

A Prospective, Multi-Center Study of the IlluminOss[®]
Photodynamic Bone Stabilization System for the
Treatment of Impending and Actual Pathological
Fractures in the Humerus from Metastatic Bone Disease

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Statistical Analysis Plan (SAP)

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IlluminOss Medical, Inc.
Protocol Number: 14-03-PATHOLHUM-02

A Prospective, Multi-Center Study of the IlluminOss® Photodynamic Bone Stabilization System for the Treatment of Impending and Actual Pathological Fractures in the Humerus from Metastatic Bone Disease

STATISTICAL ANALYSIS PLAN
FOR CE SUBMISSION

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LIST OF ABBREVIATIONS

Abbreviation	Term
aCRF	Annotated Case Report Form
ADL	Activities of Daily Living
AE	Adverse Event
CE	European Conformity
CI	Confidence Interval
CM	Concomitant Medication
CRF	Case Report Form
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
FI	Functional Interference
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IRB	Internal Review Board
ITT	Intent-to-treat Population
MBD	Metastatic Bone Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
MSTS	Musculoskeletal Tumor Society
N, n	Number of subjects/subjects in a sample from a population or analysis group
PA	Psychosocial Aspects
PBSS	IlluminOss Photodynamic Bone Stabilization System
PC	Pain Characteristics
PET	polyethylene terephthalate
PI	Principal Investigator
PS	Painful Sites
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent AE
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale

1.0 INTRODUCTION

The purpose of this document is to provide further details about the statistical analysis methods, data derivations and data summaries to be employed in the CE submission analysis of 14-03-PATHOLHUM-02: *A Prospective, Multi-Center Study of the IlluminOss® Photodynamic Bone Stabilization System for the Treatment of Impending and Actual Pathological Fractures in the Humerus from Metastatic Bone Disease*. This statistical analysis plan (SAP) for CE submission has been based on International Conference on Harmonisation (ICH) E3 and E9 guidelines and in reference to protocol 14-03-PATHOLHUM-02 version 4.0: date 24 September 2015. The statistical analysis plan covers statistical analysis, tabulations and listings of data including effectiveness and safety data.

For the purposes of this SAP for CE submission, the effectiveness success criteria (subject success) will be defined as a composite endpoint of $\geq 33\%$ change from baseline in VAS and $\geq +10\%$ improvement from baseline in MSTs Upper Extremity Functional Outcome. This effectiveness success criteria is a deviation from the original US protocol but remains in line with the original success criteria specified in the EU protocol.

Any major deviations from the methods specified in this document and the protocol will be discussed and documented in the CE submission study report.

2.0 STUDY OBJECTIVES

The primary objective of this study is to evaluate safety and performance data of the IlluminOss Photodynamic Bone Stabilization System (PBSS) when used for the treatment of painful impending and actual fractures of the humerus secondary to metastatic malignancy.

3.0 STUDY DESIGN

3.1 Description of the Disease

Metastases from cancer are the most common malignancy involving the skeletal system.¹ In the United States alone, of the over 1.4M (2011) patients diagnosed with cancer annually, over 700,000 will be diagnosed with metastases to bone in addition to an underlying prevalence of 280,000 cases.^{1, 2} Compared to the relatively few primary bone cancers per year, with an incidence of 3,010 (2013)³, the economic burden of metastatic disease to bone is enormous: consuming \$12.6B (2007) in healthcare spend and 17% of the \$74B in total direct cost of oncologic care estimated by the National Institutes of Health.⁴ Prevalence, incidence, and cost estimates for metastatic bone disease (MBD) are projected to continue growing as with improved medical treatment of many primary cancers, patients are living longer, becoming more likely to develop distant bone metastases.⁵

The skeleton is the third most common target of distant metastases⁴, following lung and liver. The axial skeleton is predominantly affected, with MBD of the spine occurring 40 times more frequently than all primary bone tumors combined.⁶ After the axial skeleton, MBD affects the femur, humerus, and tibia in decreasing incidence. Please refer protocol section 1.1 for more details.

