encompass health states for both local and advanced LE-STs populations.<sup>33</sup> A "vitality" domain was added to the reference health state for future studies in mapping to the SF-6D.<sup>35, 36</sup> The health states had language that included walking and running long distances as it relates to the domain of physical function. This was important to

anchor surgeons that the focus was LE-STS where the trade-off between function and margin status can be difficult.

From the reference health states, sixteen health states were created to meet the objective of this study. There are five “main” health states: Disease-Free Survival (DFS), Alive with Disease (AWD), Local Recurrence (LR), Metastatic (MET), and Re-excision (REEX). Within the DFS, AWD, LR, MET and REEX state, attribute level was varied depending on original margin status (Adequate (AM) vs. Inadequate (IM)) following primary surgery and functional status (Acceptable (+A) vs. Adverse (-A)) pathways (published previously).

### III.C.iii Visual Analogue Scale (VAS) and Standard Gamble Scoring

Utility was measured three different ways in this study: 1) visual analogue scale (VAS), 2) standard gamble (SG), and 3) VAS-SG converted (VAS-SGc) utility measures. Standard gamble is the preferred method for eliciting health state values as it is based in expected utility theory.<sup>37</sup> By including the other two techniques, we can assess the validity of the standard gamble utility values. For the VAS, respondents used a slider bar to measure on a 0 – 100 scale the same health states valued in the SG. The VAS is useful for interpreting the rank order preference of the health states presented. Mean and median VAS ratings were then transformed to a 0.00 – 1.00 scale and then converted to VAS-SGc utility scores using power functions ( $u_{SG} = 1 - (1 - VAS)^x$ ) reported in prior studies as well as a power function calculated using the data in this study (Figure 2).<sup>38, 39</sup> The power function for this study when aggregated across all the mean VAS health state ratings was found to closely approximate the original function by Torrance et al. ( $u=1 - (1-V_{mean})^{1.6}$ ), with the best power estimate for this study found to be between 1.5 – 1.6 (Figure 2).<sup>39</sup>

SG tasks mimicked the use of the standard SG prop probability wheel by presenting “virtual health state cards”.<sup>37</sup> Participants were given training questions that forced a “rational” answer to make sure they understood the gaming task. The display and skip logic allowed for the “ping-pong” effect that aids in decreasing “anchor point bias”.<sup>24, 40</sup> For each set of SG tasks, one utility score was given. An additional test of reliability was given using chaining methods to see if the utility decrement was valued the same if the health state was anchored against something other than perfect health.<sup>41</sup> For example, the health state of adequate margin with adverse function (HS2 – DFS) was compared to the next worse health state – inadequate margin with acceptable function (HS3 – AWD) to understand if the utility decrement was consistent regardless of the anchor point. Code was written to score each set of SG questions to yield one utility score per task for each respondent, and then each utility score for a specified health state was averaged across those surgeons who performed the specified SG task for the health states they were presented. Utility decrements were calculated when surgeons responded to a set of SG exercises by which utility decrements for function, margin status, local recurrence, and re-excision could be calculated.

### III.C.iv Surgical Strategies and Probabilities

A series of questions were developed to measure a surgeons’ surgical strategies for treating LE-STs. Questions were also written to measure how surgeons synthesize the current literature as it relates to margin status and local control by asking them to provide transition probabilities for some specific health states. These questions can be found in the Appendix of this chapter (Figure 7). A clinical vignette that described the following scenario was presented in this set of questions to anchor surgeons to the treatment of a specific LE-STs:

For the next set of questions, we are asking you to mark your **acceptable level of the probability** for the following scenarios following primary surgical excision **with curative intent** during the coming year for a patient who is: 55 years old with a large (>10cm), deep, high-grade, lower extremity soft tissue sarcoma that may invade a critical structure (nerve, vessel, or bone).

Due to the extreme poles and clear split of the responses for the question of highest probability of local recurrence that one would be willing to accept, it seems highly likely that those in the upper tail (>40%) of respondents did not understand the question and meant the inverse of their response.(Figure 3a) Therefore, a sensitivity analysis was performed and the question was recoded such that anyone who responded with a probability of local recurrence willingness to accept >0.50, their response was recalculated to be the inverse. For example, if someone responded a probability of 0.80 willing to accept a local recurrence, their response was inverted to equal a probability of 0.20 ( $1.0 - 0.80$ ). In doing so, the willingness to accept local recurrence was distributed more normally.(Figure 3b). The values for the willingness to accept functional loss were distributed normally, so no transformation was performed.(Figure 3).

### III.C.v Analysis

A descriptive analysis was used to summarize the elicited HSU values. For surgeon demographic variables that were continuous Student's two sample t-test were used and where categorical, Chi-square tests and Fisher's Exact tests (where cell counts were low) were used to compare differences between surgical specialty groups. Due to the large variation in the data where means were reported, the coefficient of variation was also calculated ( $=SD/mean*100\%$ ). Because of the data variability and low sample size we choose to focus the primary analysis using the median values of the VAS-SGc utilities where sample size was higher and we could better measure central tendency. To best assess surgeons self-reported utilities for LE-STS health states, the median utility decrement (i.e., the median of the differences between two health

states) was the primary measure of interest. To calculate the median utility decrement, the *somersd* and *cendif* commands in STATA were used to run pairwise median difference tests between the health states (Table 2) and to calculate confidence intervals for the median differences between the two paired health states being tested. A descriptive sub-analysis is also presented that compares HSU values between the two surgical specialties. Using the VAS-SGc utility values, a logistic regression model with the STATA *margins* command to calculate predicted probabilities was performed to understand if the surgeon utilities for the health states of local recurrence and adequate margin with adverse function predicted how much a surgeon favored local control (using the recoded local control values from the sensitivity analysis). Results were analyzed using STATA 11.0 (STATA Corp. College Station, TX)

### III.D Results

It was found that the results did not vary statistically significantly between the raw VAS values, SG utilities, and the VAS-SGc utilities: therefore, due the advantage of producing a larger sample size, the VAS-SGc utilities values were the primary measures for analysis.

#### III.D.i Surgeon Demographics

There were 67 total survey participants, of whom 43 were surgeons (N=43/67, 64%), and almost 50% completed the survey (N=21/43, 49%). Almost two-thirds (65%) identified as orthopaedic oncology surgeons (n=28) and the remaining were trained through general surgery (n=15). The majority of surgeons were male (N=32/43, 78%) and one-third (N=14/38, 37%) of the cohort originating from countries outside of North America. There was a statistically significant difference ( $p=0.001$ ) between surgical specialties and their country of origin with the majority of orthopaedic oncologists (83%) coming from North America compared with the



majority of surgical oncologists coming from countries outside the United States and Canada. The majority (N=22/41, 54%) reported their own health on a 5-point Likert scale as “Excellent”, followed by almost a third (N=13/41, 32%) of surgeons reporting “Very Good”, with the remaining reporting “Good” or “Fair”. No surgeon reported having “Poor” overall health. When asked about their health at the time of the survey using a VAS Rating Scale, surgeons on average reported having a mean health of 86.1 (sd=9.5) out of 100 point scale. This was not statistically different between groups. The majority of surgeons (81%) reported receiving fellowship or post-graduate training for sarcoma surgery, but this was statistically different when comparing orthopaedic oncology and surgical oncology surgeons ( $p=0.008$ ). With the majority of orthopaedic surgeons doing post-graduate or fellowship training (93%), compared to only 60% of general surgeons receiving dedicated post-graduate sarcoma training (Table 1).

#### III.D.ii Practice Description

There was no statistical difference in years of practice between surgical groups with the mean years in practice approaching 14 years (Table 1). The majority of surgeons from both specialties practiced in an academic setting. The majority of surgeons (49%) perform < 50 sarcoma cases annually, and 60% of the surgical oncologists, compared to 47% of orthopaedic oncologists performed >50 cases annually. As described above practice location reflected similar results to the surgeons county of origin with the majority (96%) of orthopaedic oncologists who participated in the survey practicing in North America and two-thirds (67%) of surgical oncologists practicing mostly in Europe ( $p<0.001$ ).

### III.D.iii Health State Utilities and Disutilities

The following reported utility values are all median values unless otherwise stated. The utility decrement between health states for functional loss due to lower LE-STS was statistically significantly different ( $p<0.01$ ) between an acceptable function health state and an adverse function health state when pairwise comparisons were made, regardless of margin status. These utility decrements ranged between -0.20 (95% CI:-0.25, - 0.15) with an adequate margin and - 0.26 (95% CI:-0.34, -0.15) with an inadequate margin. There was no statistically significant difference when comparing the utility decrement between an adequate margin health state and an inadequate margin health state, and this held true independent of functional status. The re-excision health state had the lowest statistically significant utility decrement of -0.08 (95% CI: - 0.13, -0.01). For local recurrence, the utility decrement was the highest (or worst health state) at -0.29 (95% CI:-0.42, -0.19). For the chained SG of HS3 versus HS2, the utility decrement was very similar to the functional utility decrement (+0.20, 95% CI: 0.15, 0.27,  $p<0.01$ ). The mean and median values for each health state across all elicitation methods can be found in Table 6 and the Appendix for Chapter III, Table 7.

### III.D.iv Surgical Strategies

In valuing surgical strategy choices, surgeons were willing to accept a larger probability of loss of function ( $p=0.68$ , range: 0.18, 1.00) (Appendix for Chapter 3, Question Q23), compared to a much lower probability of willingness to accept a local recurrence ( $p=0.28$ , range: 0.01, 1.00) (Appendix X, Question Q21). Eight surgeons were directly able to evaluate the trade-off between preferring a local control surgical strategy=0.0 (i.e., low risk of local recurrence) versus preferring a functional preservation surgical strategy=1.0 (higher risk of local

recurrence). When having to weigh directly between the two surgical strategies, the probability of willingness to accept a local recurrence was lower  $p=0.14$  (range: 0.05, 0.61), than when the willingness to accept a local recurrence was weighed on a scale from 0 – 1.0 as previously described (Appendix X, Question 24).

The distribution of responses for the willingness to accept a local recurrence was distinctly bimodal (Figure 3a), and accordingly a sensitivity analysis was performed as described in the methods. When adjusted the responses for local recurrence followed a more normal distribution. For functional loss the responses remained normally distributed in both the unadjusted and adjusted analysis (Figure 4). When sensitivity methods were used, the willingness to accept a local recurrence fell to  $p=0.10$  (range: 0 – 0.28) and the in the sensitivity analysis based on the recoded values, the relationship that surgeons valued a larger probability of loss of function and a lower probability of local recurrence remained the same.

A plot of the predicted probabilities ( $N=13$ ) demonstrated that the higher a surgeon valued the local recurrence health state (HS16) the lower their predicted probability of favoring a local control surgical strategy (Figure 5). For example, if a surgeon valued  $HS\ 16 = 0.80$  then their predicted probability of favoring a local control was only 36% (95% CI: -1.20, 1.93). However, if the value for HS 16 was lower, (e.g.,  $HS16=0.20$ ), then the predicted probability of favoring local control was very high—97% (95% CI: 0.86, 1.08). The inverse was true for the adequate margin, adverse function health state (HS2). If a surgeon valued  $HS2 = 0.80$  then their predicted probability of favoring a local control surgical strategy was higher at 95% (95% CI: 0.80, 1.09), but if the health state was valued low,  $HS2 = 0.20$ , then the predicted probability of favoring a local control strategy was lower a 76% (95% CI: -0.26, 1.78). The relationship for functional loss also demonstrated that surgeons who valued the adverse function health state

higher had a higher probability of favoring a surgical strategy of favoring functional loss. However, if the surgeons valued the acceptable function health state higher, then their predicted probability of favoring a surgical strategy of functional loss was lower (Figure 6).

#### III.D.v Surgical Specialty

For all health states, surgical oncologists rated the health states higher than did the orthopaedic oncologists. However, this was only statistically significant when comparing the median health state difference for local recurrence between orthopaedic (N=10) and surgical oncologists (N=4), respectively (-0.24, 95% CI: -0.39, -0.08,  $p<0.01$ ), although one should be careful in the interpretation of this finding given the small sample (Table 4). This was also the worst health state as valued by both surgeon groups. The highest utility health state for surgical oncologists was the acceptable function state regardless of margin status (HS1=0.92 and HS3=0.94), but for the orthopaedic oncologists, the inadequate margin, acceptable function health state was slightly higher than the adequate margin, acceptable function health state (HS3=0.87 and HS1= 0.85, respectively) (Table 4).

For surgical strategy, surgical oncologists had a higher probability of accepting a local recurrence than compared to their orthopaedic colleagues, but this was not statistically significantly different. The reverse was true for function, where orthopaedic oncologists were more willing to accept a functional loss compared to surgical oncologists (Table 5). The only statistically significant difference in surgical strategy between the two surgical specialties was the probability of metastatic disease after re-excision of a local recurrence ( $p<0.05$ ): orthopaedic oncologists reported that the median probability of metastatic disease following local recurrence was higher,  $p=0.45$  (range: 0.28 -1.00), compared to the value given by surgical oncologists,  $p=0.35$  (range: 0.22 – 0.51). The median difference was -0.09 (95% CI: -0.19, 0.0) (Table 5).

### III.E Discussion

#### III.E.i Health State Utilities

The utility decrements for both functional loss and local recurrence demonstrate a 6- to 10-fold meaningful change as experts have agreed that anything  $\geq 0.03$  signifies a meaningful change. Even at higher thresholds reported in other studies, where the minimal clinically important difference (MCID) for MAUIs has ranged from 0.01 – 0.075 this would still be a 2.5- to an almost 4-fold MCID, demonstrating that the health state of functional loss and local recurrence can impact quality of life significantly.<sup>42-44</sup>

Compared to other valuations in the literature, these utility decrements are similar or even worse in some cases for LE-STIS patients experiencing severe pain following surgery ( $u_{\bar{x}} = 0.24$ ), dyspnea requiring help with activities of daily living ( $u_{\bar{x}} = 0.24$ ), and extreme fatigue ( $u_{\bar{x}} = 0.26$ ).<sup>33</sup> Naturally, following an LE-STIS surgery that might result in functional loss, a patient could also experience severe pain. Therefore, is it possible that the summed utility decrement (if the decrements are additive--adverse function surgery at 0.20 to 0.26 plus severe pain at 0.24) could be significantly greater ( $\sim 0.50$ ) than the utility decrement of experiencing a local recurrence (0.30).<sup>45</sup> It is also important to note the time spent in a functional loss health state is permanent compared to a local recurrence health state which in most cases is transient. As this study found a loss of function can decrease quality of life between 0.20 and 0.26 and with a 71.5% survival rate at 10 years this means patients might lose the equivalent of 2.0 to 2.6 QALYs due to adverse function – obviously a very substantial loss. While a local recurrence has a higher utility decrement of 0.29, this only has 0.29 QALY since the majority of patients have their local recurrence re-excised within 4 months.<sup>46, 47</sup> However, if re-excision results in adverse function, then the permanent loss could again be substantial.

Another interesting finding of this study is the idea that an inadequate margin early on does not yield a poor HSU: in fact, in most scenarios when compared to other health states, it leads to a utility increase when compared to an adequate margin with adverse functional outcome health state. While the utility increase of margin status was not statistically significant when compared with functional base comparisons, it was significant when directly compared to the trade-off of an adequate margin with adverse function, but in an unexpected direction where an inadequate margin with acceptable function was the higher utility health state ( $p < 0.01$ ) (Table 5). This is surprising because the utility decrements for a local recurrence (-0.29) and re-excision (-0.08) are significantly higher, and these health states might be thought to be a result of an inadequate margin, in most cases.

An adequate margin surgery with adverse function was valued by surgeons at a median HSU= 0.57. If a patient has an inadequate surgery with acceptable function, their health state was valued much higher by surgeons at 0.83 (Table 6). Then, if this same patient goes on to have a local recurrence in the same year, their health state drops to 0.54 (0.83-0.30) and factoring in re-excision (-0.08, 95% CI: -0.13, -0.01)), this patient now has a HSU= 0.46. Finally, in this same patient, adding in functional loss as a result of the re-excision taking more tissue (-0.20 to 0.26), by the end of the year the patient could very well end up in a health state valued between 0.19 and 0.25. In one year, the inadequate margin with acceptable function patient goes from HSU= 0.83 to HSU= 0.19 – 0.25, while the adequate margin with adverse function patient remains at 0.57 health state valuation for the remainder of their life. This is not to say that all adequate margin with adverse function patients will never experience a local recurrence or re-excision, but the probability of this occurring is much lower in this health state than in the inadequate margin health state. As further confirmation of the validity of these results, the result

when directly eliciting the health state value for an inadequate margin with adverse function and a local recurrence health state (HS 16), the median differential VAS-SG HSU value was 0.26 (range: 0.17 – 0.43) (Table 6), which is comparable to our previously calculated example of HSU = 0.19 – 0.25 when using the utility decrements.

### III.E.ii Surgical Strategies

The better way to measure a surgeon's general surgical strategy choice would be to review their last 100 cases, adjusting for case mix difference, and determine through pathology specimens and operative reports what "type" of surgeon they were, i.e., function-preserving at the expense of margin adequacy or local control oriented at the expense of functional loss. Since this was not feasible for this study, we chose to measure surgical strategy using a series of questions to elicit from surgeons (i.e., by self-report) what type of strategy they generally favor. We did this in three ways, and the questions are listed in Appendix X. It was found that, overall, surgeons had a higher threshold or probability of accepting a functional loss surgical strategy compared to the willingness to accept a local recurrence surgical strategy. However, while not conclusive, we found a predictive association that may support that how a surgeon values a health state influences their treatment strategy. If a surgeon valued the local recurrence health state low (HSU < 0.30), they had a higher predicted probability ( $p > 90\%$ ) of favoring local control, meaning favoring a treatment strategy that would reduce the risk of local recurrence. For those surgeons who valued the adequate margin with adverse function health state higher (HSU > 0.80), they had a higher predicted probability ( $p > 90\%$ ) of favoring local control, meaning they were more willing to accept a treatment strategy that left the patient with functional loss at the expense of an adequate margin. These findings suggest that a surgeon's valuation of these health states may influence their treatment strategy for LE-STs.

As found in a previous study, surgeons are not reliable sources for transition probabilities.<sup>28</sup>

Surgeons in this study stated that the median transition probability of a local recurrence following a primary excision of LE-STs with an adequate margin was 0.11 (range: 0 – 0.97) and for an inadequate margin it was 0.55 (range: 0.13 – 1.00). There is significant variability in these values, while there is considerable evidence in the literature that at 10 years the probability of having a local recurrence is ~ 10% for an adequate margin. For an inadequate margin, the probability of a local recurrence ranges from 30% - 41% at 10 years, which is considerably less than estimate here of 55%.<sup>5</sup> The only time a local recurrence probability is close to 55% is at > 5 years if the patient had unexpected inadequate margins.

While estimates of the correlation between local recurrence and subsequent metastatic disease have not been well established, surgeons in this study rated the probability of metastatic disease following a re-excised local recurrence to have a median transition probability of 40% (range 22% - 100%); and with no re-excision of the local recurrence, the median probability of metastatic disease rose to 61% (range: 31% - 100%). One study found that those with a prior local recurrence were 8.6 (95% CI: 3.87 – 19.04) more likely to develop metastatic disease.<sup>48</sup> This same study also suggested that having a re-excision led to worse outcomes, but surgeons in this analysis reported the opposite, that a re-excision of a local recurrence decreased the probability of metastatic disease.

### III.E.iii Surgical Specialty

Surgical training influences variations not only in health state valuations, but also in treatment strategy. Surgical oncologists and orthopaedic oncologists differed on their views about local recurrence and the trade-off with functional loss. This could be due in part to the



different types of STSs that these two surgical specialties typically treat. While both surgical specialties were similar in their personal decisions about willingness to accept a local recurrence and a loss of physical function, they differed in the valuations when presented with health states that reflect trade-offs that result for these treatment decisions. In all cases, surgical oncologists valued the health states over average about 25% higher than did the orthopaedic oncologists, and in one case—for local recurrence—this difference was statistically different and clinically meaningful. While both specialties agree that local recurrence is a poor health state, the finding that they differ so significantly in their utility valuation of this health state suggests that initial treatment of LE-STs in terms of margin status is likely to be influenced by what type of surgeon one sees for the initial primary excision. These findings may suggest that surgical oncologists, compared to orthopaedic surgeons, may be more willing to accept a higher local recurrence probability at the expense of preserving functional outcomes. One reason for this might be that many STS treated by surgical oncologists, are not LE-STs, but are adjacent to or involve critical structures such as organs or vessels such as the vena cava where sacrifice is not an option due to loss of life. In this scenario, surgical oncologists are more willing to accept local recurrence because “functional” loss is not a realistic option.

Most studies in the literature that have reported utility values for STS health states have focused on advanced stage sarcoma and were developed with input and perspective from an chemotherapeutic perspective. Even for the one study that described their health state vignettes, the physical function domain of the health state was related to chemotherapy and the side effects of chemotherapy, but did not necessarily address function as it relates to the surgical treatment of sarcoma. Arguably, the first line of treatment for soft tissue sarcoma is primary surgical removal of the tumor so when developing health states for this disease, the influence of surgical treatment

should be accounted for in the health state vignette being valued. This study aimed to not only address this gap in the literature, but also to understand the surgeon's valuation of these health states. Surgical treatment decision-making for the patient in most situations is highly influenced by the surgeon's perspective about the treatment they are offering as is demonstrated in this study.

As with any study, there are limitations to the analysis and results. The first and most notably is the small sample size. Conducting a standard gamble online was difficult, and it was assumed a well-educated population would better understand probabilities and use the standard gamble method. While training questions were put in place to help explain the standard gamble exercise, there remains some question as to whether the task was well understood: this resulted in the analysis making assumptions that required transformation of the raw data. It is recommended in future studies to limit the number of standard gamble scenarios to 4 – 6 exercises. As seen in Tables 6 and 7, there was participant drop-off from completing the VAS rating scale and then proceeding to the eight standard gamble exercises. While this study a small sample, it is interesting and important to note that all the utility decrements reported in this study reached the MCID threshold and signify that there is clinically meaningful difference between an adequate margin and inadequate margin (for most health states) and between acceptable and adverse function, as well as between having a local recurrence and a re-excision of a local recurrence. Those conducting future studies of patients with STS taking a societal perspective for resource allocation of treatments should aim to capture these important trade-offs in QoL for this patient population.

### III.F Conclusions

This study aimed to provide understanding of how surgeons' value STS health states and understand their opinions and evidence synthesis of the literature about the tradeoff of local control versus physical function in the treatment of STS. The results generally support our hypothesis that surgeons' utility for LE-STs-related health states would influence their choice of surgical treatment strategy for STS. It further demonstrates the need for those conducting cost-effectiveness analysis in the field of surgery to consider not only the standard societal perspective, but to consider—at least in understanding real-world outcomes--the surgeon's perspective, as they have the ability to influence how surgical treatment is allocated directly or indirectly through how they counsel the patient. The findings in this study have implications for clinical decision-making and support the idea of the informed decision-making model when there is equipoise for surgical treatment.<sup>49</sup>

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### III.H Tables

Table 1. Surgeon Demographics, Training and Practice Characteristics

|                                                           | <b>Total<br/>(n=43)</b> |      | <b>Surgical Oncology<br/>(n=15)</b> |      | <b>Orthopaedic Oncology<br/>(n=28)</b> |      | <b>p-value</b> |
|-----------------------------------------------------------|-------------------------|------|-------------------------------------|------|----------------------------------------|------|----------------|
| <b>Surgeon Demographics</b>                               | Mean/n                  | SD/% | Mean/n                              | SD/% | Mean/n                                 | SD/% |                |
| Age (n=39)                                                | 45.1                    | 8.9  | 43.7                                | 10.0 | 46.0 (n=24)                            | 8.3  | 0.44           |
| Gender (n=41)                                             |                         |      | n=15                                |      | n=26                                   |      | 0.31           |
| <i>Male</i>                                               | 32                      | 78%  | 11                                  | 73%  | 21                                     | 81%  |                |
| <i>Female</i>                                             | 9                       | 22%  | 4                                   | 27%  | 5                                      | 19%  |                |
| Country of Origin (n=38)                                  |                         |      | n=14                                |      | n=24                                   |      | < 0.01         |
| <i>Canada &amp; United States</i>                         | 24                      | 63%  | 4                                   | 29%  | 20                                     | 83%  |                |
| <i>Other Countries</i>                                    | 14                      | 37%  | 10                                  | 71%  | 4                                      | 17%  |                |
| Overall Health (n=41)                                     |                         |      | n=15                                |      | n=26                                   |      | 0.55           |
| <i>Excellent</i>                                          | 22                      | 54%  | 10                                  | 67%  | 12                                     | 46%  |                |
| <i>Very Good</i>                                          | 13                      | 32%  | 4                                   | 27%  | 9                                      | 35%  |                |
| <i>Good</i>                                               | 5                       | 12%  | 1                                   | 7%   | 4                                      | 15%  |                |
| <i>Fair</i>                                               | 1                       | 2%   |                                     |      | 1                                      | 4%   |                |
|                                                           |                         |      | n=14                                |      | n=25                                   |      |                |
| Health at Time of Survey<br>(VAS Rating) (n=39)           | 86.1                    | 9.5  | 85.3                                | 8.5  | 86.6                                   | 10.2 | 0.67           |
| Dedicated Sarcoma<br>Fellowship/Post-Graduate<br>Training |                         |      |                                     |      |                                        |      | < 0.01         |
| <i>Yes</i>                                                | 35                      | 81%  | 9                                   | 60%  | 26                                     | 93%  |                |
| <i>No</i>                                                 | 8                       | 19%  | 6                                   | 40%  | 2                                      | 71%  |                |
| <b>Practice Description</b>                               |                         |      |                                     |      |                                        |      |                |
|                                                           |                         |      | n=14                                |      | n=25                                   |      |                |
| Practice Years (n=39)                                     | 13.9                    | 8.6  | 15.5                                | 9.5  | 13.0                                   | 8.1  | 0.42           |
| Practice Type (n=43)                                      |                         |      | n=15                                |      | n=28                                   |      | 0.58           |
| <i>Medical School/University</i>                          | 24                      | 56%  | 7                                   | 47%  | 17                                     | 61%  |                |
| <i>Hospital</i>                                           | 13                      | 30%  | 6                                   | 40%  | 7                                      | 25%  |                |
| <i>Other</i>                                              | 6                       | 14%  | 2                                   | 13%  | 4                                      | 14%  |                |
| Practice Location (n=33)                                  |                         |      | n=9                                 |      | n=24                                   |      | < 0.01         |
| <i>Canada &amp; United States</i>                         | 26                      | 79%  | 3                                   | 33%  | 23                                     | 96%  |                |
| <i>Other Countries</i>                                    | 7                       | 21%  | 6                                   | 67%  | 1                                      | 4%   |                |
| Sarcoma Case Volume per<br>Average Year (n=43)            |                         |      | n=15                                |      | n=28                                   |      | 0.12           |
| <25                                                       | 7                       | 16%  | 4                                   | 27%  | 3                                      | 11%  |                |
| 25 - 50                                                   | 14                      | 33%  | 2                                   | 13%  | 12                                     | 43%  |                |
| 50 - 100                                                  | 11                      | 26%  | 3                                   | 20%  | 8                                      | 29%  |                |
| >100                                                      | 11                      | 26%  | 6                                   | 40%  | 5                                      | 18%  |                |

Table 2. Median Utility Values Directly Elicited from All Surgeons for Health States

| Health State                                                                                     | HS #  | <i>Visual Analogue Scale<br/>converted to Standard<br/>Gamble*</i> |        |             | <i>Standard Gamble</i> |        |             | <i>VAS</i> |        |          |
|--------------------------------------------------------------------------------------------------|-------|--------------------------------------------------------------------|--------|-------------|------------------------|--------|-------------|------------|--------|----------|
|                                                                                                  |       | N                                                                  | Median | Range       | N                      | Median | Range       | N          | Median | Range    |
| <b>Adequate Margin + Function (DFS)</b>                                                          | 1     | 27                                                                 | 0.81   | 0.14 – 0.93 | 17                     | 0.85   | 0.35 – 0.95 | 27         | 75.0   | 24 – 100 |
| <b>Adequate Margin – Function (DFS)</b>                                                          | 2     | 29                                                                 | 0.57   | 0.23 – 0.77 | 18                     | 0.67   | 0.05 – 1.00 | 29         | 50.3   | 0 – 87   |
| <b>Inadequate Margin + Function (AWD)</b>                                                        | 3     | 29                                                                 | 0.83   | 0.15 – 0.93 | 17                     | 0.85   | 0.45 – 1.00 | 29         | 76.9   | 24 – 97  |
| <b>Inadequate Margin – Function (AWD)</b>                                                        | 4     | 17                                                                 | 0.55   | 0.20 – 0.76 | 9                      | 0.65   | 0.05 – 0.85 | 17         | 44.3   | 1.7 – 82 |
| <b>Adequate Margin – Function &amp;<br/>Excised Local Recurrence (REEX)</b>                      | 10    | 26                                                                 | 0.37   | 0.27 – 0.76 | 16                     | 0.77   | 0.05 – 1.00 | 26         | 42.3   | 2.7 – 73 |
| <b>Inadequate Margin - Function &amp; Local<br/>Recurrence (LR)</b>                              | 16    | 14                                                                 | 0.26   | 0.17 – 0.43 | 9                      | 0.30   | 0.05 – 0.85 | 14         | 22.1   | 0 – 41   |
| <b>Inadequate Margin + Function<br/>(anchored to Adequate Margin -<br/>Function) (AWD v DFS)</b> | 2 v 3 |                                                                    | -      | -           | 11                     | 0.25   | 0.05 – 1.00 | -          |        |          |

\*using Torrance, 1986, 1982; +=*Acceptable Function*; - =*Adverse Function*; DFS = Disease Free Survival; AWD=Alive with Disease; REEX=Re-excision; LR=Local Recurrence



Table 3. Median Utility Decrement from Varied Base Comparisons (VAS- converted SG utilities)

| Health State Under Evaluation                      | Base Comparison                      | Clinical Health State Descriptions | Health State Comparison | Median Utility Decrement |                   |                 |
|----------------------------------------------------|--------------------------------------|------------------------------------|-------------------------|--------------------------|-------------------|-----------------|
| Function                                           |                                      |                                    |                         | N                        | Median Difference | 95% CI          |
| <i>Acceptable Function v Adverse Function</i>      | Adequate Margin                      | DFS                                | HS 1 v HS 2             | 30                       | -0.20             | -0.25 , -0.15** |
| <i>Acceptable Function v Adverse Function</i>      | Inadequate Margin                    | AWD                                | HS 3 v HS 4             | 29                       | -0.26             | -0.34 , -0.15** |
| <b>Margin</b>                                      |                                      |                                    |                         |                          |                   |                 |
| <i>Adequate Margin v Inadequate Margin</i>         | Acceptable Function                  | DFS (HS 1)<br>AWD (HS 3)           | HS 1 v HS 3             | 30                       | +0.004            | -0.03 , +0.04   |
| <i>Adequate Margin v Inadequate Margin</i>         | Adverse Function                     | DFS (HS 2)<br>AWD (HS 4)           | HS 2 v HS 4             | 29                       | -0.04             | -0.12 , +0.05   |
| <b>Re-excision</b>                                 | Adequate Margin & Adverse Function   | REEX                               | HS 2 v HS 10            | 29                       | -0.08             | -0.13 , -0.01*  |
| <b>Local Recurrence</b>                            | Inadequate Margin & Adverse Function | LR                                 | HS 4 v HS 16            | 17                       | -0.29             | -0.42 , -0.19** |
| <b>Inadequate Margin &amp; Acceptable Function</b> | Adequate Margin & Adverse Function   | AWD (HS 3)<br>DFS (HS 2)           | HS 3 v HS 2             | 29                       | +0.20             | 0.15 , 0.27**   |

\*p<0.05; \*\*p<0.01; DFS = Disease Free Survival; AWD=Alive With Disease; REEX=Re-excision; LR=Local Recurrence

Table 4. Surgical Strategy for Lower Extremity Soft Tissue Sarcoma

|                                                              | <b>Total</b> |               |              |             |           |           |
|--------------------------------------------------------------|--------------|---------------|--------------|-------------|-----------|-----------|
|                                                              | <i>N</i>     | <i>Median</i> | <i>Range</i> | <i>Mean</i> | <i>SD</i> | <i>CV</i> |
| <b>Personal Opinion</b>                                      |              |               |              |             |           |           |
| Probability of Local Recurrence Willing to Accept            | 35           | 0.28          | 0.01 – 1.00  | 0.49        | 0.39      | 80%       |
| Probability of Loss of Physical Function Willing to Accept   | 35           | 0.68          | 0.18 – 1.00  | 0.60        | 0.26      | 43%       |
| Trade-off Between Local Recurrence and Function              | 8            | 0.14          | 0.05 – 0.61  | 0.22        | 0.19      | 87%       |
| <b>Evidence Synthesis</b>                                    |              |               |              |             |           |           |
| Probability of a Local Recurrence Following Primary Excision |              |               |              |             |           |           |
| <i>with an adequate margin</i>                               | 34           | 0.11          | 0 – 0.97     | 0.22        | 0.25      | 114%      |
| <i>with an inadequate margin</i>                             | 34           | 0.55          | 0.13 – 1.00  | 0.54        | 0.28      | 52%       |
| Probability of Metastatic Disease Following Local Recurrence |              |               |              |             |           |           |
| <i>after re-excision</i>                                     | 34           | 0.40          | 0.22 – 1.00  | 0.44        | 0.17      | 39%       |
| <i>after NO re-excision</i>                                  | 34           | 0.61          | 0.31 – 1.00  | 0.64        | 0.23      | 36%       |

**\*\*CV=coefficient of variation (=SD/mean\*100%)**

Table 5. VAS-SG Converted Utility Values by Surgical Specialty

| Health State                                                         | Surgical Oncology |        |             |      |       |     | Orthopaedic Oncology |        |              |      |      |     |
|----------------------------------------------------------------------|-------------------|--------|-------------|------|-------|-----|----------------------|--------|--------------|------|------|-----|
|                                                                      | N                 | Median | Range       | Mean | SD    | CV  | N                    | Median | Range        | Mean | SD   | CV  |
| <b>Adequate Margin + Function (HS 1)</b>                             | 11                | 0.92   | 0.72 – 1.00 | 0.91 | 0.082 | 9%  | 16                   | 0.85   | 0.36 – 0.98  | 0.82 | 0.16 | 20% |
| <b>Adequate Margin – Function (HS 2)</b>                             | 10                | 0.74   | 0.30 – 0.96 | 0.68 | 0.182 | 27% | 19                   | 0.64   | 0 – 0.89     | 0.60 | 0.25 | 41% |
| <b>Inadequate Margin + Function (HS 3)</b>                           | 10                | 0.94   | 0.68 – 1.00 | 0.91 | 0.098 | 11% | 19                   | 0.87   | 0.35 – 1.00  | 0.83 | 0.16 | 20% |
| <b>Inadequate Margin – Function (HS 4)</b>                           | 4                 | 0.67   | 0.56 – 0.94 | 0.71 | 0.180 | 25% | 13                   | 0.61   | 0.027 – 0.85 | 0.59 | 0.21 | 35% |
| <b>Adequate Margin – Function + Excised Local Recurrence (HS 10)</b> | 10                | 0.68   | 0.07 – 0.88 | 0.64 | 0.236 | 37% | 16                   | 0.53   | 0.04 – 0.82  | 0.47 | 0.27 | 58% |
| <b>Inadequate Margin - Function + Local Recurrence (HS 16)</b>       | 4                 | 0.51   | 0.37 – 0.56 | 0.49 | 0.091 | 19% | 10                   | 0.29   | 0 – 0.43*    | 0.25 | 0.15 | 58% |

\*CV=coefficient of variation ( $=SD/mean*100\%$ ), +=Acceptable Function, - =Adverse Function; \* $p<0.01$  for median difference

Table 6. Surgical Strategy for Lower Extremity Soft Tissue Sarcoma by Surgical Specialty

|                                                              | Surgical Oncology |               |              |             |           |           | Orthopaedic Oncology |               |              |             |           |           |
|--------------------------------------------------------------|-------------------|---------------|--------------|-------------|-----------|-----------|----------------------|---------------|--------------|-------------|-----------|-----------|
|                                                              | <i>N</i>          | <i>Median</i> | <i>Range</i> | <i>Mean</i> | <i>SD</i> | <i>CV</i> | <i>N</i>             | <i>Median</i> | <i>Range</i> | <i>Mean</i> | <i>SD</i> | <i>CV</i> |
| <b>Personal Opinion</b>                                      |                   |               |              |             |           |           |                      |               |              |             |           |           |
| Probability of Local Recurrence Willing to Accept            | 14                | 0.80          | 0.08 -0.96   | 0.65        | 0.35      | 54%       | 21                   | 0.15          | 0.007 – 1.00 | 0.38        | 0.39      | 103%      |
| Probability of Loss of Physical Function Willing to Accept   | 14                | 0.70          | 0.18 – 0.91  | 0.63        | 0.26      | 41%       | 21                   | 0.51          | 0.19 – 1.00  | 0.57        | 0.26      | 46%       |
| Trade-off Between Local Recurrence and Function              | 1                 | -             | -            | 20.0        | -         |           | 7                    | 0.09          | 0.05 – 0.61  | 21.7        | 20.1      | 93%       |
| <b>Evidence Synthesis</b>                                    |                   |               |              |             |           |           |                      |               |              |             |           |           |
| Probability of a Local Recurrence Following Primary Excision |                   |               |              |             |           |           |                      |               |              |             |           |           |
| <i>with an adequate margin</i>                               | 13                | 0.15          | 0.03 – 0.97  | 0.28        | 0.30      | 107%      | 21                   | 0.10          | 0 – 0.93     | 0.18        | 0.22      | 122%      |
| <i>with an inadequate margin</i>                             | 13                | 0.51          | 0.14 – 0.99  | 0.54        | 0.27      | 50%       | 21                   | 0.60          | 0.13 – 1.00  | 0.54        | 0.29      | 54%       |
| Probability of Metastatic Disease Following Local Recurrence |                   |               |              |             |           |           |                      |               |              |             |           |           |
| <i>after re-excision</i>                                     | 13                | 0.35          | 0.22 – 0.51  | 0.36        | 0.10      | 28%       | 21                   | 0.45          | 0.28 – 1.00* | 0.49        | 0.19      | 39%       |
| <i>after NO re-excision</i>                                  | 13                | 0.50          | 0.31 – 1.00  | 0.54        | 0.19      | 35%       | 21                   | 0.71          | 0.36 – 1.00  | 0.70        | 0.23      | 33%       |

\* $p < 0.05$  for median difference, \*\*CV=coefficient of variation (=SD/mean\*100%)