3.2 Study Design and Population

Study 14-03-PATHOLHUM-02 is a prospective, multi-center, open label study to evaluate the PBSS in the treatment of impending and actual pathological fractures of the humerus.

The investigation population consists of skeletally mature adults, suffering from pain due to impending and actual pathological fractures of the humerus secondary to confirmed metastatic malignancy.

A subject is considered enrolled in the clinical investigation after providing informed consent and after insertion of the device is attempted. Subjects who fail one or more of the eligibility criteria are considered screening/enrollment failures and are exited from the study.

After obtaining informed consent, the screening procedures will be performed at the screening visit as per the schedule of activities (Appendix 1). Subjects will be followed for 90 days after treatment and then followed in an extended follow up phase for up to 360 days.

Once the subject has been enrolled in the study, the subject may withdraw consent to participate in the study at any time without prejudice. Participation in this clinical investigation is entirely voluntary. The Principal Investigator (PI) may prematurely discontinue any subject's participation in the study if the PI feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. If a subject prematurely discontinues from the study, the reason for study termination will be recorded, if available. If termination was the result of an AE or death, completion of the appropriate AE forms and/or notifications will ensue. Whenever possible, an exit/final visit examination will be conducted prior to termination from the study. If possible, permission for contacting the subject for the assessment of long-term outcomes will be obtained. All reasonable efforts will be made to obtain complete data for all subjects.

3.3 Study Treatments and Assessments

PBSS is the only investigational device used in this study. At the investigator's discretion supplementary hardware in the form of bone screws and/or bone plates can be used for additional stabilization. Neither placebo nor any comparator is used. The PBSS is comprised of an inflatable, thin walled polyethylene terephthalate (PET; Dacron™) balloon mounted on an insertion catheter. This balloon catheter system is designed to deliver the monomer cement to the fracture site via the medullary canal of the bone. The study treatment is a onetime procedure and surgery will be done on visit 2. The follow-up evaluations will be scheduled for 7-14 (visit 3), 30 (visit 4), 90 (visit 5) days post-index procedure and the extended follow up at 180 (visit 6) and 360 (visit 7) days post-index procedure.

Throughout the study, subjects will be assessed for the study objectives as outlined in the schedule of activities (Appendix 1). The visit window details are outlined in the Appendix 2.

3.4 Randomization and Blinding

This study is an open-label, prospective clinical trial. There is no randomization of subjects or blinding.

3.5 Sample Size Justification

Approximately 80 subjects are being enrolled into 14-03-PATHOLHUM-02 study. At the time of this CE submission analysis, the study is still ongoing and all data entered into the database will be presented.

4.0 STATISTICAL CONSIDERATIONS

4.1 General Considerations

Statistical analyses will be performed using SAS software, version 9.2 or higher.

Continuous data will be summarized using number (n), mean, standard deviation (SD), minimum value, median, maximum value. Unless noted otherwise, summaries will be produced by visit (where applicable). If more than one value is reported at a scheduled visit, the value collected closest to the intended visit date will be used. In the case of a tie, the latest version will be summarized. If there are more than one value reported at the same date, take the average value of multiple values.

Categorical data will be summarized using number (n) and percentages. Percentages will be calculated based on the number of non-missing values. The number of missing values will be presented as a separate category with no percentage, if 1 or more subjects have missing data for the summary. Otherwise, all categories will be presented (even if no subjects are counted in the category). Counts of zero in any category will be presented without percentage.

All data will be presented on listings in order of site, subject and assessment date/time. Dates will be presented in the format DDMMYYYY. Times will be displayed in 24-hour clock format. Numbering of tables, figures and listings will follow ICH E3 guidelines.

Unscheduled measurements will be excluded from the descriptive statistical analysis. All the unscheduled measurements will be included in the listing.

4.2 Specification of Baseline Values

Baseline values are defined as the last non-missing assessment result collected prior to the surgery, unless otherwise noted.