# APPENDIX

Table 7. Mean Utility Values Directly Elicited from All Surgeons for Health States

| Health State                                                                      | HS #  | Visual Analogue Scale<br>converted to Standard<br>Gamble* |      |      |     | Standard Gamble |      |      |     | VAS |      |      |     |
|-----------------------------------------------------------------------------------|-------|-----------------------------------------------------------|------|------|-----|-----------------|------|------|-----|-----|------|------|-----|
|                                                                                   |       | N                                                         | Mean | SD   | CV  | N               | Mean | SD   | CV  | N   | Mean | SD   | CV  |
| Adequate Margin + Function (DFS)                                                  | 1     | 27                                                        | 0.86 | 0.14 | 16% | 17              | 0.82 | 0.17 | 20% | 27  | 0.73 | 0.17 | 23% |
| Adequate Margin – Function (DFS)                                                  | 2     | 29                                                        | 0.63 | 0.23 | 36% | 18              | 0.66 | 0.30 | 45% | 29  | 0.48 | 0.20 | 41% |
| Inadequate Margin + Function (AWD)                                                | 3     | 29                                                        | 0.86 | 0.15 | 17% | 17              | 0.84 | 0.14 | 16% | 29  | 0.73 | 0.17 | 23% |
| Inadequate Margin – Function (AWD)                                                | 4     | 17                                                        | 0.62 | 0.20 | 33% | 9               | 0.54 | 0.30 | 55% | 17  | 0.47 | 0.18 | 38% |
| Adequate Margin – Function & Excised Local Recurrence (REEX)                      | 10    | 26                                                        | 0.54 | 0.27 | 50% | 16              | 0.66 | 0.34 | 51% | 26  | 0.40 | 0.22 | 55% |
| Inadequate Margin - Function & Local Recurrence (LR)                              | 16    | 14                                                        | 0.32 | 0.17 | 53% | 9               | 0.39 | 0.31 | 79% | 14  | 0.22 | 0.12 | 55% |
| Inadequate Margin + Function (anchored to Adequate Margin - Function) (AWD v DFS) | 2 v 3 |                                                           |      |      |     | 11              | 0.46 | 0.44 | 95% | -   | -    | -    |     |

\*using Torrance, 1986, 1982, \*\*CV=coefficient of variation ( $=SD/mean*100\%$ ), +=Acceptable Function, -=Adverse Function; DFS = Disease Free

Survival; AWD=Alive with Disease; REEX=Reexcision; LR=Local Recurrence

Table 8. Rank Order of Health States by Method of Elicitation

| Health State                                          | HS # | Rank Order by Median (1=best, 6=worst) |                  |     |
|-------------------------------------------------------|------|----------------------------------------|------------------|-----|
|                                                       |      | SG                                     | VAS-SG converted | VAS |
| Adequate Margin + Function                            | 1    | 2                                      | 2                | 2   |
| Adequate Margin - Function                            | 2    | 4                                      | 3                | 3   |
| Inadequate Margin + Function                          | 3    | 1                                      | 1                | 1   |
| Inadequate Margin - Function                          | 4    | 5                                      | 4                | 4   |
| Adequate Margin – Function + Excised Local Recurrence | 10   | 3                                      | 5                | 5   |
| Inadequate Margin - Function + Local Recurrence       | 16   | 6                                      | 6                | 6   |

### III.I Figures

Figure 1. Study Population and Respondents by Health States

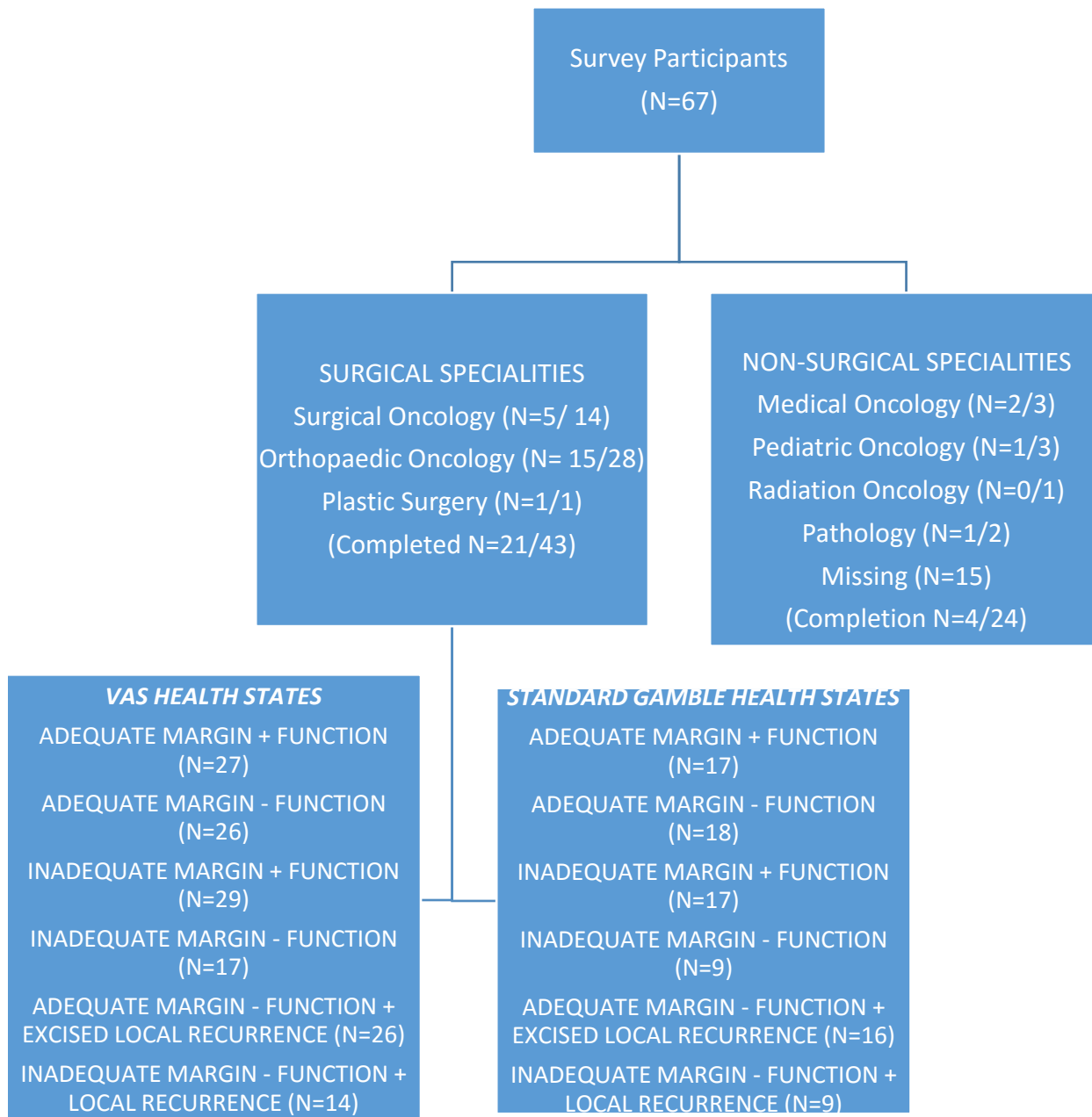


Figure 2. Relationship between VAS mean scores and SG utilities using power function equations

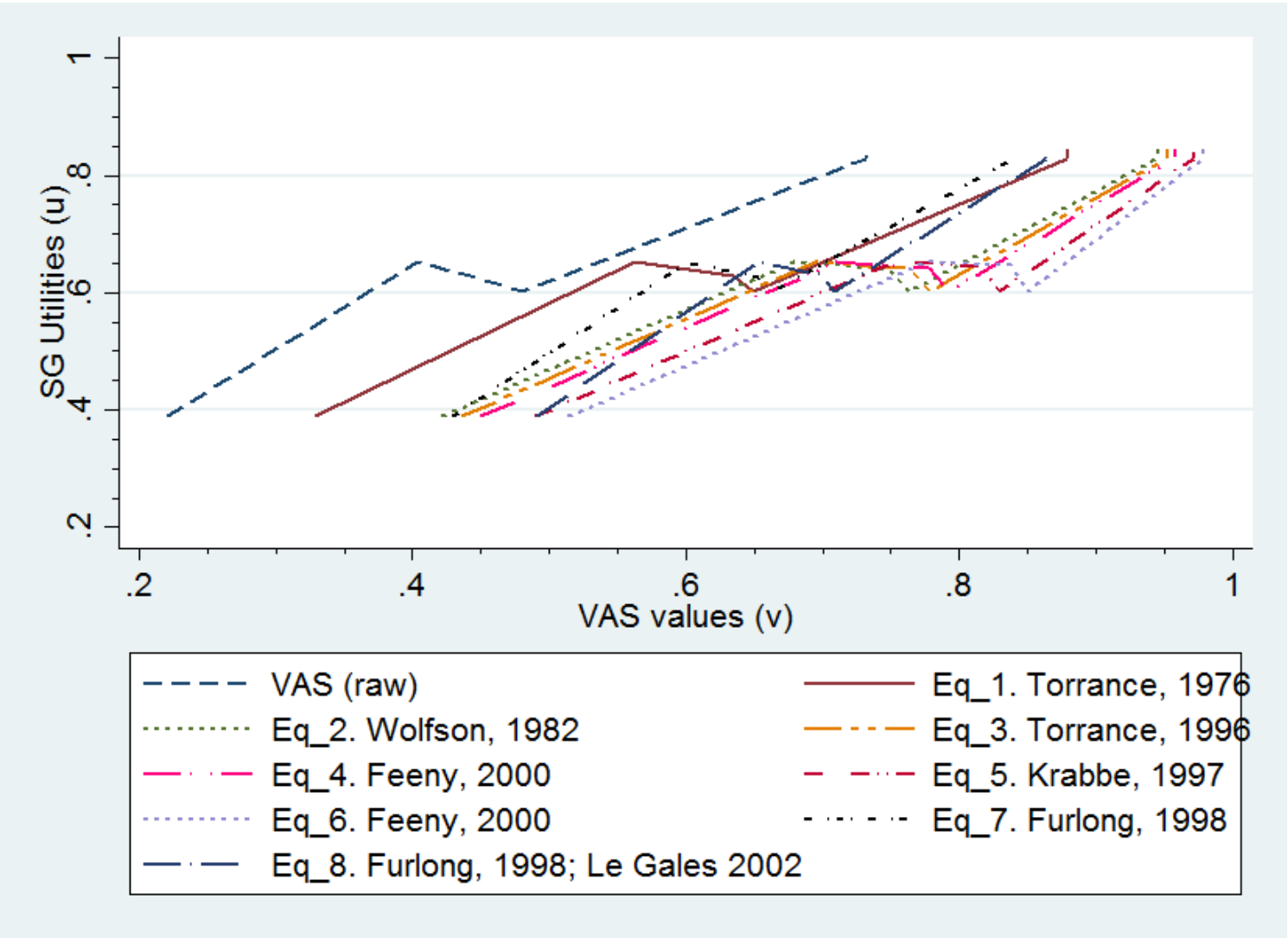




Figure 3. Unadjusted and Adjusted Q-Q plot for Highest Probability of a Local Recurrence Willing to Accept

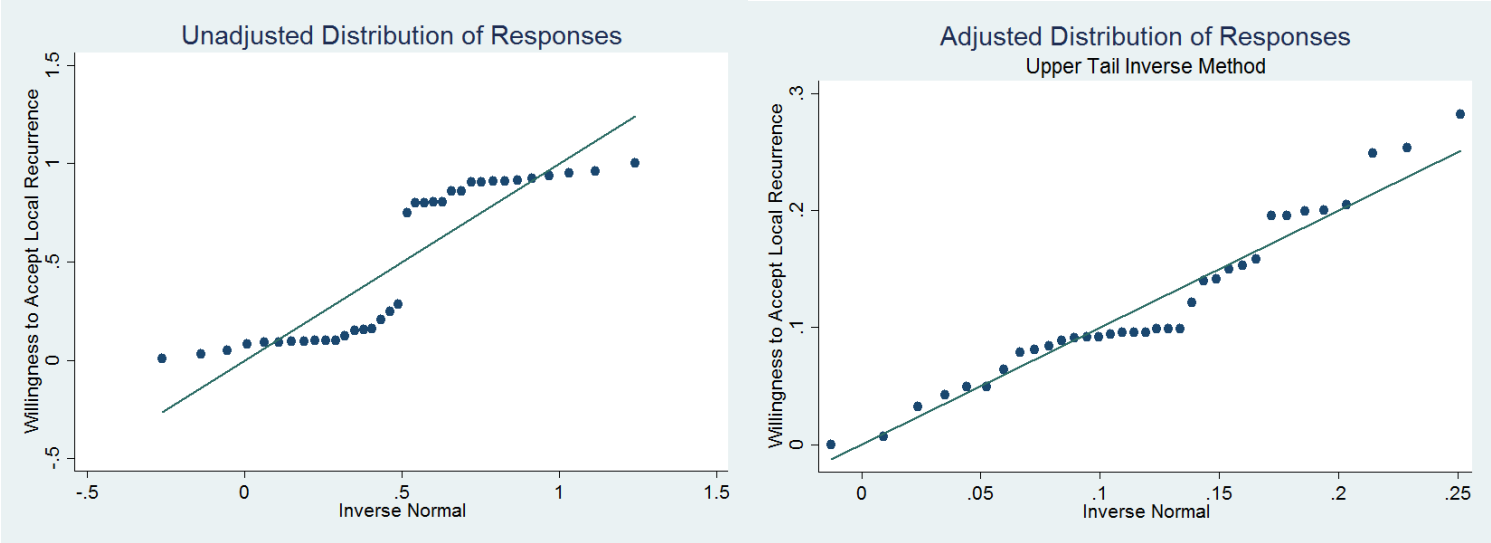


Figure 4. Unadjusted and Adjusted Q-Q plot for Functional Loss Willing to Accept

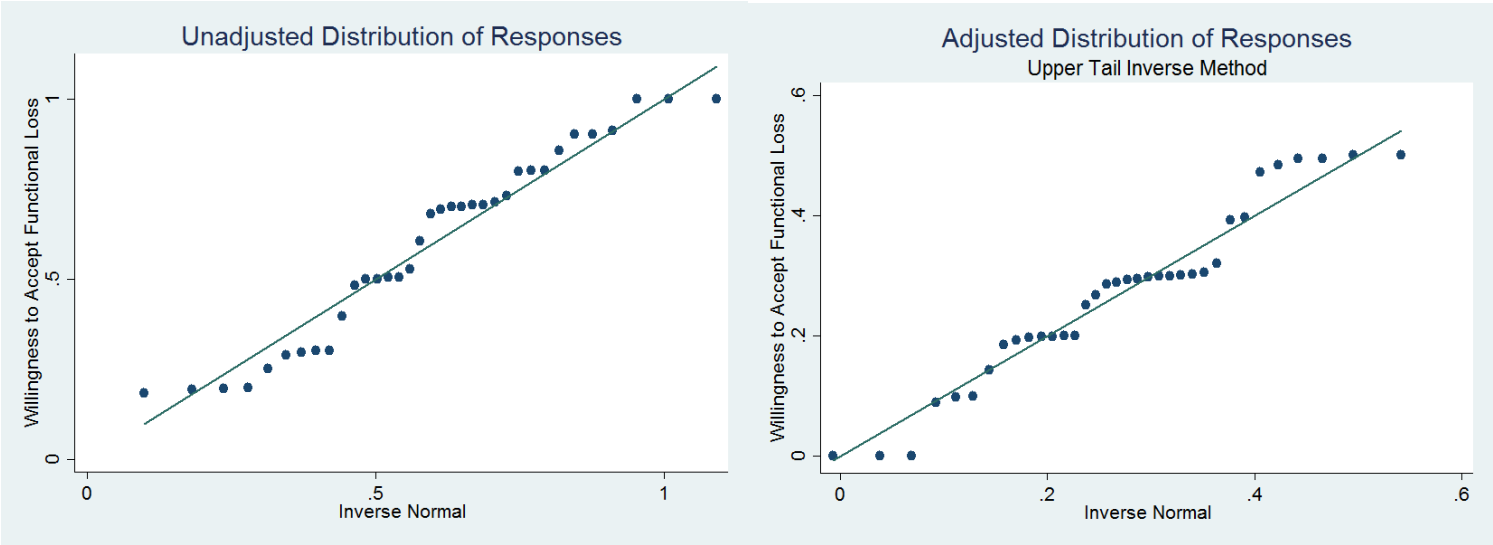


Figure 5. Predicted Probability of Favoring Local Control (Low Probability of Local Recurrence) by Health State Utility Value

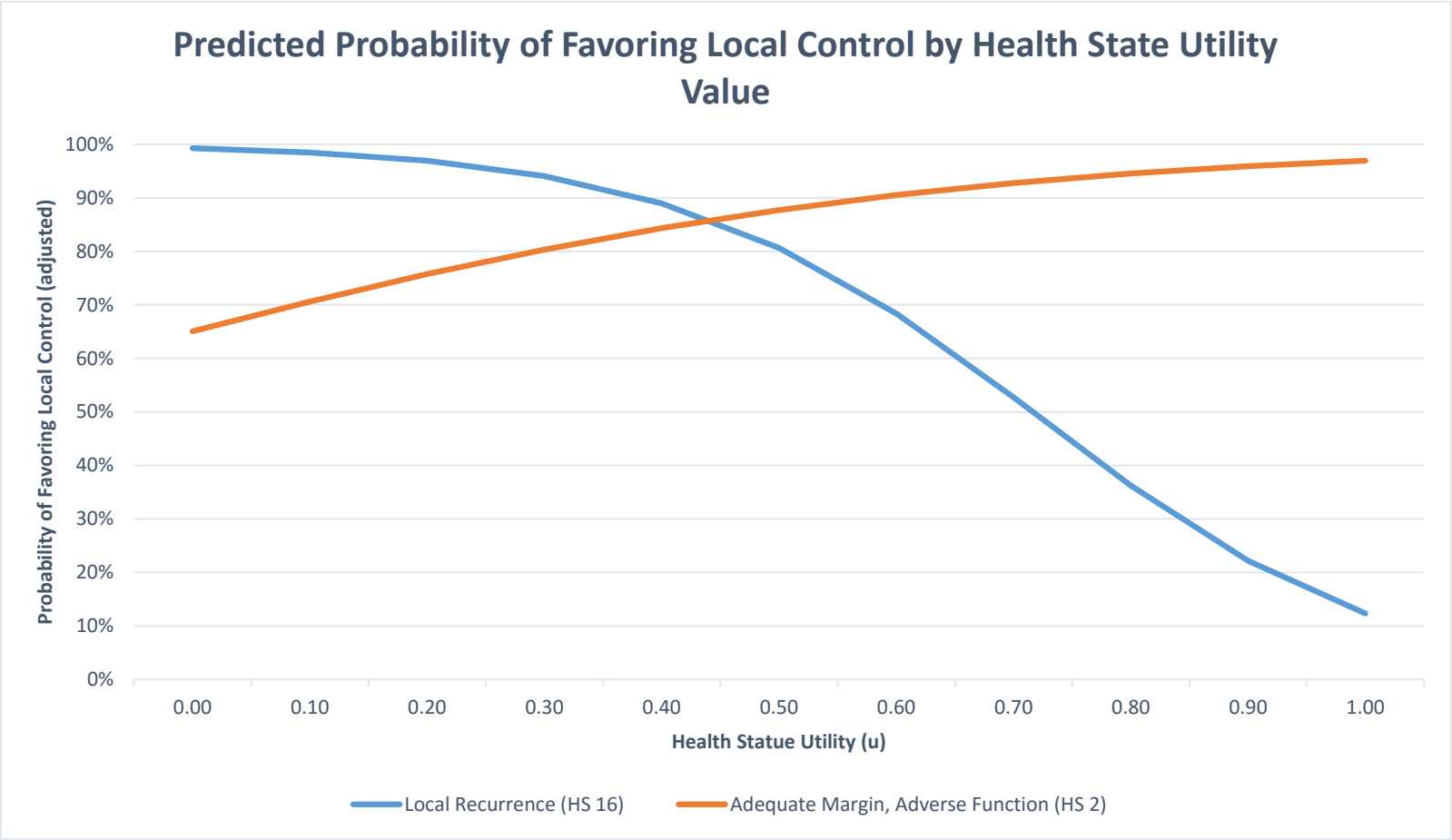
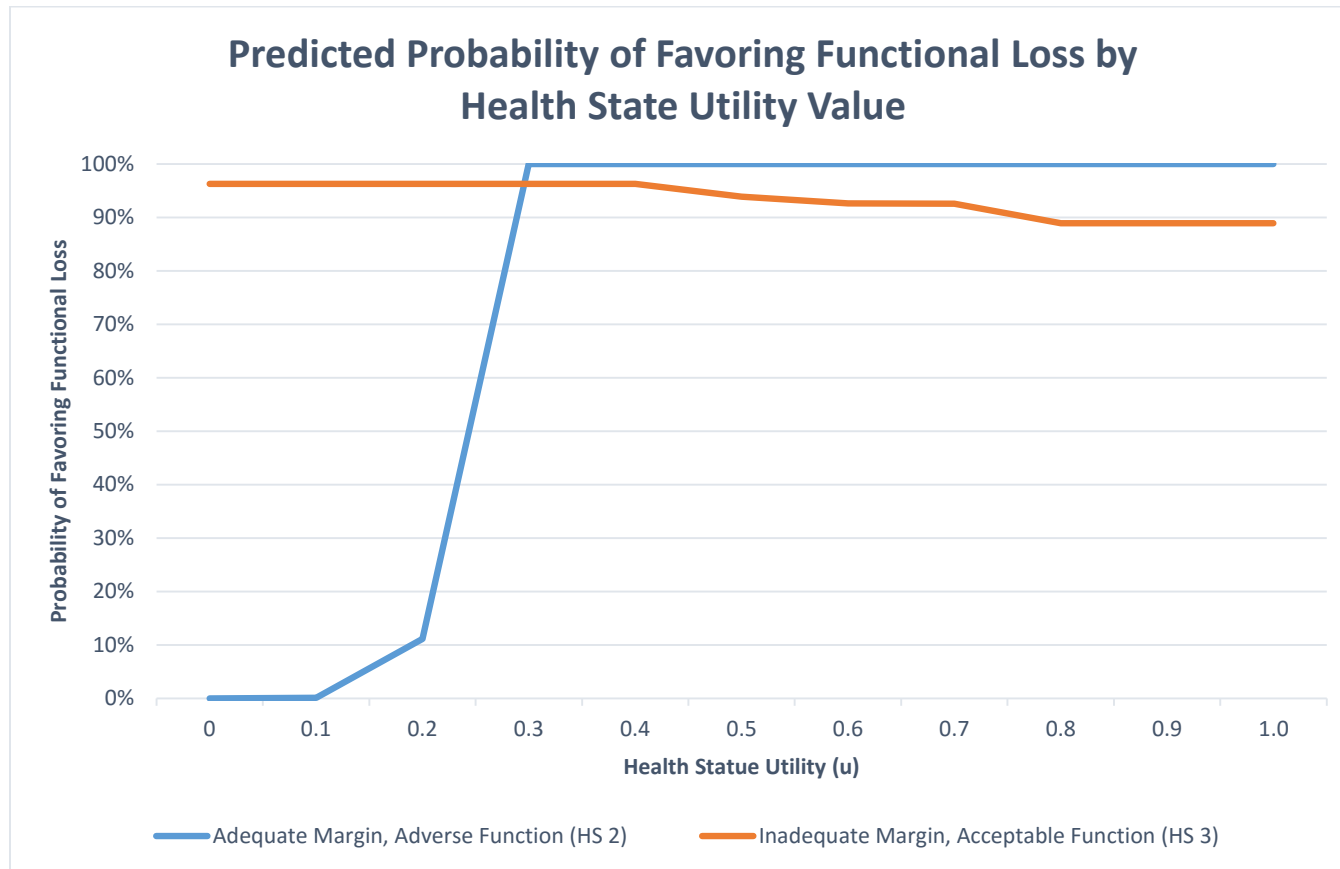


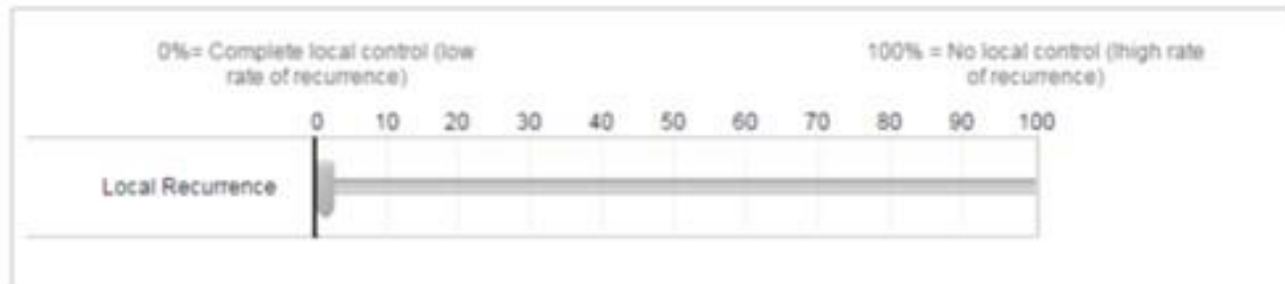
Figure 6. Predicted Probability of Favoring Functional Loss by Health State Utility Value



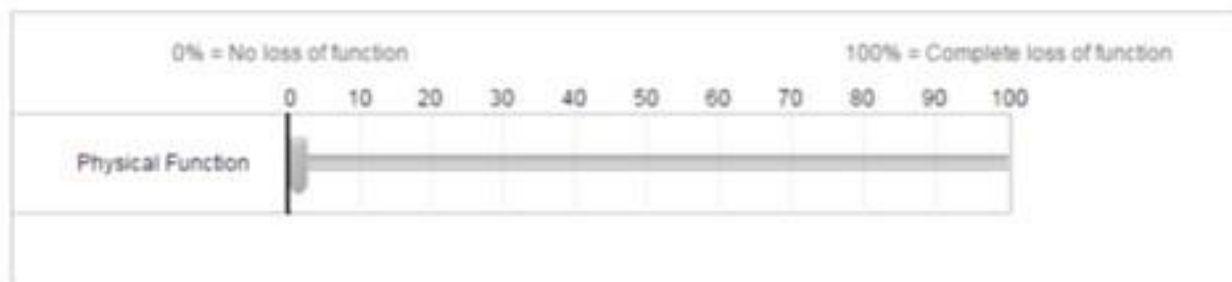
## APPENDIX

Figure 7. Surgical Strategy Questions for Local Recurrence, Physical Function and Trade-Off

Q21 What is the highest probability of local recurrence you would be willing to accept?  
\_\_\_\_\_ Local Recurrence (1)



Q23 What is the highest probability of loss of physical function you would be willing to accept?  
\_\_\_\_\_ Physical Function (1)



Q24 For the following questions please read the following: For the next set of questions, we are asking you to mark the PROBABILITY of certain scenarios following primary surgical excision during the coming year for a patient who is 55 years old with a large (>10cm), deep, high-grade, lower extremity soft tissue sarcoma that may invade a critical structure (nerve, vessel, or bone). Drag the slider bar below to show that in the next year for the patient described above you are willing to accept the following probability:

Q510 For the following clinical scenario where you need to make a trade-off between local control and function what is surgical strategy you favor: 55 year old patient with a large (>10cm), deep, high-grade, lower extremity soft tissue sarcoma that may invade a critical structure (nerve, vessel, or bone). Do you prefer more function or local control?

\_\_\_\_\_ Local Control vs. Function (1)

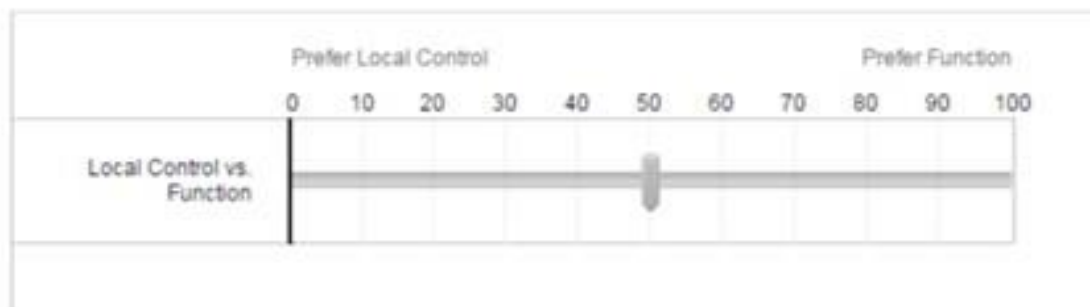
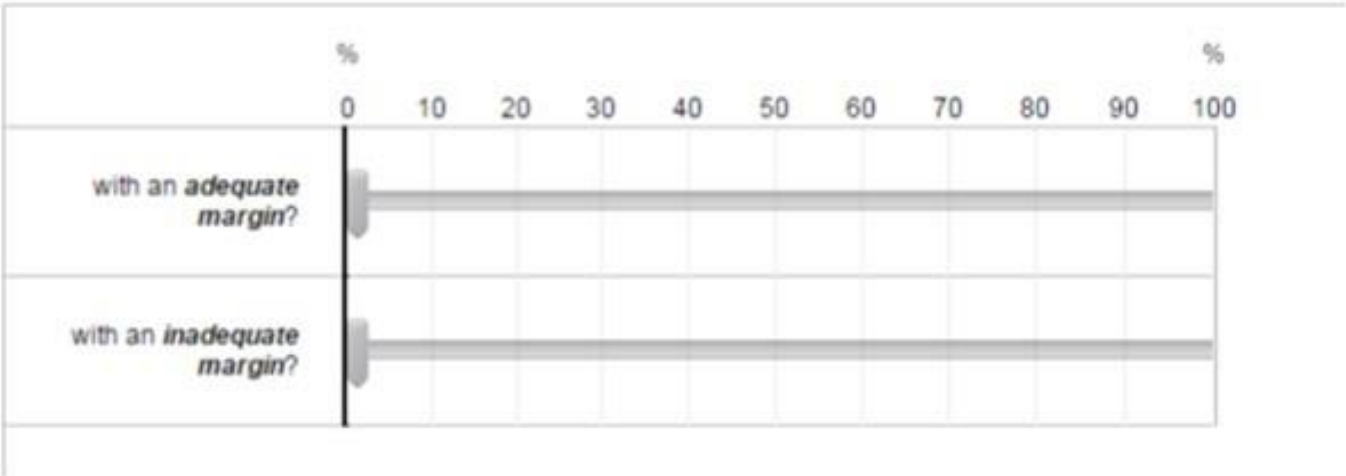


Figure 8. Evidence Synthesis Questions

Q25 What is the probability of a local recurrence following primary surgical excision?  
\_\_\_\_\_ with an adequate margin? (1)  
\_\_\_\_\_ with an inadequate margin? (2)



Q29 What is the probability of metastatic disease following local recurrence?  
\_\_\_\_\_ after re-excision? (1)  
\_\_\_\_\_ after NO re-excision? (2)