4.3 Multiple Comparisons and Multiplicity

Not applicable.

5.0 ANALYSIS POPULATION

The Intent-to-Treat (ITT) population will be used as the analysis population for the primary endpoints, secondary endpoints, and safety endpoints. The Intent-to-Treat (ITT) analysis population is defined as all subjects who provide informed consent, undergo surgery, and have an implantation or attempted implantation of the IlluminOss Photodynamic Bone Stabilization System into the intramedullary canal; this includes subjects for whom implantation of the IlluminOss device is attempted but fails; such patients will be followed and included in the

ITT population. The ITT population is equivalent to the Full Analysis Set (FAS). The ITT population will serve as the primary analysis population. Effectiveness will be evaluated in the ITT population as primary.

6.0 METHODS OF ANALYSES AND PRESENTATIONS

6.1 Subject Disposition

The number of subjects enrolled, treated, and study completion status will be summarized. Subjects who discontinued from the study will be summarized and listed by their primary reason for discontinuation. Inclusion/exclusion criteria evaluation will be listed. These summaries will include all patients screened.

6.2 Protocol Deviations

Protocol deviation will be collected on CRF page. A summary of protocol deviations will be provided by visit and type. All protocol deviations collected on CRF will be listed. All enrolled patients will be included in the summary.

6.3 Demographic and Baseline Characteristics

Demographic data and subject characteristics at baseline will be summarized using descriptive summary statistics. The demographic and baseline characteristics of age, sex, ethnicity, race, work status, occupation, disability status, history of pain, smoking history, hand dominance, oncologic specific history (Yes or No) and fracture characteristics if evident will be summarized. All demographic and baseline characteristics will be listed.

6.4 Medical History

Medical history data will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0). Incidences of medical history will be tabulated by SOC and PT. All medical history data will be listed.

6.5 Prior and Concomitant Medication/Procedures

Concomitant medication is defined as any medications that are ongoing before and continue during the study as well as any potential medication started during the course of the study. Medications taken for a surgical procedure should also be included.

Prior medication is defined as any medication starting and ending before the surgery.

All prior/concomitant medication and concomitant procedure will be listed as recorded on CRF.

6.6 Effectiveness Endpoints and Analyses

The primary effectiveness analysis will be based on the ITT population. Descriptive summary statistics mentioned in section 4.1 will be performed for all. Summaries will be presented by visit. Comprehensive listings of all data will be presented.

6.6.1 Primary Efficacy Endpoint Analysis

The primary endpoint is the proportion of subjects who are confirmed to be a subject success at the Day 90 Visit. The number and percent along with the corresponding 95% binomial confidence intervals will be presented. If the proportion of subjects considered a subject success at the Day 90 Visit is at least 80%, then the primary endpoint will be met.

Subject success is determined by achieving the following effectiveness endpoints at the Day 90 Visit.

- Pain Reduction
 - VAS pain score change of $\geq -33\%$ compared to baseline
- Functional Improvement
 - MSTS Upper Extremity Functional Outcome improvement of $\geq +10\%$

6.6.2 Secondary Efficacy Endpoints and Analyses

6.6.2.1 Individual Components of the Primary Endpoint (Subject Success)

The individual components of the primary endpoint of subject success will be presented at the Day 90 Visit and the follow-up visits.

6.6.2.1.1 Pain Reduction

The number and percentage of subjects who have a VAS Pain Score change of $\geq -33\%$ compared to baseline at the day 90 visit will be presented along with the corresponding 95% binomial confidence interval. The percentage of subjects who have a VAS Pain Score change of $\geq -33\%$ compared to baseline at the day 180 and 360 visits will also be summarized for patients that have reached that time point. Summary statistics for VAS scores at baseline and changes from baseline to each follow-up visit will also be presented.