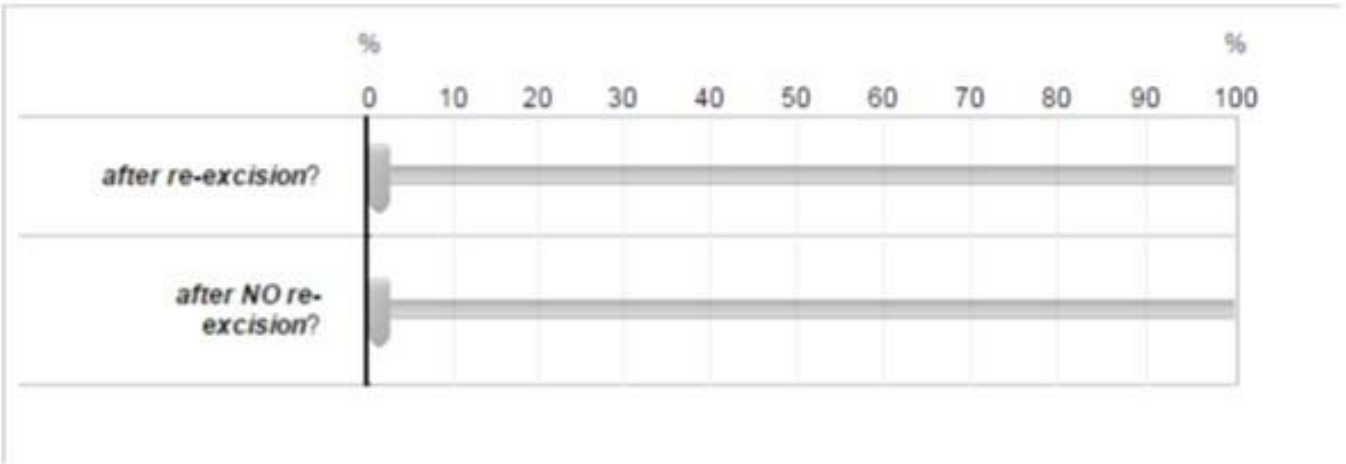


Figure 9. Median Utility Decrement from Varied Base Comparisons

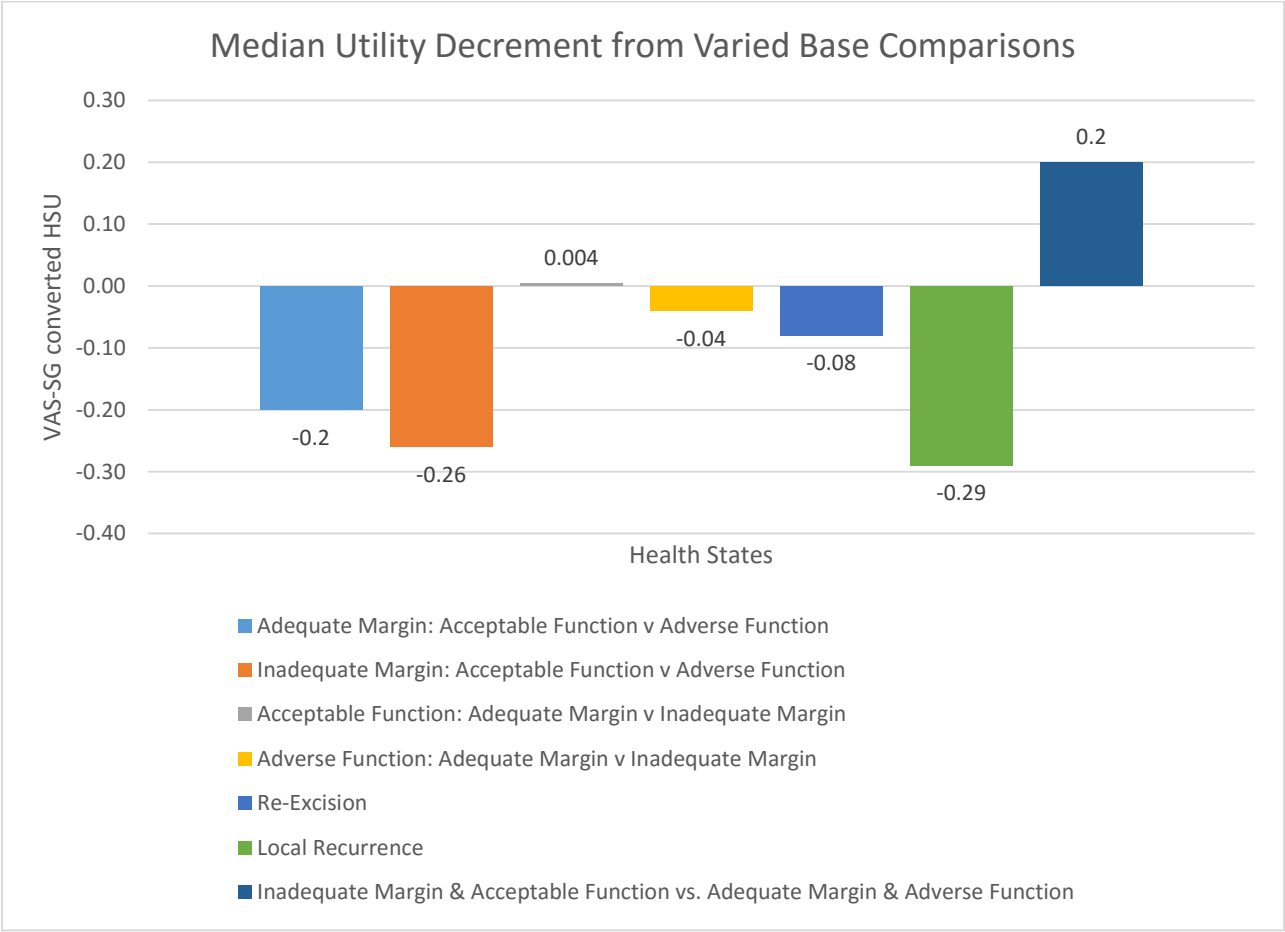


Figure 10. Median Health State Utility for All Surgeons

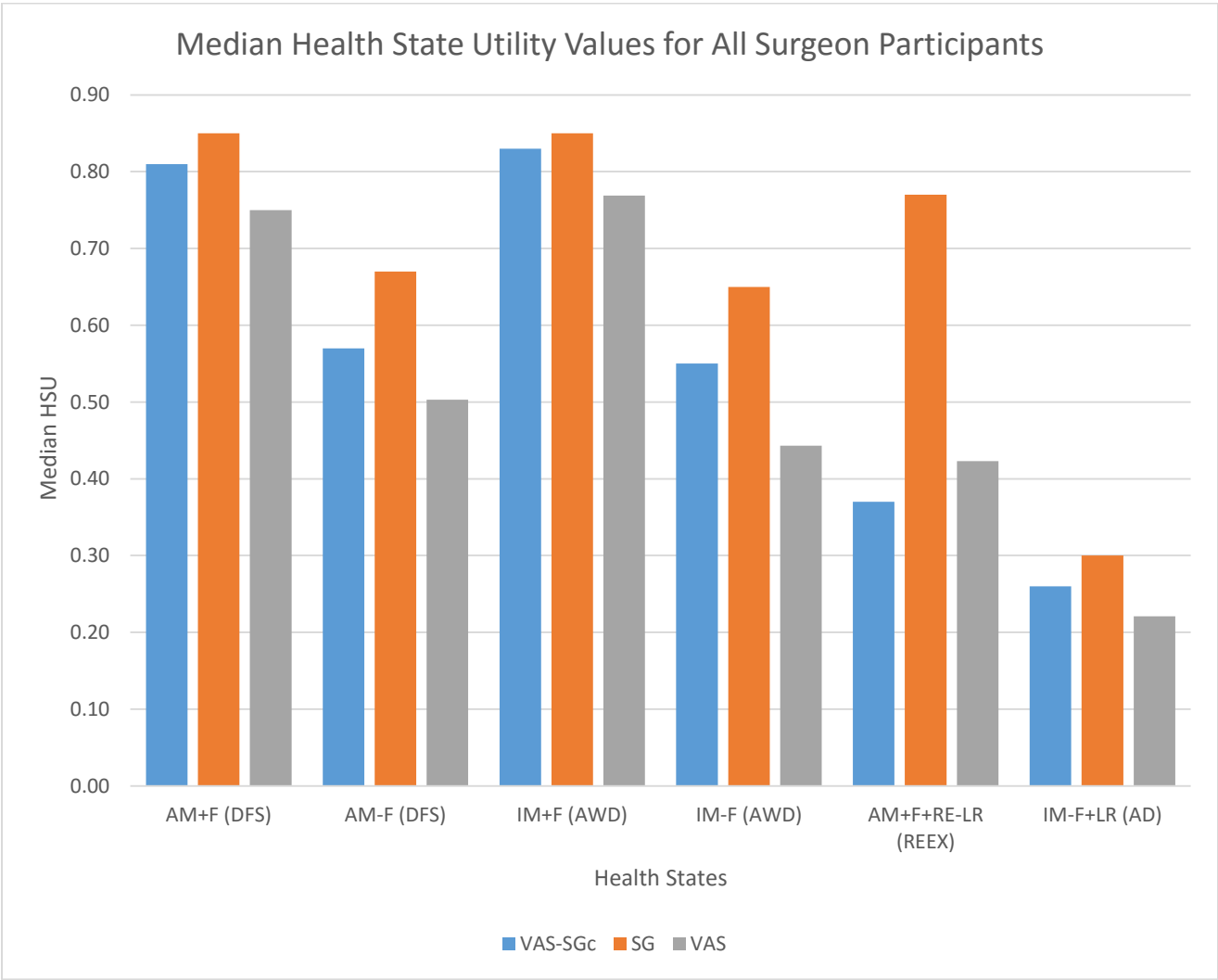
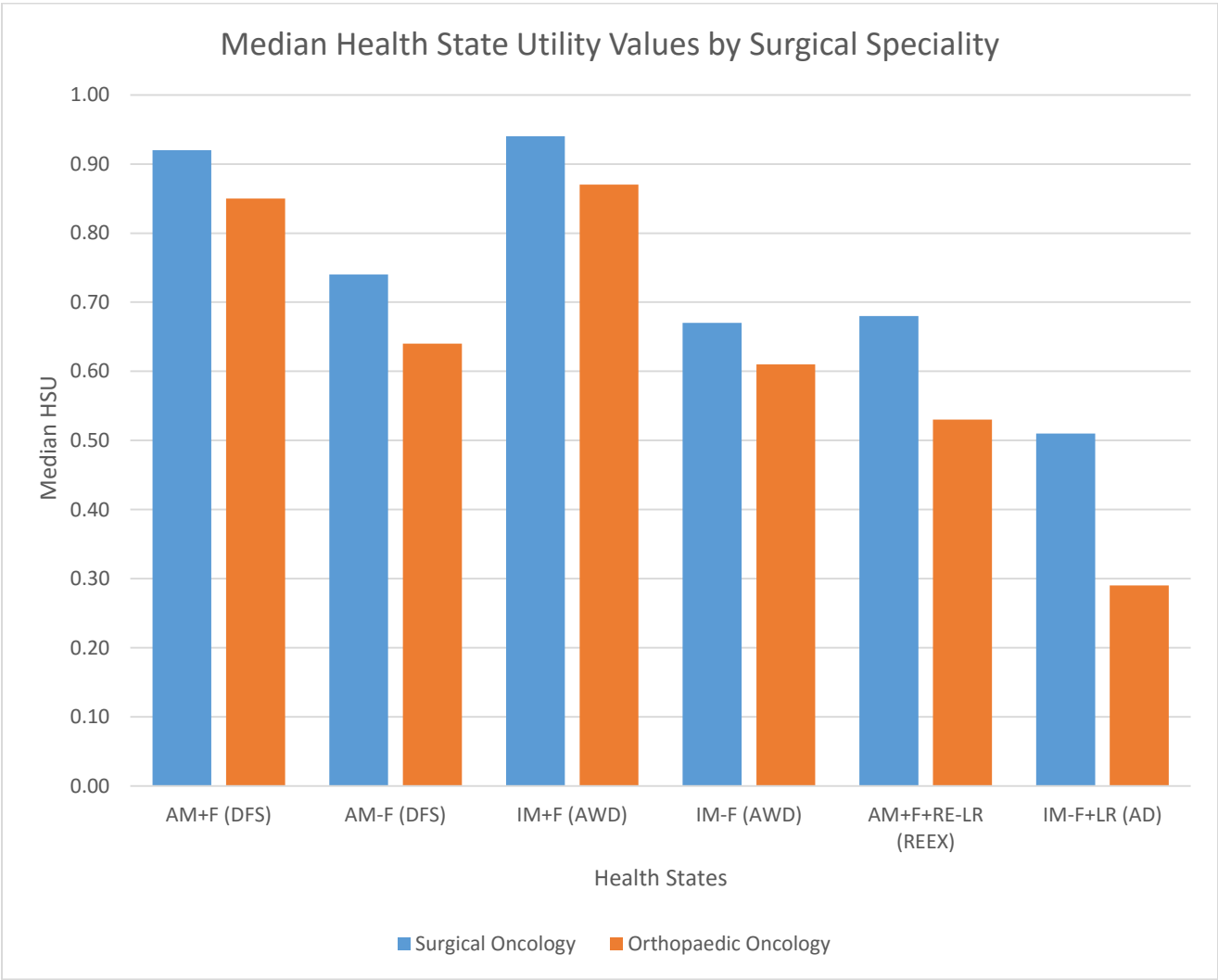




Figure 11. Median Health State Utility Values by Surgical Specialty



## Chapter IV. Surgical Treatment Strategies in Soft Tissue Sarcoma: Are Surgeons Good Agents for Patients and Society?

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Health state utilities; decision analysis; soft tissue sarcoma; local recurrence

Running Title: Perspectives in Cost-Utility for Sarcoma

## IV.A Abstract

### Background

There is considerable variability in surgical treatment patterns of surgery for lower extremity (LE) soft-tissue sarcoma, reflecting in part the controversy about the appropriate margin width to lower the risk of recurrence and the trade-off of this with functional outcomes following surgical excision of the sarcoma.

### Objective

Using a cost-utility framework, the analysis in this chapter compares the projected cost-utility of alternative surgical strategies based on surgeon preferences about health states as compared to those of either patients or the general population.

### Methods

A decision-analytic, cost-utility model was constructed with a 10-year and lifetime time horizon to allow comparisons across three different perspectives based on differences in their health state utility valuations.

### Results

For the patient and societal perspectives over both a 10-year and lifetime time horizon, the surgical strategy of Adequate Margin with an Adverse Functional Outcome (AM-F) dominates—i.e., lower cost and better outcomes—the surgical strategy of Inadequate Margin with an Acceptable Functional Outcome (IM+F) (Table 2). For surgeons, the incremental cost-effectiveness ratio (ICER) of IM+F compared with AM-F was \$8,284 per QALY gained over a 10-year time horizon, but the AM-F strategy was dominant in the lifetime horizon. However, in the lifetime horizon analysis for surgeons and for all time horizons for the patient and general public the AM-F surgical strategy dominates. The difference in effectiveness varies among the three perspectives, with surgeons not only valuing the IM+F strategy higher, but only slightly, while patients valued almost a 1-year QALY gain for the AM-F strategy over the IM+F strategy and the public perspective doubled that to a 2-year QALY gain from choosing the dominate AM-F strategy.

## Discussion

In terms of the average strategy—based on cost-utility analysis—surgeons would slightly favor the narrow (inadequate) margin surgery aimed to preserve limb function while patients and the general population would favor wide margin surgery that maximizes life expectancy with less risk of recurrence. Furthermore, if the default strategy followed the surgeons' preferences, it would cost society more than if it followed patient's or society's preferences. From the standpoint of cost-utility from a health system perspective, therefore, there will be a welfare loss if the default strategy is based on surgeons' preferences. It is important to understand the surgeons' values of treatment-related health states to understand variations in treatment preferences and in turn their treatment recommendations to the patient.

## IV.B Introduction

Soft tissue sarcomas (STS) are rare cancers with the majority of tumors in the lower extremities. In the U.S. in 2013, some 11,000 new STS cases were diagnosed and an estimated 4,390 STS-related deaths reported.<sup>(1, 2)</sup> First-line treatment for lower extremity (LE) STS is surgical resection of the tumor.<sup>(3, 4)</sup> Yet, there is considerable variability in surgical treatment patterns, reflecting in part the controversy about the appropriate margin width to lower the risk of recurrence and the trade-off of this with functional outcomes following surgical excision of lower extremity (LE) STS.<sup>(3, 5-7)</sup> Surgical resection of these tumors is undertaken with curative intent by planning for a sufficient margin of healthy tissue surrounding the tumor for complete excision, while maximizing functionality of the extremity by removing as little healthy tissue as possible.<sup>(6-9)</sup> By estimating surgeons' health state utility (HSU) valuations, Chapters 1 and 2 of this dissertation provide a basis (a) for a comparison with "patient" and "societal" preferences (i.e., of the general population, who are potential STS patients), and (b) for considering the implications of any differences. Using a cost-utility framework, the analysis in this chapter compares the projected cost-utility of alternative surgical strategies based on surgeon preferences as compared to either patient or population preferences.

## IV.C Methods

### IV.C.i Perspective

The generally recommended perspective for cost-utility analysis in the reference case, as defined by the Panel on Cost Effectiveness in Health and Medicine is the "societal" perspective. One key criterion for the societal perspective has been to base health state valuations on "a representative sample of fully informed members of the community."<sup>10</sup> The basic idea is that optimal social decisions—a normative ideal—should be based on these preferences. Clearly, these community preferences may not be the same as those of specific patients with a particular disease. This study is not a typical cost-utility analysis from the societal perspective. Instead, the utility outcomes are being compared across three different groups: the community/population (i.e., potential

patients), STS patients, and STS surgeons. These are all hypothetical comparisons for typical patients; however, they may suggest how surgical strategies that would be based on either surgeon or patient preferences might well differ from the presumed social optimum, which would be based on community preferences.

#### IV.C.ii Model structure

A cost-utility analysis was used to compare the costs and outcomes of surgical strategy approaches for the treatment of LE STS. The two strategies compared was the choice between an Adequate Margin with an Adverse Functional Outcome (AM-F) or an Inadequate Margin with an Acceptable Functional Outcome (IM+F). A decision-analytic model was used to analyze the cost-effectiveness for this comparison (Figure 1). Due to limitations in the treatment patterns data that could characterize the complex nature of the treatment of STS—which includes recursive rounds of chemotherapy, radiation, local recurrence, and re-excision surgeries,, a simple model structure was constructed.<sup>11</sup> The target population for this analysis was an average 50-year old undergoing primary surgical removal of a lower extremity soft tissue sarcoma.<sup>12</sup>

#### IV.C.iii Surgical Strategy Comparators

For the reference case in this study, it was assumed that all adequate margin surgeries included an adverse functional outcome and that all inadequate margin surgeries included an acceptable functional outcome. This is a straightforward way to model the scenario of why a surgeon or a patient would choose to have an inadequate margin surgery when it is known that this type of surgical approach increases the risk of location recurrence.<sup>13</sup> Prior to entering the model, it was assumed that all LE STS patient received the same pre-operative care that followed the National Comprehensive Cancer Network (NCCN) guidelines for treating a Stage II or III soft tissue sarcoma with acceptable or adverse functional outcomes.<sup>14</sup> Diagnostic testing and neoadjuvant treatment for patients could have included: a biopsy (core needle or incisional), chemotherapy, radiation therapy, or a combination of both therapies. Primary excision of the tumor for definitive treatment was considered to be a surgery to obtain surgical margins and functional status corresponding with the

interventions described previously – AM-F or IM+F. It is also presumed that treatment is occurring in tertiary multi-disciplinary sarcoma centers and that the probabilities and mortality data are reflective of receiving this level of care. For the local recurrence health state, it was assumed that all patients would have their local recurrence excised within the same year of a local recurrence diagnosis. Patients would then either go on to advanced disease or have no advanced disease, and then either survive within the 10-year time period or die either from advanced disease or die from other causes if they had no advanced disease.

It is assumed that as all patients entering the model have identical upfront costs before receiving primary surgical excision. For the societal perspective, the cost analysis was conducted with all costs being equal across all three perspectives to understand the effect of different preferences for health states. All surgical costs were applied only once in the model, except for those cost related to advanced disease. Following standard practice, a discount rate of 3% was chosen for both the outcomes and only for costs advanced related to advanced disease.

The model is based on the average 50-year old patient who is diagnosed with LE STS who if lives is followed for 10 years through age 59. A ten-year time horizon was chosen, in large part, because of the availability of excellent long-term follow-up registry data for this duration.<sup>15</sup> Since LE STS is a chronic condition, a lifetime horizon was also considered and results presented.

#### IV.C.iv Measurement of Effectiveness and Preference-based Outcomes

The primary outcome was discounted quality-adjusted life-years (dQALYs). Survival as a probability, undiscounted QALYs, and discounted and undiscounted LYs were also calculated. We performed a cost-utility analysis using utilities on surgeons estimated as described in Chapters 1 and 2, and patient and population utilities were gathered from the literature (Table 3). Probability estimates were based primarily on a single-study gathered from a STS tumor registry who have received treatment at a tertiary sarcoma center from 1986 –

2009.<sup>15</sup> Also, this study provided estimates for local-recurrence free survival and cause-specific survival conditional on margin status, which was important given the primary question of interest.

As described in Chapter 2, surgeon preferences were elicited using standard gamble (SG) and visual analogue scale (VAS) ratings with median health state utilities reported as VAS-SG converted values. A key component of this study was measuring the utility decrement for local recurrence, which was valued at -0.29 (95% CI:-0.42, -0.19). A literature review was conducted to find HSU values from a patient and societal perspective. Across these studies, all methods of preference elicitation were used: SG, VAS, time trade-off (TTO) and multi-attribute utility instruments (MAUIs), such as the EQ-5D and the SF-6D.<sup>16-20</sup> For the general public values the TTO study by Shingler et al. was used as their health state descriptions best matched those used in the surgeon study – for AM-F HSU=0.79 and for IM-+F HSU=0.74.<sup>16</sup> A study examining patient preferences validating a known STS functional outcome legacy measure with the SF-6D MAUI found that patients with a walking aid (functional loss) reported an HSU=0.53 (95% CI: 0.48, 0.59), while those using no assistive device reported an HSU=0.61 (95% CI: 0.57, 0.65), these values were assigned to the AM-F and the IM+F, respectively.<sup>19</sup> Using these study values a utility decrement of -0.29 was applied to all perspectives to obtain a HSU value for local recurrence based on margin status.

#### IV.C.v Measurement of Costs

Two studies were used to estimate costs for the treatment of LE STS. All costs were reported in 2016 U.S. dollars (\$USD) and adjusted for inflation using the United States Department of Labor annual average medical care consumer price index (CPI).<sup>21</sup> One study from the United States described the charge difference between a primary excision and re-excision of “incompletely excised sarcomas” for LE STS at a tertiary sarcoma center.<sup>22</sup> Since charges were reported the Cost-to-Charge ratio (CCR) for the hospital from 2007 (the midpoint) was used to convert the charges to actual cost. The yearly cost of maintenance treatment for progression-free survival and disease progression survival were estimated from a CEA study for



chemotherapeutic treatment of advanced STS.<sup>23</sup> Values were converted from 2012 Canadian Dollars (\$CAD) to \$USD and adjusted for inflation as described above.

#### IV.C.viAnalysis

All analyses were performed using a decision-analytic framework in TreeAge Pro 2016 (Williamstown, MA). One-way sensitivity analyses are presented in a tornado diagram for each perspective to show the most influential parameters in each model (Figures 2 – 4).

#### IV.D Results

The parameters for the model can be found in Table 1. Across the patient and societal perspectives the surgical strategy of AM-F dominates—i.e., lower cost and better outcomes—the surgical strategy of IM+F (Table 2). For surgeons, the incremental cost-effectiveness ratio (ICER) of IM+F compared with AM-F was \$8,284 per QALY gained in the 10-year time horizon. The difference in effectiveness varies among the three perspectives, with surgeons not only valuing the IM+F strategy better, but only slightly, while patients valued almost a 1-year QALY gained for the AM-F strategy over the IM+F strategy and the public perspective doubled that to a 2-year QALY gained choosing the dominate AM-F strategy. For all perspectives, over the lifetime horizon the AM-F strategy dominated the IM+F.

Surgeons valued the IM+F health state the highest (HSU=0.83), but valued significantly lower the health state of AM-F (HSU=0.57). Overall, the general public has the highest values for LE STS health states with HSU=0.79 and HSU=0.74, for AM-F and IM+F, respectively. The patient values were the lowest with HSU=0.53 and HSU=0.61, for AM-F and IM+F, respectively. Based on these values and with the utility decrement for local recurrence (LR) of -0.29, patients had the lowest utility for local recurrence adequate margin (LR-AM) of HSU=0.24 and for LR-IM HSU=0.32, the community had the highest overall utilities for local recurrence: LR-AM HSU=0.50, LR-IM HSU=0.45. Surgeons' HSU values for local recurrence varied

widely depending on the margin status with LR-AM HSU=0.28 and LR-IM HSU=0.54. This was due to the low base starting value for the AM-F health state.

To evaluate the impact of uncertainty in this hypothetical CUA one-way sensitivity analyses (OWSA) and probabilistic sensitivity analysis identified those parameters that had the most influence on the model outcomes. The mortality from STS following an IM+F and AM-F surgical strategy followed by the probabilities of having advanced disease, were the most influential predictors of incremental survival (Figure 2). For the outcome of incremental dQALYs, the most influential parameter was how long a patient spent time in one of the two surgical margin strategies, followed by the utilities for each of the surgical margin health states. (Figure 3) The lifetime model predicted that the average AM-F surgical strategy, 50-year old patient to have an 88% survival with 12.67 dQALYs. The longer time spent in a margin health state (either AM-F or IM+F), and not progressing to local recurrence or advanced disease the more QALYs a patient is expected to gain. The probabilities of local recurrence following either of the two surgical margin strategies had the most impact on the outcome of incremental costs. (Figure 4) The PSA revealed a 0% probability of the IM+F being cost-effective at any willingness-to-pay threshold as it was dominated by the AM-F surgical strategy. In Figure 6 after 10,000 simulations in 0% of the simulations was the IM+F cost-effective with 100% of the simulations demonstrating a mean incremental cost decrease of -\$4,492 (95% Credible Interval: \$1,708 - \$8,680) for the AM-F strategy and a notable increase in dQALYs of 3.3 (95% Credible Interval: -1.82 - 7.55). The time spent in the initial surgical strategy health state and the advanced disease health state were highly influential variables in the surgeon model, followed by the HSU value for the AM-F health state. For the patient model the time spent in advanced disease followed by the HSU value for the AM-F strategy were the most influential points. The general community model was most influenced by the time spent in the AM-F health state followed by the value of that health state.

#### IV.E Discussion

By comparing two alternative hypothetical cost-utility analyses, this analysis makes a normative comparison of the potential outcomes of decisions that would follow the preferences of patients or society versus those that would follow the preferences of surgeons. Our main finding is that—in terms of the average strategy—based on cost-utility analysis, surgeons would slightly favor the narrow (inadequate) margin surgery aimed to preserve limb function while patients and the general population would favor wide margin surgery that maximizes life expectancy with less risk of recurrence. The average surgical strategy followed the preferences of surgeons, it would produce lower health gains (i.e., QALYs) for a typical patient as compared to a strategy reflecting community or patient's valuation of health states. Furthermore, if default strategy followed the surgeons' preferences, it would cost society more than if it followed patient's or society's preferences. From the standpoint of cost-utility from a health system perspective, therefore, there will be a welfare loss if the default strategy is based on surgeons' preferences.

In other words, in this study we conduct alternative cost-utility analyses to assess the potential consequences of any divergence between surgeons' valuations of health state utilities and those of the general public (and patients) in terms of the cost-utility of the surgical strategies used for LE STS, comparing the strategy of adequate margin with functional loss surgery to inadequate margin but function-preserving surgery. It was hypothesized that if surgeons base their STS treatment recommendations on their own health state preferences rather than those of the general public, then the cost-utility ratio could differ significantly from that of the preferred perspective. On average, it is clearly different.

The results of this model predict relatively high survival, 88% and 12.67 dQALYs for those in the AM-F strategy and 80% and 9.33 dQALYs in the IM+F strategy. In this model 59.2% of patients have an AM-F strategy with no local recurrence and no advanced disease and go on to be disease-free or die from other causes. Another 38.6% of patients have the IM+F strategy with no local recurrence and no advanced disease and proceed to either die from other causes or remain disease free. The remaining patients are divided among

pathways that have local recurrence or not and advanced disease or not. The cause-specific survival probabilities were from O'Donnell and colleagues.<sup>15</sup> But that study did not report survival estimates for advanced disease by margin status. However, they did report the proportion of those who went on to have metastatic/advanced disease: 49% for inadequate margin and 28% for adequate margin. This hypothetical model assumed that to die from sarcoma all patients had to have metastatic or advanced disease progression and based on a study by Biau, we assumed that about 30% of patients went on to advanced disease regardless of margin status or local recurrence status.<sup>24</sup> Often in STS the quote for survival of the average patient is about 50%: however, this is based on old data. This study may indicate that the STS surgical community is doing better at improving the survival of those diagnosed with STS than what has been historically quoted.

As emphasized in Chapter 2, the basis for these differences in surgical treatment preferences among surgeons is not well understood. Surgeons may believe that: 1) narrow margin surgery is preferred because it can increase the function of the limb or 2) the probability of a local recurrence is generally low; or 3) the patient prefers functionality at an increased risk of local recurrence.<sup>25-27</sup> The rationale for considering the surgeon's perspective by using cost-utility methods is two-fold: 1) surgeons have conflicting roles as they must both represent their patient that they took an oath to care for, and 2) surgeons should consider societal preferences for allocating the limited resource of surgical care. Using a cost-utility modeling framework can provide a method for assessing the consequences of surgeons' choices for different surgical strategies.<sup>28, 29</sup> Empirical data have not been collected to assess directly whether the STS surgeon, the ostensible agent of the patient, is substituting their own health state preferences for those of patients or if they are a true agent and are representing the patient's health state preferences.

When physicians, including surgeons, are consulting with patients they often take on the role of the "agent" or advisor of the patient (called the "principal" in economics terminology).<sup>30</sup> The surgeon is clearly the expert on the potential clinical outcomes for the alternative surgical procedures—in this case, choosing a wider margin for the initial excision of STS versus a narrower margin, which would preserve more limb function, but increase the

risk of local recurrence. However, the patient is clearly the expert on his or her own preferences, i.e. the valuation alternative outcomes in terms of health state valuation. In theory, the surgeon would be a perfect agent by recommending the strategy that maximizes the patient's utility by combining the information on the probabilities of clinical outcomes with the information on patient preferences about outcomes.<sup>27</sup> However, it is obviously difficult and costly for surgeons to learn patient preferences, and only to realize those preferences also may not be well formed. Hence, one alternative that is examined in this study is if the surgeon were to recommend strategies based more on his or her perceptions of the health state values. Of course, this is a hypothetical exercise, and we are not directly assessing what surgeons are actually doing in current practice; however, even among surgeons there appears to be considerable variability, which does not seem to be necessarily related to patient preferences,

Although health state utility valuations would vary substantially among different surgeons, different patients, and different members of society, on average, there appears to be a misalignment of the typical surgical strategy that surgeons would recommend compared what patients and the general population would prefer. On the one hand, the difference in QALYs of the strategies is small in absolute terms, and one could argue that they could approach their agent role with equipoise. On the other hand, if they didn't listen to their patients, they might not realize that many patients would favor survival over limb function. One could argue who better to be a fully informed member of the community than the surgeons who by the very treatment they perform "create" certain health states. Surgeons possess superior knowledge and have better access to information about surgical treatments: such as Treatment A (less function/QoL, with better local control) vs. Treatment B (better function/QoL, with less local control and potentially higher local recurrence risk). If a surgeon has a strong preference for one treatment over another, then the surgeon may be highly influential to a patient's preference for treatment. Therefore, this study demonstrates it is important to understand the surgeons' values of treatment-related health states to understand variations in treatment preferences and in turn their treatment recommendations to patients.<sup>31</sup>

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## IV.G Tables

Table 1. Surgeon Model Parameters

| Parameters                        | Baseline    | Low      | High      | Reference       |
|-----------------------------------|-------------|----------|-----------|-----------------|
| <b>Probabilities</b>              |             |          |           |                 |
| Local recurrence                  |             |          |           |                 |
| Adequate margin                   | 0.10        | 0.08     | 0.12      | O'Donnell, 2014 |
| Inadequate margin                 | 0.41        | 0.33     | 0.50      | O'Donnell, 2014 |
| Advanced disease                  | 0.31        | 0.22     | 0.61      | Biau, 2011      |
| <b>10-year mortality</b>          |             |          |           |                 |
| Adequate margin                   | 0.29        | 0.23     | 0.34      | O'Donnell, 2014 |
| Inadequate margin                 | 0.53        | 0.42     | 0.64      | O'Donnell, 2014 |
| General population                | 0.05        | 0.04     | 0.06      | www.cdc.gov     |
| <b>Utilities</b>                  |             |          |           |                 |
| Adequate margin (AM)              | 0.57        | 0.23     | 0.77      | Cizik, 2016     |
| Inadequate margin (IM)            | 0.83        | 0.15     | 0.93      | Cizik, 2016     |
| Local recurrence_AM               | 0.28        | 0.15     | 0.38      | Cizik, 2016     |
| Local recurrence_IM               | 0.54        | 0.26     | 0.67      | Cizik, 2016     |
| No local recurrence               | 0           | 0        | 0.05      | Cizik, 2016     |
| Advanced disease                  | 0.26        | 0.17     | 0.43      | Cizik, 2016     |
| No advanced disease               | 0           | 0        | 0.10      | Cizik, 2016     |
| <b>Costs</b>                      |             |          |           |                 |
| Surgery                           | \$ 12,810.0 | \$ 8,157 | \$ 17,463 | Alamanda, 2013  |
| Re-excision                       | \$ 14,256.0 | \$ 7,898 | \$ 20,613 | Alamanda, 2013  |
| <b>Cost of treatment (yearly)</b> |             |          |           |                 |
| Advanced disease                  | \$ 5,308    | \$ 2,654 | \$ 7962   | Delea, 2014     |
| No advanced disease               | \$ 2,654    | \$ 1,327 | \$3,981   | Delea, 2014     |



Table 2. Model Results for LE STS Treatment Strategies from Three Perspectives

| Strategy                                           | Mean cost<br>(\$) | QALYs<br>(discounted<br>) | QALYs<br>(undiscounted) | ICER      |
|----------------------------------------------------|-------------------|---------------------------|-------------------------|-----------|
| <b>Surgeon</b>                                     |                   |                           |                         |           |
| <b>10-year time horizon</b>                        |                   |                           |                         |           |
| Adequate (Wide) Margin and Adverse Function        | \$17,707          | 5.31                      | 5.77                    |           |
| Inadequate (Narrow) Margin and Acceptable Function | \$22,169          | 5.85                      | 6.26                    | \$8284    |
| <i>Incremental Difference</i>                      | \$- 4,462         | 0.54                      | 0.49                    |           |
| <b>Lifetime horizon</b>                            |                   |                           |                         |           |
| Adequate (Wide) Margin and Adverse Function        | \$17,707          | 12.67                     | 18.91                   |           |
| Inadequate (Narrow) Margin and Acceptable Function | \$22,169          | 9.48                      | 14.31                   | Dominated |
| <i>Incremental Difference</i>                      | \$ -4,462         | -3.20                     | -4.60                   |           |
| <b>Patient</b>                                     |                   |                           |                         |           |
| <b>10-year time horizon</b>                        |                   |                           |                         |           |
| Adequate (Wide) Margin and Adverse Function        | \$17,707          | 4.95                      | 5.37                    |           |
| Inadequate (Narrow) Margin and Acceptable Function | \$22,169          | 4.18                      | 4.49                    | Dominated |
| <i>Incremental Difference</i>                      | \$-4,462          | -0.77                     | -0.88                   |           |
| <b>Lifetime horizon</b>                            |                   |                           |                         |           |
| Adequate (Wide) Margin and Adverse Function        | \$17,707          | 11.79                     | 17.59                   |           |
| Inadequate (Narrow) Margin and Acceptable Function | \$22,169          | 6.85                      | 10.40                   | Dominated |
| <i>Incremental Difference</i>                      | \$-4,462          | -4.94                     | -7.19                   |           |
| <b>Community/Societal</b>                          |                   |                           |                         |           |
| <b>10-year time horizon</b>                        |                   |                           |                         |           |
| Adequate (Wide) Margin and Adverse Function        | \$17,707          | 7.31                      | 7.95                    |           |
| Inadequate (Narrow) Margin and Acceptable Function | \$22,169          | 5.23                      | 5.60                    | Dominated |
| <i>Incremental Difference</i>                      | \$-4,462          | -2.08                     | -2.35                   |           |
| <b>Lifetime horizon</b>                            |                   |                           |                         |           |
| Adequate (Wide) Margin and Adverse Function        | \$17,707          | 17.55                     | 26.21                   |           |
| Inadequate (Narrow) Margin and Acceptable Function | \$22,169          | 8.45                      | 12.74                   | Dominated |
| <i>Incremental Difference</i>                      | \$-4,462          | -9.09                     | -13.47                  |           |

Table 3. Comparison of Health State Utility Values by Perspective

| Health State Descriptions                                                                                                 | Surgeon (median)      |      |      | General Public (mean)     |                           |                          | Patient (mean)              |                             |                    |                             |                             |
|---------------------------------------------------------------------------------------------------------------------------|-----------------------|------|------|---------------------------|---------------------------|--------------------------|-----------------------------|-----------------------------|--------------------|-----------------------------|-----------------------------|
|                                                                                                                           | VAS-<br><i>SGEq.1</i> | SG   | VAS  | <i>TTO</i> <sup>(1)</sup> | <i>TTO</i> <sup>(2)</sup> | <i>SG</i> <sup>(2)</sup> | <i>SF-6D</i> <sup>(3)</sup> | <i>EQ-5D</i> <sup>(4)</sup> | VAS <sup>(4)</sup> | <i>SF-6D</i> <sup>(5)</sup> | <i>EQ-5D</i> <sup>(5)</sup> |
| Adequate Margin + Adverse Function (HS2) (DFS)                                                                            | 0.57                  | 0.67 | 50.3 | 0.79                      |                           |                          | 0.53                        |                             |                    |                             |                             |
| Inadequate Margin + Acceptable Function (HS3) (Diseased State)                                                            | 0.83                  | 0.85 | 76.9 | 0.74                      |                           |                          | 0.61                        | 0.64 - 0.77                 | 63.75 - 68.82      |                             |                             |
| Inadequate Margin and Adverse Functional Outcomes with Local Recurrence and No Reexcision (HS16) (Advanced Disease State) | 0.26                  | 0.30 | 22.1 | 0.26                      | 0.17                      | 0.30                     |                             | 0.56                        | 50.79              | 0.67                        | 0.65                        |

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#### IV.H Figures

Figure 1. Decision Tree Showing the Consequences of LE STS Surgical Strategies

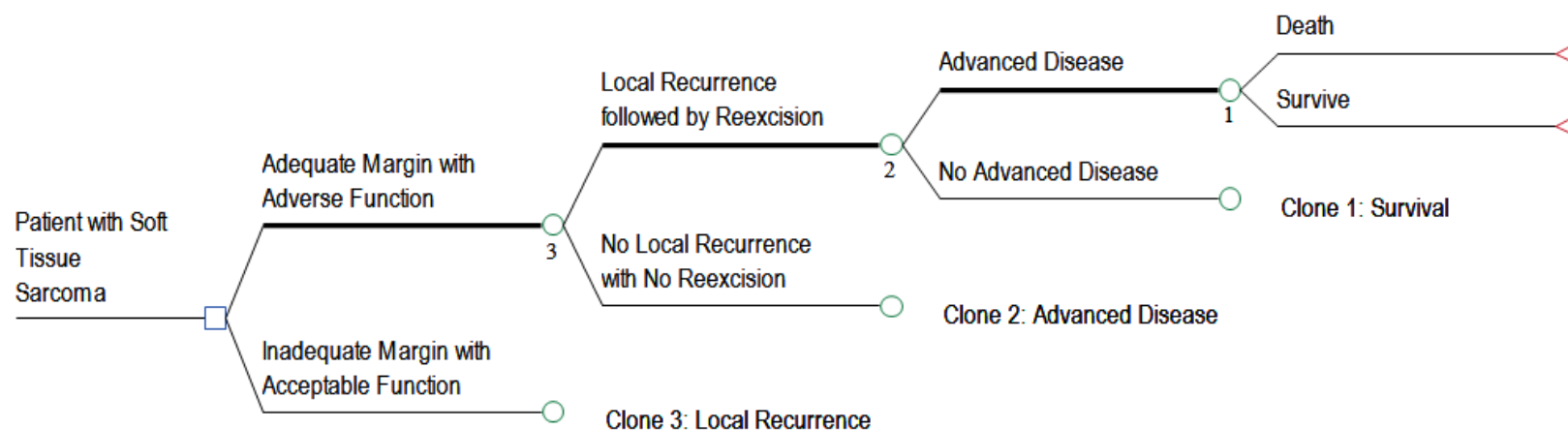


Figure 2. Tornado Diagram of One-Way Sensitivity Analyses for Survival (Surgeon Model)

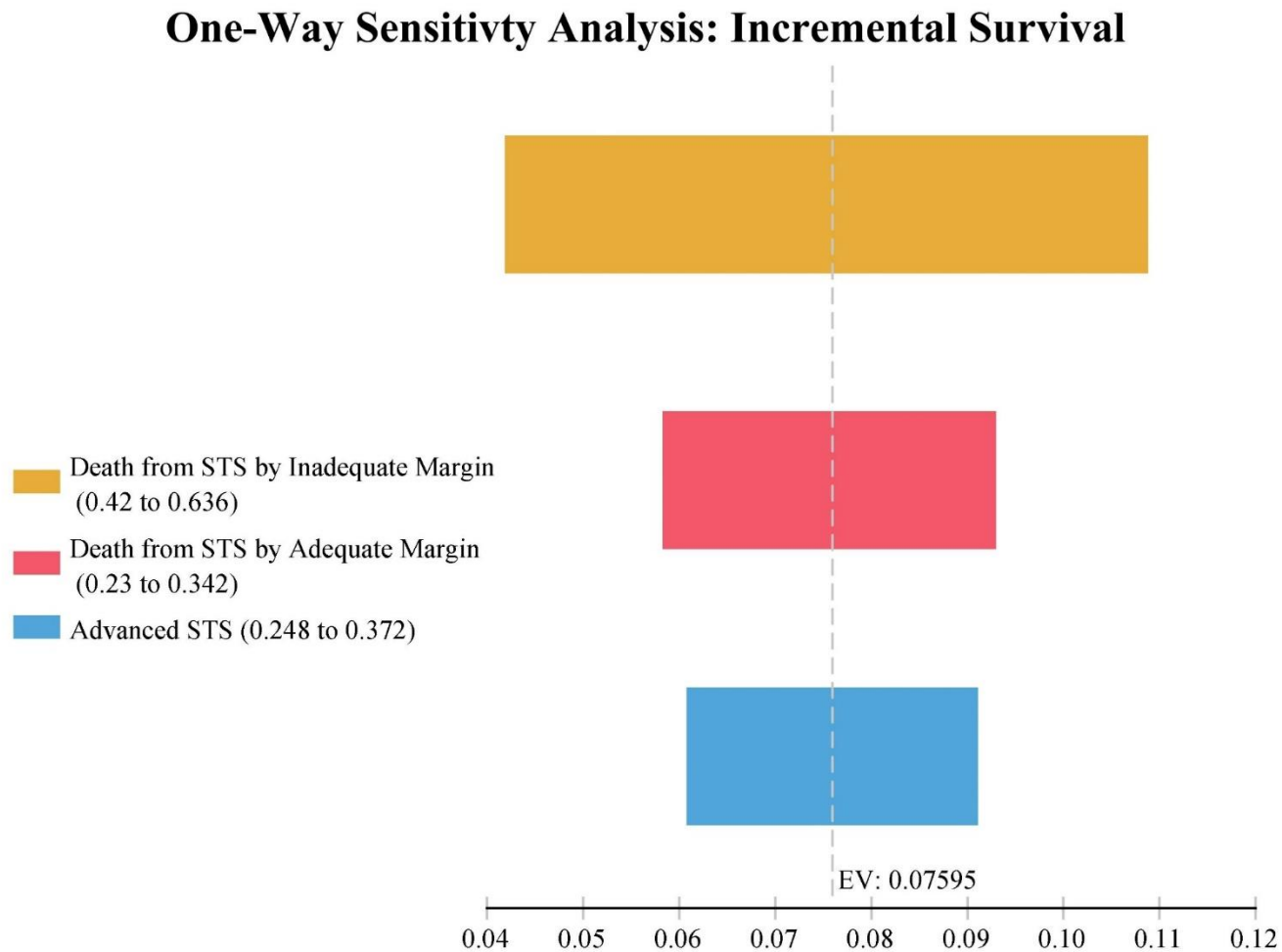


Figure 3. Tornado Diagram of One-Way Sensitivity Analyses for Discounted Quality-Adjusted Life Years (Surgeon Model)

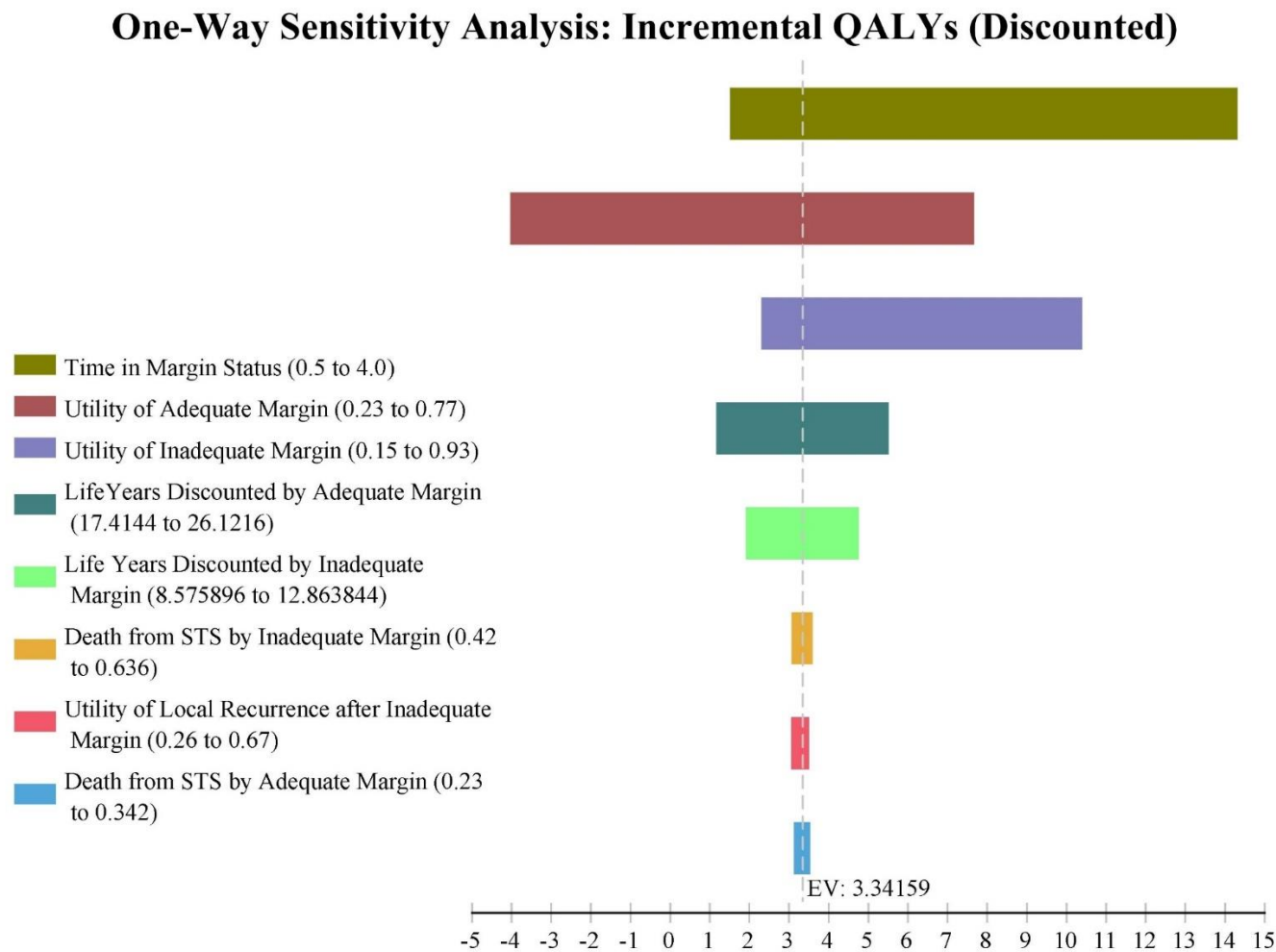


Figure 4. Tornado Diagram of One-Way Sensitivity Analyses for Costs (Surgeon Model)