6.6.2.1.2 MSTS Upper Extremity Functional Outcome

The number and percentage of subjects who have an MSTS Upper Extremity Functional Outcome improvement of $\geq +10\%$ compared to baseline at the day 90 visit will be presented along with the corresponding 95% binomial confidence interval. The percentage of subjects who have an MSTS Upper Extremity Functional Outcome improvement of $\geq +10\%$ compared to baseline at the day 180 and 360 visits will also be summarized for patients who have reached that time point. Summary statistics for VAS scores at baseline and changes from baseline to each follow-up visit will also be presented. Details of MSTS scoring are in Appendix 3.

6.6.2.2 Procedure- and Device-related Complication Rate

The number and percentage of subjects who experience a procedure- or device-related complication by the day 90 visit will be presented along with the corresponding 95% binomial confidence interval. Subjects with more than one device malfunction will be counted only once. The percentage of subjects who experience the complications by the day 180 and 360 visits will also be summarized.

6.6.2.3 Duration of Index Procedure and Length of Hospital Stay

Date of surgery, start time and end time of procedure, date of admission, date of discharge, time of discharge are recorded on CRF. Duration of index procedure will be calculated as (End time of procedure - Start time of procedure) and summarized in hours. Length of hospital stay will be calculated as (Date of discharge - Date of admission) and summarized in days. Duration of index procedure and length of hospital stay during reoperation will also be summarized.

6.6.2.4 Pain at Palpation

Pain on palpation (Yes/No/Not done) is collected at each visit along with Grade (Mild/Moderate/Severe) and whether the pain is clinically significant (Yes/No). This information will be summarized.

6.6.2.5 Range of Motion

Range of motion tests for flexion, extension, abduction, lateral rotation, and medial rotation for both affected arm and unaffected arm will be summarized as both a categorical and a continuous variable. Change of range of motion values from baseline will be categorized as <0, <=10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, 91-100, 171-180 degrees. Number and percentage of subjects in each category will be summarized by visit and test. Range of motion test values and change from baseline values will be summarized by visit and test. Within each test the values will be summarized by active or passive and affected or unaffected arm. Baseline is defined as the 7 Day follow-up visit for this endpoint.

6.6.2.6 Activities of Daily Living Score (EORTC QLQ-BM22)

EORTC QLC-BM22 has four scales, two symptom scales (painful sites, pain characteristics) and two functional scales (functional interface, psychosocial aspects). Observed values and changes from baseline for the four scales will be summarized by visit. Details of EORTC QLC-BM22 scoring are in Appendix 4.

6.6.2.7 Assessment of Post-Surgery Status

The number and percent of subjects who receive physical therapy, supportive orthopedic device, or analgesic medication will be presented. Subjects who are prescribed with “Over-the-counter” or “Prescription” for analgesic medication will be counted as “Yes” to receive analgesic medication.

6.7 Safety Endpoints and Analyses

All safety endpoints will be summarized for ITT population. The safety endpoints are evaluated through Day 90 and extended follow up portion of the trial at Day 180 and 360.

6.7.1 Adverse Events (AEs)

Adverse events (AEs) will be collected from the time of surgery until the last study visit or premature discontinuation from the study.

Treatment-emergent adverse events (TEAEs) are those AEs which worsen in severity on or after date of surgery or with onset date on or after date of surgery. AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be considered TEAEs. Treatment-related includes possibly or probably or definitely relationship of the event to the investigational device, procedure, anesthesia, or oncology medicine.

All AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0). Incidences of TEAEs will be tabulated by SOC and PT. Incidences of TEAEs will also be presented by maximum severity, seriousness, un-anticipated adverse device effect (UADE) and relatedness (device or procedure related) at Day 90 and during the extended follow up visits. This includes the reporting of device revisions, reoperations, removals, supplemental fixations, or other procedures. Subjects who discontinued due to TEAEs will be summarized by SOC and PT in a separate table. Patients are counted only once in each SOC, and only once in each PT category.

The following tables will be developed for summarizing AEs.