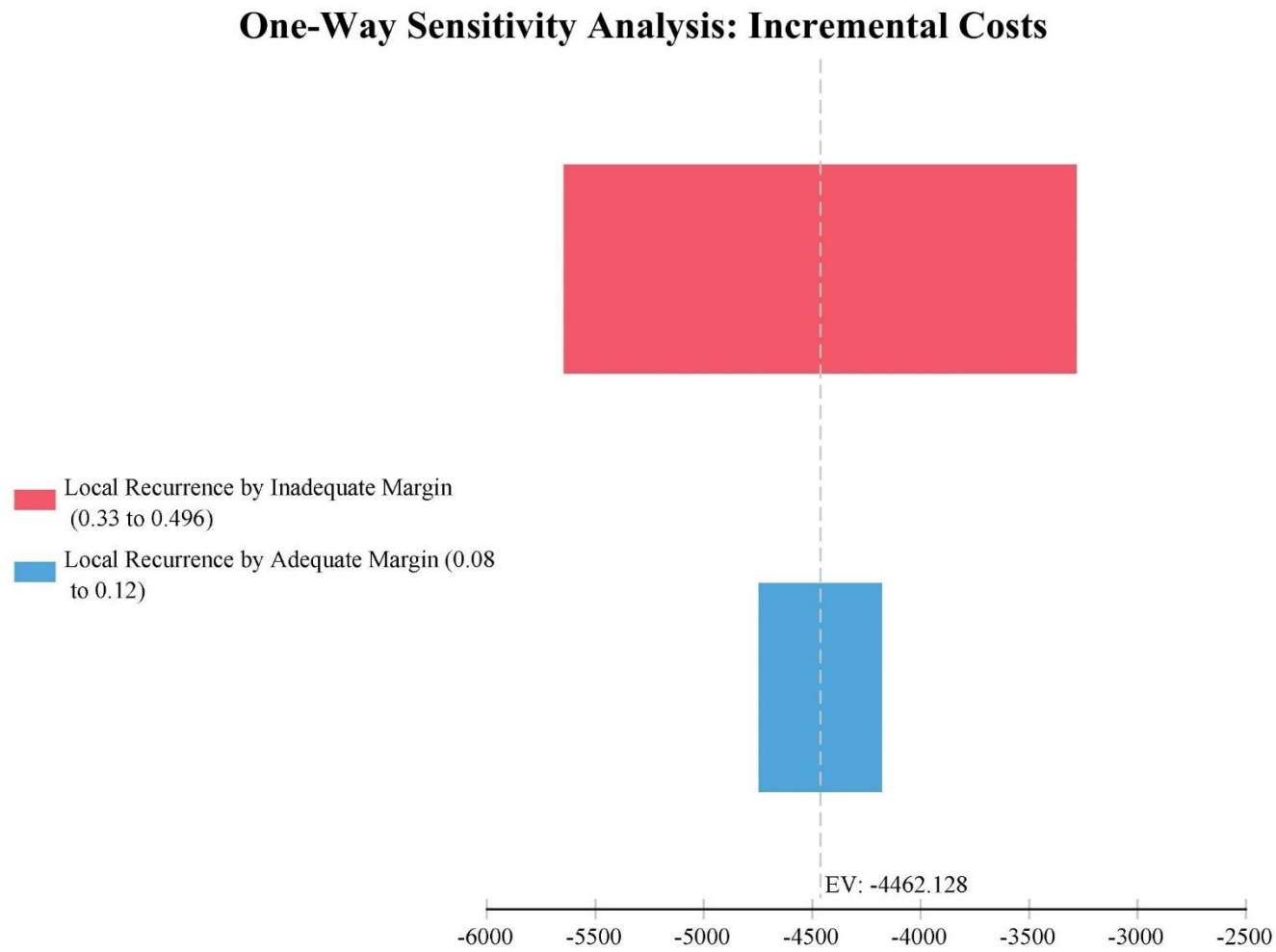
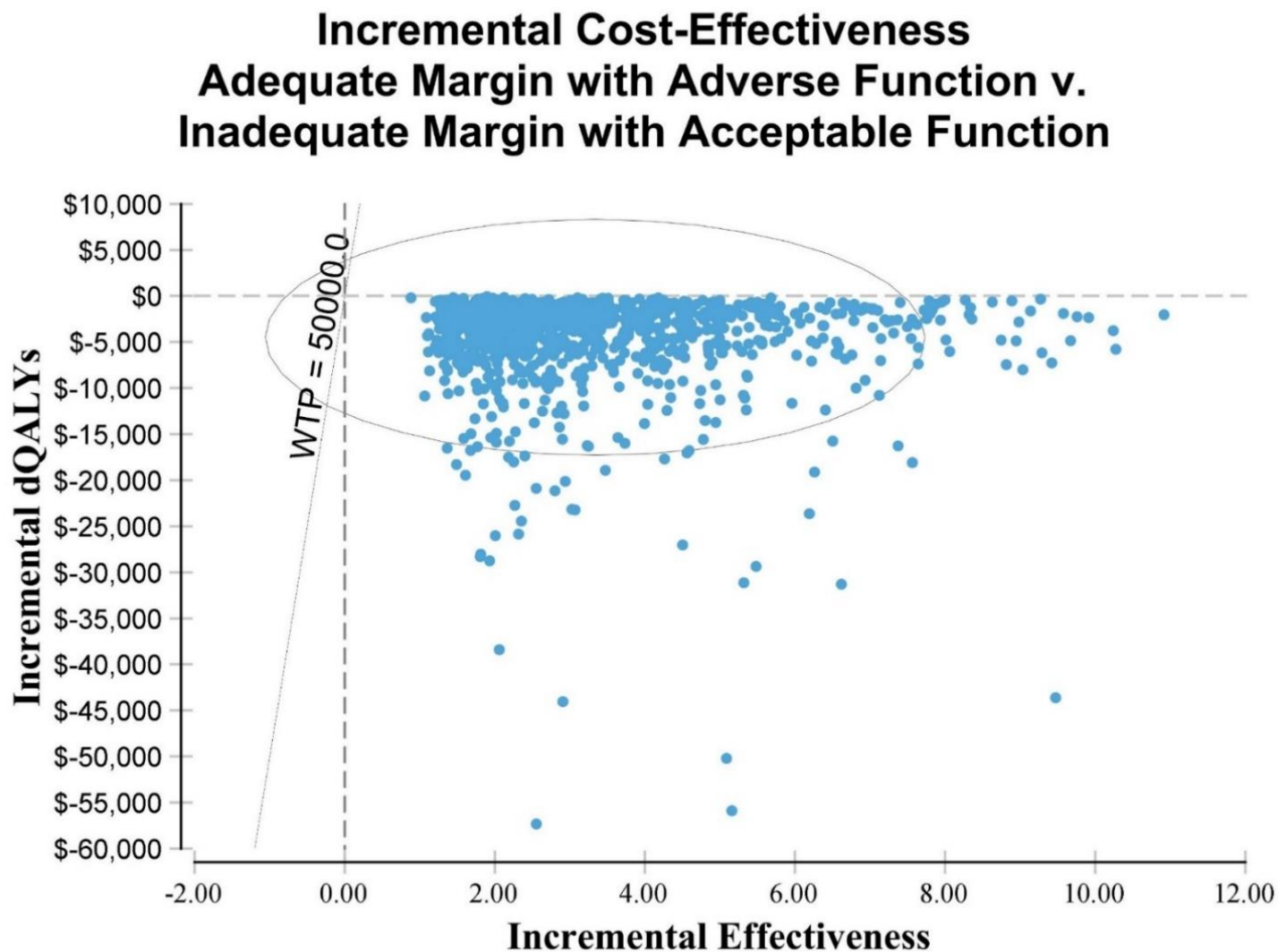
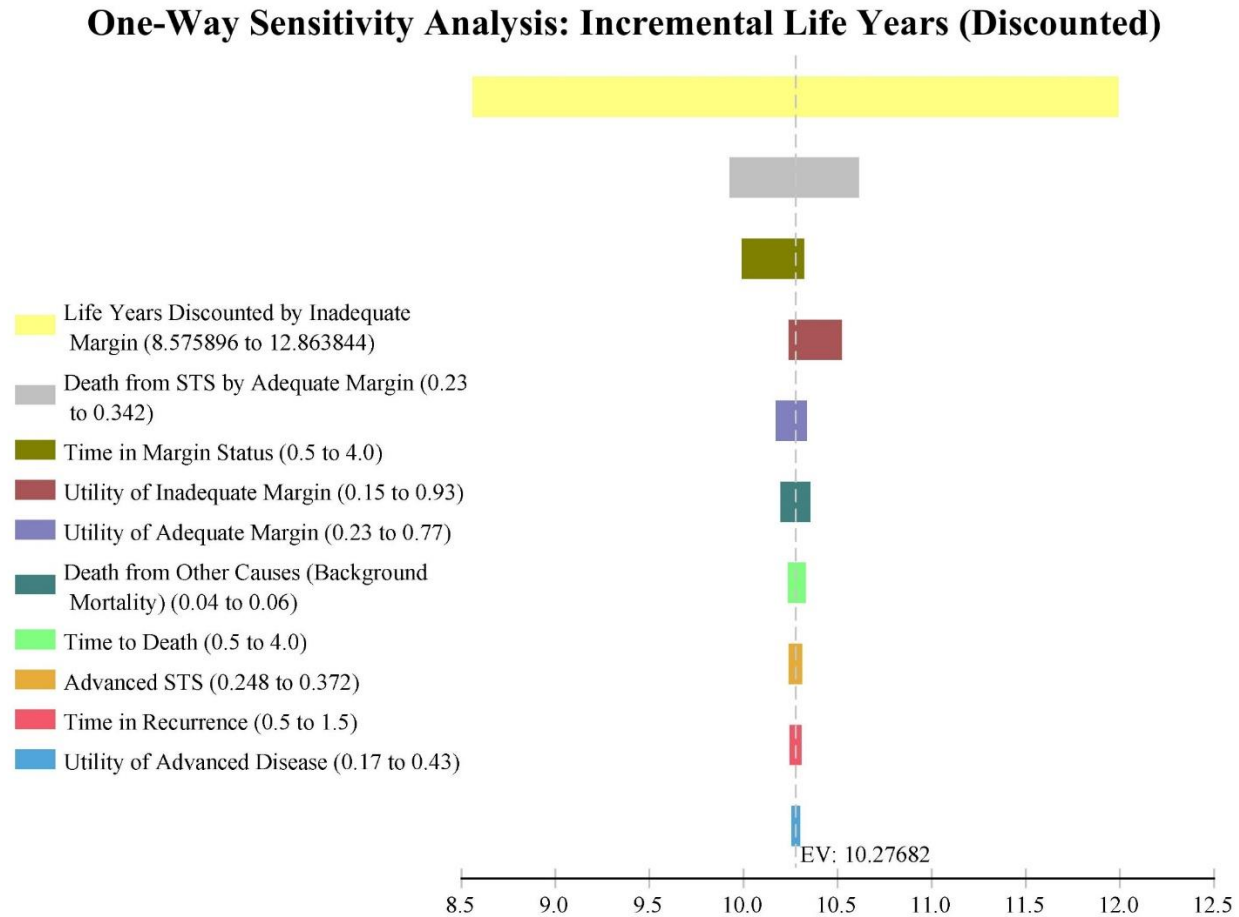


Figure 5. Cost-Effectiveness Plane Scatterplot (Surgeon Model) DOMINATE



#### IV.I APPENDIX

Figure 6. Tornado Diagram of One-Way Sensitivity Analyses for Discounted Life Years (Surgeon Model)





## Chapter V. Appendices

### Appendix I: Human Subjects Approval

Date: September 24, 2014

PI: Mrs. Amy Cizik, PhD Graduate Student  
Pharmacy

RE: Exempt Status Request, HSD Study #48324  
"Variations in Surgeon Treatment Preferences and Their Impact on the Cost-Utility of Surgery for Soft Tissue Sarcoma: Surgeon-Based Preference Values"

Dear Mrs. Cizik:

The University of Washington Human Subjects Division (HSD) has determined that your research qualifies for exempt status in accordance with the federal regulations under 45 CFR 46.101/ 21 CFR 56.104. Details of this determination are as follows:

**Exempt category determination: 7**

**Determination period: 9/24/2014 - 9/23/2019**

Although research that qualifies for exempt status is not governed by federal requirements for research involving human subjects, investigators still have a responsibility to protect the rights and welfare of their subjects, and are expected to conduct their research in accordance with the ethical principles of *Justice*, *Beneficence* and *Respect for Persons*, as described in the Belmont Report, as well as with state and local institutional policy.

**Determination Period:** An exempt determination is valid for five years from the date of the determination, as long as the nature of the research activity remains the same. If there is any substantive change to the activity that has determined to be exempt, one that alters the overall design, procedures, or risk/benefit ratio to subjects, the exempt determination will no longer be valid. Exempt determinations expire automatically at the end of the five-year period. If you complete your project before the end of the determination period, it is not necessary to make a formal request that your study be closed. Should you need to continue your research activity beyond the five-year determination period, you will need to submit a new *Request for Determination of Exempt Status* form for review and determination *prior to implementation*.

**Revisions:** Only modifications that are deemed "minor" are allowable, in other words, modifications that do not change the nature of the research and therefore do not affect the validity of the exempt determination. **Please refer to the Guidance document for more information about what are considered minor changes.** If changes that are considered to be "substantive" occur to the research, that is, changes that alter the nature of the research and therefore affect the validity of the exempt determination, a new *Request for Determination of Exempt Status* must be submitted to HSD for review and determination *prior to implementation*.

**Problems:** If issues should arise during the conduct of the research, such as unanticipated problems, adverse events or any problem that may increase the risk to the human subjects and change the category of review, notify HSD promptly. Any complaints from subjects pertaining to the risk and benefits of the research must be reported to HSD.

Please use the HSD study number listed above on any forms submitted which relate to this research, or on any correspondence with the HSD office.

Good luck in your research. If we can be of further assistance, please contact us at (206) 543-0098 or via email at [hsdinfo@uw.edu](mailto:hsdinfo@uw.edu). Thank you for your cooperation.

Sincerely,  
Marya Kinsler  
Human Subjects Review Coordinator  
Subcommittee EB  
(206) 543 – 0471 [maryaj@uw.edu](mailto:maryaj@uw.edu)

## Appendix II: Terminology

For the purposes of this proposal, the following surgical margin and functional dissertation descriptions will be used. Dissertation terms were defined in such a way that they can be used interchangeably with the following clinical/surgical terms and Enneking margin classification system definitions:

| Dissertation Terms     | Clinical/Surgical Terms               | Enneking Margin Classification <sup>(119)</sup> |
|------------------------|---------------------------------------|-------------------------------------------------|
| Positive Margin Status | Inadequate/Inappropriate              | Narrow/Intralesional                            |
| Negative Margin Status | Adequate/Appropriate/Planned Positive | Wide/Radical                                    |
| Good Functional Status | Acceptable                            |                                                 |
| Poor Functional Status | Adverse                               |                                                 |

Appendix III: Table 2. Power and Sample Size Estimates

| <b>Power</b> | <b>True Mean Difference between Health States or Groups</b> | <b>Standard Deviation (SD<sub>sample</sub>)</b> | <b>Total Sample Size for Paired Measurements (N)</b> | <b>If Comparing to Population (two sample t test)</b> | <b>Total Sample Size Comparing Surgeons to Population (2N)</b> |
|--------------|-------------------------------------------------------------|-------------------------------------------------|------------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------------|
| 75%          | 0.03                                                        | 0.062                                           | 32                                                   | 60                                                    | 120                                                            |
| 75%          | 0.03                                                        | 0.036                                           | 12                                                   | 21                                                    | 42                                                             |
| 80%          | 0.03                                                        | 0.062                                           | 35                                                   | 68                                                    | 136                                                            |
| 80%          | 0.03                                                        | 0.036                                           | 13                                                   | 24                                                    | 48                                                             |
| 85%          | 0.03                                                        | 0.062                                           | 40                                                   | 78                                                    | 156                                                            |
| 85%          | 0.03                                                        | 0.036                                           | 15                                                   | 27                                                    | 54                                                             |
| 90%          | 0.03                                                        | 0.062                                           | 47                                                   | 91                                                    | 182                                                            |
| 90%          | 0.03                                                        | 0.036                                           | 17                                                   | 31                                                    | 62                                                             |
| 95%          | 0.03                                                        | 0.062                                           | 57                                                   | 112                                                   | 224                                                            |
| 95%          | 0.03                                                        | 0.036                                           | 21                                                   | 38                                                    | 76                                                             |
| 97%          | 0.03                                                        | 0.062                                           | 65                                                   | 127                                                   | 254                                                            |
| 97%          | 0.03                                                        | 0.036                                           | 23                                                   | 43                                                    | 86                                                             |
| 99%          | 0.03                                                        | 0.062                                           | 80                                                   | 158                                                   | 316                                                            |
| 99%          | 0.03                                                        | 0.036                                           | 28                                                   | 54                                                    | 108                                                            |
| 100%         | 0.03                                                        | 0.062                                           | 140                                                  | 276                                                   | 552                                                            |
| 100%         | 0.03                                                        | 0.036                                           | 48                                                   | 94                                                    | 188                                                            |