- Overall summary of TEAEs, it includes number of treatment-emergent adverse events, subjects with any TEAE, subjects with any serious adverse events (SAE), subjects with any severe TEAEs, subjects with any device related TEAEs, subjects with any procedure related TEAEs, subjects with any anesthesia related TEAEs, subjects with any Oncology Medicine related TEAEs, subjects with any unanticipated adverse device effect (UADE), subjects with TEAEs leading to study discontinuation and death.
- Summary of TEAEs by system organ class and preferred terms
- Summary of TEAEs by system organ class, preferred terms and maximum severity
- Summary of treatment-related TEAEs by system organ class, preferred terms (device related, procedure related, anesthesia related and oncology medicine related).
- Summary of unanticipated adverse device effect (UADE) by system organ class and preferred terms
- Summary of serious adverse events (SAE) by system organ class and preferred terms

Serious SAEs, discontinuations due to TEAEs and deaths due to TEAEs will be listed.

6.7.2 Serious Device Related Complications

The number and percentage of subjects who experience a serious device related complication by the day 90 visit will be presented along with the corresponding 95% binomial confidence interval. Subjects with more than one serious device related complication will be counted only once. The percentage of subjects who experience the complications by the day 180 and 360 visits will also be summarized.

6.7.3 Surgical Interventions

The number and percentage of subjects who have additional surgical interventions (revisions, supplements, fixations or removals) by the day 90 visit will be presented along with the

corresponding 95% binomial confidence interval. Subjects with more than one surgical intervention will be counted only once. The percentage of subjects who have additional surgical interventions by the day 180 and 360 visits will also be summarized.

7.0 HANDLING OF MISSING VALUES

In general, for all variables only the observed data from the patients will be used in the analysis.

Missing data handling for the EORTC-QLQ-BM22 is described in Appendix 4.

No imputation of values for other missing data will be performed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. Adverse events with missing severity will be summarized as severe. Adverse events with missing causal relationship will be summarized as related. Missing safety data will not be replaced, except for AE and Concomitant Medication (CM) dates as described below.

Adverse Event:

If due to partial dates or times it is not possible to definitively conclude that an AE is not treatment emergent, then a conservative approach will be taken whereby it will be classified as a TEAE. e.g. if the surgery date is “13May” and the AE starts in “May”, then that AE will be classified as a TEAE, unless the AE stop date precludes this (i.e. the AE stop date is definitively prior to the surgery date).

See some more imputation scenarios;

- If onset date is completely missing, onset date is set to date of surgery.
- If (year is present and month and day are missing) or (year and day are present and month is missing):

If year = year of surgery, then set month and day to month and day of surgery

If year < year of surgery, then set month and day to December 31st unless the calculation results in a negative time duration.

If year > year of surgery, then set month and day to January 1st.

- If month and year are present and day is missing:

If year=year of surgery and month = month of surgery then set day to day of surgery date

If year=year of surgery and month < month of surgery then set day to last day of month

If year=year of surgery and month > month of surgery then set day to first day of month

If year < year of surgery then set day to last day of month

If year > year of surgery then set day to first day of month

For all other cases, set onset date to date of surgery.

Concomitant Medications:

Missing or partially missing medication date and prior or concomitant medication determination:

If due to partial dates it is not possible to categorize a medication as prior or concomitant, then a conservative approach will be taken whereby it will be classified as such e.g. if the surgery date is “13May” and another medication is started in “May”, then that medication will be classified as both previous and concomitant, unless the medication stop date precludes one of these classifications.

See some more imputation scenarios;

- If start date is completely missing, start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 1st.
- If year and month are present and day is missing, set day to 1st day of month.
- If end date is completely missing, end date will not be imputed.
- If year and month are present and day is missing, set day to last day of the month.

Incomplete diagnosis or treatment date

The incomplete diagnosis or treatment date will be imputed as below unless the calculation results in negative time duration. No imputation will be performed on time.

If day is missing, day will be set to 15th of the month.

If month is missing, month and day will be set to July 1st.

If year is missing, date will be set to missing.

8.0 INTERIM ANALYSIS

Not applicable.