Appendix IV: Standard Gamble Scoring Sheet

**Standard Gamble Score Sheet (HS2 v HS3)**

|                 | Prefer A                         | Prefer B                         | Equal                            |
|-----------------|----------------------------------|----------------------------------|----------------------------------|
| 1. 100/0 (Q61)  | <input type="checkbox"/><br>Q78  | <input type="checkbox"/><br>1.0  | <input type="checkbox"/><br>1.0  |
| 2. 0/100 (Q65)  | <input type="checkbox"/><br>0.0  | <input type="checkbox"/><br>Q66  | <input type="checkbox"/><br>0    |
| 3. 90/10 (Q66)  | <input type="checkbox"/><br>Q67  | <input type="checkbox"/><br>Q79  | <input type="checkbox"/><br>0.90 |
| 4. 10/90 (Q78)  | <input type="checkbox"/><br>Q65  | <input type="checkbox"/><br>Q66  | <input type="checkbox"/><br>0.10 |
| 5. 95/5 (Q79)   | <input type="checkbox"/><br>0.05 | <input type="checkbox"/><br>0.95 | <input type="checkbox"/><br>0.95 |
| 6. 80/20 (Q68)  | <input type="checkbox"/><br>Q69  | <input type="checkbox"/><br>0.85 | <input type="checkbox"/><br>0.80 |
| 7. 20/80 (Q67)  | <input type="checkbox"/><br>0.15 | <input type="checkbox"/><br>Q68  | <input type="checkbox"/><br>0.20 |
| 8. 70/30 (Q70)  | <input type="checkbox"/><br>Q71  | <input type="checkbox"/><br>0.75 | <input type="checkbox"/><br>0.70 |
| 9. 30/70 (Q69)  | <input type="checkbox"/><br>0.25 | <input type="checkbox"/><br>Q70  | <input type="checkbox"/><br>0.30 |
| 10. 60/40 (Q72) | <input type="checkbox"/><br>Q73  | <input type="checkbox"/><br>0.65 | <input type="checkbox"/><br>0.60 |
| 11. 40/60 (Q71) | <input type="checkbox"/><br>0.35 | <input type="checkbox"/><br>Q72  | <input type="checkbox"/><br>0.40 |
| 12. 50/50 (Q73) | <input type="checkbox"/><br>0.45 | <input type="checkbox"/><br>0.55 | <input type="checkbox"/><br>0.50 |

## Consent and Demographic Questions

To see the survey in its entirety please go to the following websites to test the surveys:

First Run: [http://washington.co1.qualtrics.com/SE/?SID=SV\\_71nn68QjeUaHT8N](http://washington.co1.qualtrics.com/SE/?SID=SV_71nn68QjeUaHT8N)

Revision: [http://washington.co1.qualtrics.com/SE/?SID=SV\\_39Q0jhluqtXKHmB](http://washington.co1.qualtrics.com/SE/?SID=SV_39Q0jhluqtXKHmB)

Surgeon STS Health State Randomized

Q2 CONSENT FORM FOR RESEARCH

Study

Title: Variations in Surgeon Treatment Preferences and Their Impact on the Cost-Utility of Surgery for Soft Tissue Sarcoma IRB Number: 48324 Version: 1.0 Approved:

09/24/2014

Researchers:

Amy M. Cizik, MPH Graduate

Student Pharmaceutical Outcomes Research and Policy Program Box 357630, 206-616-1383

Research Scientist Department of Orthopaedics and Sports Medicine Box 356500, 206-543-

3690 Darin J. Davidson, MD, MHSc, FRCSC Assistant Professor Department of

Orthopaedics and Sports Medicine Box 356500, 206-543-3690 Beth Devine, PhD,

PharmD, MBA Associate Professor Pharmaceutical Outcomes Research and Policy Program

Box 357630, 206-616-1383 Lou Garrison, PhD Professor and Graduate Student Advisor

Pharmaceutical Outcomes Research and Policy Program Box 357630, 206-616-1383

Investigator's Statement Soft tissue sarcomas are rare neoplasms most commonly found in the extremities. However, due to variability in surgical treatment patterns, there is continued debate on how to best treat this disease. The basis for these differences in surgical treatment preferences among surgeons is not well understood.

PURPOSE OF THE STUDY We

would like to better understand surgeon perspective in the surgical treatment of soft tissue sarcoma.

STUDY PROCEDURES

If you agree to be in this study, we will ask you to fill out an online questionnaire. The questionnaire will include information about your surgical training and sarcoma practice. Additionally, you will be presented health states that describe various stages of sarcoma treatment. The survey will be completed online. We may wish to take a photograph of you filling out the survey on your laptop, tablet or the study's

IPads. BENEFITS OF THE STUDY We hope that the results of this study will help

patients with sarcoma in the future. You may benefit directly from taking part in this study in

thinking about how you surgically treat patients with sarcoma.

ALTERNATIVES TO

BEING IN THIS STUDY Being in this study is voluntary. You do not have to be in this study if you do not want to be. You can stop at any time. You may refuse to participate and you are free to withdraw at any time from this study without penalty or loss of benefits to which you are otherwise entitled.

OTHER INFORMATION

Information about you is confidential. We will code information that you give. The principal investigator will keep your responses confidential and private. If you are photographed we will not identify you in the photograph. Photographs will be used in future research presentations to demonstrate feasibility of conducting this type of research using this technology. The information is stored using Transport Layer Security (TLS) encryption (also known as HTTPS) for all transmitted data. The survey is also protected with passwords. When we publish the results of this study, no identifying information will be used. The following groups may need to review your responses: institutional oversight review offices at the research site, the UW, or state; and federal regulators.

Amy M. Cizik, MPH Subject's

statement This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later on about the research I can ask one of the researchers listed above. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098. I give my permission for the researchers use my medical records as described in this consent form. I will receive a copy of this consent form.

☐ Yes

☐ No

Q9 If you wish to receive further communication about this survey or the results of this study, please provide the following below: (optional)

Q8 First Name

Q8 Last Name

Q9 Email Address

Q11 How would you describe your practice type? (Please check all boxes that apply)

☐ Solo/2-Physician Practice

☐ Group Practice, 3 - 5

☐ Group Practice, 6 - 50

☐ Group Practice, 51+

☐ Group / Staff HMO

☐ Community Health Center

☐ Medical School / University

☐ Hospital

☐ Government Employee/National Health Service

☐ Other (Please Specify) \_\_\_\_\_

Q12 Where is your practice located? (City, State, Country)

Q10 What is your highest degree?

☐ MD/MBChB/BMBCh/DO/BMBS/MBBS

☐ ARNP

☐ RN

☐ Physician Assistant

- ☐ PhD or other non-medical doctoral or terminal degree
- ☐ Masters
- ☐ Bachelors

Q10 How many years in practice?

Q11 What is your specialty?

- ☐ Surgical Oncology
- ☐ Orthopaedic Oncology
- ☐ Medical Oncology
- ☐ Radiation Oncology
- ☐ Pathology
- ☐ Other (Please Specify) \_\_\_\_\_

Q16 How many sarcoma cases do you diagnosis/treat on average each year?

- ☐
- ☐ 1 - 4
- ☐ 5 - 24
- ☐ 25 - 50
- ☐ 50 - 100
- ☐ > 100

Q12 Did you complete a dedicated fellowship or post-graduate training specializing in sarcoma?

- ☐ No
- ☐ Yes

Q13 Where did you complete your post-graduate sarcoma specialty training? Please provide the following information:

Q14 Institution Name

Q15 Institution Location (city, state, country)

Q17 What is your age?

Q18 What is your gender?

☐ Male

☐ Female

Q19 What is your country of origin?

Q20 In general, how would you rate your overall health?

☐ Poor

☐ Fair

☐ Good

☐ Very Good

☐ Excellent

Q22 For the following questions please read the following For the next set of questions, we are asking you to mark your **acceptable level of the probability** of local recurrence and physical function for the following scenario: primary surgical excision **with curative intent** during the coming year for a patient who is > 18 years of age (adult), diagnosed with a soft tissue sarcoma, which is high grade, located deep in the extremity.

For treatment with curative intent - how would you mark your level? Drag the slider bar below to show that in the next year for the patient described above you are willing to accept the following probability:

Q21 What is the highest probability of local recurrence you would be willing to accept?

\_\_\_\_\_ Local Control (i.e. Recurrence Rate)

Q23 What is the highest probability of loss of physical function you would be willing to accept?

\_\_\_\_\_ Physical Function



Q24 For the following questions please read the following: For the next set of questions, we are asking you to mark the PROBABILITY of certain scenarios following primary surgical excision during the coming year for a patient who is > 18 years of age (adult), who was diagnosed with a soft tissue sarcoma, which is high grade, located deep in the extremity. Drag the slider bar below to show that in the next year for the patient described above you are willing to accept the following probability:

Q25 What is the probability of a local recurrence following primary surgical excision?  
\_\_\_\_\_ with an adequate margin?  
\_\_\_\_\_ with an inadequate margin?

Q29 What is the probability of metastatic disease following local recurrence?  
\_\_\_\_\_ after re-excision?  
\_\_\_\_\_ after NO re-excision?

Q502 How good or bad is your health TODAY?  
\_\_\_\_\_ My health TODAY

## Appendix V: Health States

**Key: \* - Used in First Run Survey Only, + - Used in Both First Run and Revision Survey**

### Perfect Health State (Full Health - HS01) +

You are healthy. You do not have a life-threatening illness.  
You do not have dysfunction that limits you physically. You do have difficulty in running long distances.  
You are able to wash and dress yourself and do jobs around the home.  
You have no problems in your ability to shop and perform other daily activities.  
You are able to socialize with friends and family.  
You have no pain  
You feel calm and happy and experience no worry related to your health.  
You have a lot of energy all of the time.

### Death +

Imagine that sometime within the next month you will die, without pain and discomfort. .

### Adequate Margin and Acceptable Functional Outcomes (311222 – HS1) +

You had a life-threatening illness which has responded to treatment.  
You have undergone an operation which has left you with some unsightly scarring.  
You have lost some weight.  
You have a little difficulty in walking long distances.  
You are able to wash and dress yourself and do jobs around the home.  
You have no problems in your ability to shop and perform other daily activities.  
You are able to socialize with friends and family and never have to cut it short due to your illness.  
You have pain, but it does not interfere with activities listed above.  
You experience a little anxiety but you are pleased that you are responding to treatment.  
You feel a little worried about dying and how your loved ones will manage without you.  
You have a lot of energy most of the time.

### Adequate Margin and Adverse Functional Outcomes (422332 – HS2) +

You had a life-threatening illness which has responded to treatment.  
You have undergone an operation which has left you with some unsightly scarring.  
You have lost some weight.

You have a lot of difficulty in walking long distances.  
You are able to wash and dress yourself, but limited in jobs around the home due to physical health.  
You are limited in your ability to shop and perform other daily activities due to your physical health.  
You are able to socialize with friends and family and a little of the time have to cut it short due to your illness.  
You have a little pain that interferes with activities listed above.  
You experience some anxiety but you are pleased that you are responding to treatment.  
You some of the time feel worried about dying and how your loved ones will manage without you.  
You have a lot of energy most of the time.

Inadequate Margin and Acceptable Functional Outcomes (211232-HS3) +

You had a life-threatening illness which has responded to treatment.  
You have undergone an operation which has left you with some unsightly scarring.  
You have lost some weight.  
You have a little difficulty in running long distances.  
You are able to wash and dress yourself and do jobs around the home.  
You have no problems in your ability to shop and perform other daily activities.  
You are able to socialize with friends and family and never have to cut it short due to your illness.  
You have pain, but it does not interfere with activities listed above.  
You experience some anxiety but you are pleased that you are responding to treatment.  
You some of the time feel worried about dying and how your loved ones will manage without you.  
You have a lot of energy most of the time.

Inadequate Margin and Adverse Functional Outcomes (322342-HS4) +

You had a life-threatening illness which has responded to treatment.  
You have undergone an operation which has left you with some unsightly scarring.  
You have lost some weight.  
You have a little difficulty in walking long distances.  
You are able to wash and dress yourself, but limited in jobs around the home due to physical health.  
You are limited in your ability to shop and perform other daily activities due to your physical health.  
You are able to socialize with friends and family and a little of the time have to cut it short due to your illness.  
You have a little pain that interferes with activities listed above.  
You experience anxiety most of the time but you are pleased that you are responding to treatment.

You most of the time feel worried about dying and how your loved ones will manage without you.

You have a lot of energy most of the time.

#### Adequate Margin and Acceptable Functional Outcomes with Metastatic Disease

(333333-HS5)\*

You have a life-threatening illness and your condition is getting worse despite undergoing rounds of treatment.

You have undergone an operation which has left you with some unsightly scarring.

You have lost your appetite and you have lost some weight.

You have a little difficulty in walking long distances.

You are able to wash and dress yourself and do jobs around the home.

You accomplish less than you would like due to your emotional health.

You are able to socialize with friends and family and some of the time have to cut it short due to your illness.

You have a little pain that interferes with activities listed above.

You experience anxiety some of the time about not responding to treatment.

You some of the time feel worried about dying and how your loved ones will manage without you.

You have a lot of energy some of the time.

#### Adequate Margin and Adverse Functional Outcomes with Metastatic Disease (444433-

HS6) +

You have a life-threatening illness and your condition is getting worse despite undergoing rounds of treatment.

You have undergone an operation which has left you with some unsightly scarring.

You have lost your appetite and you have lost some weight.

You have a lot of difficulty in walking long distances.

You are able to wash and dress yourself and do jobs around the home.

You are limited in your ability to shop and perform other daily activities due to your physical health and accomplish less than you would like due to your emotional health.

You are often too tired to enjoy spending time with friends and family and most of the time have to cut it short due to your illness.

You have some pain that interferes with activities listed above.

You experience anxiety some of the time about not responding to treatment.

You some of the time feel worried about dying and how your loved ones will manage without you.

You have a lot of energy some of the time.

Inadequate Margin and Acceptable Functional Outcomes with Metastatic Disease

(233343-HS7)\*

You have a life-threatening illness and your condition is getting worse despite undergoing rounds of treatment.

You have undergone an operation which has left you with some unsightly scarring.

You have lost your appetite and you have lost some weight.

You have a little difficulty in running long distances.

You are able to wash and dress yourself and do jobs around the home.

You accomplish less than you would like due to your emotional health.

You are able to socialize with friends and family and some of the time have to cut it short due to your illness.

You have a little pain that interferes with activities listed above.

You experience anxiety most of the time about not responding to treatment.

You most of the time feel worried about dying and how your loved ones will manage without you.

You have a lot of energy some of the time.

Inadequate Margin and Adverse Functional Outcomes with Metastatic Disease (344443-

HS8)\*

You have a life-threatening illness and your condition is getting worse despite undergoing rounds of treatment.

You have undergone an operation which has left you with some unsightly scarring.

You have lost your appetite and you have lost some weight.

You have a little difficulty in walking long distances.

You are able to wash and dress yourself and do jobs around the home.

You are limited in your ability to shop and perform other daily activities due to your physical health and accomplish less than you would like due to your emotional health.

You are often too tired to enjoy spending time with friends and family and most of the time have to cut it short due to your illness.

You have some pain that interferes with activities listed above.

You experience anxiety most of the time about not responding to treatment.

You most of the time feel worried about dying and how your loved ones will manage without you.

You have a lot of energy some of the time.

Adequate Margin and Acceptable Functional Outcomes with Local Recurrence and  
Reexcision (421423-HS9)\*

You had a life-threatening illness which did not respond to first treatment and required a second treatment.

You have undergone operations which has left you with unsightly scarring.

You have lost some weight.

You have a lot of difficulty in walking long distances.

You are able to wash and dress yourself, but limited in jobs around the home due to physical health.

You are limited in your ability to shop and perform other daily activities due to your physical health.

You are able to socialize with friends and family and never have to cut it short due to your illness.

You have some pain that interferes with activities listed above.

You experience some anxiety about not initially responding to treatment.

You some of the time feel worried about dying and how your loved ones will manage without you.

You have a lot of energy some of the time.

Adequate Margin and Adverse Functional Outcomes with Local Recurrence and  
Reexcision (522423-HS10) +

You had a life-threatening illness which did not respond to first treatment and required a second treatment.

You have undergone operations which has left you with unsightly scarring.

You have lost some weight.

You have a little difficulty in washing and dressing yourself and are limited in jobs around the home due to physical health.

You are able to socialize with friends and family and a little of the time have to cut it short due to illness.

You have some pain that interferes with activities listed above.

You experience a little anxiety about not initially responding to treatment.

You feel a little worried about dying and how your loved ones will manage without you.

You have a lot of energy some of the time.

Adequate Margin and Acceptable Functional Outcomes with Local Recurrence and No  
Reexcision (313333-HS11)\*

You have a life-threatening illness which did not respond to first treatment.

You have undergone an operation which has left you with some unsightly scarring.  
You have lost some weight.  
You have a little difficulty in walking long distances.  
You are able to wash and dress yourself and do jobs around the home.  
You have no problems in your ability to shop and perform other daily activities.  
You are able to socialize with friends and family and some of the time have to cut it short due to your illness.  
You have a little pain that interferes with activities listed above.  
You experience anxiety some of the time about not responding to treatment.  
You some of the time feel worried about dying and how your loved ones will manage without you.  
You have a lot of energy some of the time.

#### Adequate Margin and Adverse Functional Outcomes with Local Recurrence and No

##### Reexcision (424443-HS12) +

You have a life-threatening illness which did not respond to first treatment.  
You have undergone an operation which has left you with some unsightly scarring.  
You have lost some weight.  
You have a lot of difficulty in walking long distances.  
You are able to wash and dress yourself, but limited in jobs around the home due to physical health.  
You are limited in your ability to shop and perform other daily activities due to your physical health.  
You are often too tired to enjoy spending time with friends and family and most of the time have to cut it short due to your illness.  
You have some pain that interferes with activities listed above.  
You experience anxiety most of the time about not responding to first treatment.  
You most of the time feel worried about dying and how your loved ones will manage without you.  
You have a lot of energy some of the time.

#### Inadequate Margin and Acceptable Functional Outcomes with Local Recurrence and

##### Reexcision (321322-HS13)\*

You had a life-threatening illness which did not respond to first treatment and required a second treatment.  
You have undergone operations which has left you with unsightly scarring.  
You have lost some weight.  
You have a little difficulty in walking long distances.

You are able to wash and dress yourself, but limited in jobs around the home due to physical health.

You are limited in your ability to shop and perform other daily activities due to your physical health.

You are able to socialize with friends and family and never have to cut it short due to your illness.

You have a little pain that interferes with activities listed above.

You experience a little anxiety about not initially responding to treatment.

You feel a little worried about dying and how your loved ones will manage without you.

You have a lot of energy most of the time.

#### Inadequate Margin and Adverse Functional Outcomes with Local Recurrence and

##### Reexcision (422433-HS14)\*

You had a life-threatening illness which did not respond to first treatment and required a second treatment.

You have undergone operations which has left you with unsightly scarring.

You have lost some weight.

You have a lot difficulty in walking long distances.

You are able to wash and dress yourself, but limited in jobs around the home due to physical health.

You are limited in your ability to shop and perform other daily activities due to your physical health.

You are able to socialize with friends and family and a little of the time have to cut it short due to illness.

You have some pain that interferes with activities listed above.

You experience some anxiety about not initially responding to treatment.

You some of the time feel worried about dying and how your loved ones will manage without you.

You have a lot of energy some of the time.

#### Inadequate Margin and Acceptable Functional Outcomes with Local Recurrence and No

##### Reexcision (213343-HS15)\*

You have a life-threatening illness which did not respond to first treatment.

You have undergone an operation which has left you with some unsightly scarring.

You have lost some weight.

You are able to wash and dress yourself and do jobs around the home.

You have no problems in your ability to shop and perform other daily activities.

You are able to socialize with friends and family and some of the time have to cut it short due to your illness.

You have a little pain that interferes with activities listed above.



You experience anxiety most of the time about not responding to treatment.  
You most of the time feel worried about dying and how your loved ones will manage without you.  
You have a lot of energy some of the time.

Inadequate Margin and Adverse Functional Outcomes with Local Recurrence and No  
Reexcision (324453-HS16) +

You have a life-threatening illness which did not respond to first treatment.  
You have undergone an operation which has left you with some unsightly scarring.  
You have lost some weight.  
You have a little difficulty in walking long distances.  
You are able to wash and dress yourself, but limited in jobs around the home due to physical health.  
You are limited in your ability to shop and perform other daily activities due to your physical health.  
You are often too tired to enjoy spending time with friends and family and most of the time have to cut it short due to your illness.  
You have some pain that interferes with activities listed above.  
You are depressed about not responding to first treatment and often think about dying.  
You always feel worried about dying and how your loved ones will manage without you.  
You have a lot of energy some of the time.