9.0 CHANGES FROM ANALYSIS METHODS PLANNED IN THE PROTOCOL

The following changes from Study 14-03-PATHOLHUM-02 protocol were implemented in this SAP:

1. The effectiveness success criteria is a deviation from the original US protocol but remains in line with the original success criteria specified in the EU protocol.
2. Secondary endpoints have been identified per Section 7 of the protocol. This prioritization may vary from the study synopsis description.
3. Protocol section 7.8.6 specified “Range of motion will be assessed using ordinal variables reflecting the forward flexion, lateral elevation, external rotation, and internal rotation of the arm.” In order to reflect data collected on CRF, the range of motion measures in

section 6.6.2.4 have been modified to “At each visit, five tests for range of motion are performed: Flexion, Extension, Abduction, Lateral Rotation, and Medial Rotation.”

4. Protocol section 6.3 specified that “The values of the MSTS range from 0 to 30. The values have been divided by 30 and multiplied by 100% to facilitate interpretation.” In SAP Appendix 3, MSTS score is specified to be divided by 30 and multiplied by 100 for ease of interpretation.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1: Schedule of Activities

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening and Baseline	Surgery and Discharge	7-14 Day F/U (+3 days)	30 Day F/U (± 7 days)	90 Day F/U (± 14 days)	180 Day F/U (± 30 days)	360 Day F/U (± 30 days)
Inclusion/Exclusion Review	X						
Informed Consent	X						
Patient Medical History	X						
Physical Exam	X						
Intraoperative Data ¹		X					
Clinical Assessments ²			X	X	X	X	X
MSTS Score and EORTC QLQ BM22	X		X	X	X	X	X
Pain Visual Analog Scale (VAS)	X		X	X	X	X	X
Radiographs of Fracture Area	X		X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Concomitant/Pain Medications	X	X	X	X	X	X	X
Health Economic Assessment	X	X	X	X	X	X	X

¹ Including date of surgery, duration of surgery, impending fracture treatment used.

² Clinical assessments: standard fracture evaluations and other assessments, as appropriate, including but not limited to assessments for pain, return to pre-treatment mobility, range of motion, return to work, disability status, use of pain medication, and physical therapy prescription status.

Appendix 2: Classification of Visits

Timing of assessment (days relative to surgery ^a)	Visit	Visit Name to display for Analysis
Screening	Visit 1	Screening
Last assessment result collected prior to the surgery	Baseline	Baseline
Surgery and Discharge (ie Day 1)	Visit 2	Surgery and Discharge
7-14 Day F/U (+3 days)	Visit 3	7-14 Day F/U
30 Day F/U (± 7 days)	Visit 4	30 Day F/U
90 Day F/U (± 14 days)	Visit 5	90 Day F/U
180 Day F/U (± 30 days)	Visit 6	180 Day F/U
360 Day F/U (± 30 days)	Visit 7	360 Day F/U

a. Day 1 is the day of surgery.

Appendix 3: Musculoskeletal Tumor Society (MSTS) Rating Scale Completion Guidelines

The MSTS upper extremity functional score evaluates the functional status of patients with impending and actual fractures of the humerus. In the MSTS system, numeric values (0 to 5) are assigned to each of the six categories of pain, function, emotional, hand positioning, manual dexterity, and lifting ability. They give a total score of between 0 and 30 with 0 indicating poor and 30 good. The total MSTS score is recorded on CRF. It will be divided by 30 and multiplied by 100 to facilitate interpretation.

<i>Pain</i>		
<u>Score</u>	<u>Description</u>	<u>Clarification</u>
5	No pain	No medication
4	Intermediate	
3	Modest/Non-disabling	Non-Narcotic analgesics
2	Intermediate	
1	Moderate/Intermittently disabling	Intermittent narcotics
0	Severe/Continuously disabling	Continuous narcotics
<i>Function</i>		
<u>Score</u>	<u>Description</u>	<u>Clarification</u>
5	No restriction	No disability
4	Intermediate	
3	Recreational restriction	Minor disability
2	Intermediate	
1	Partial occupational restriction	Major disability
0	Total occupational restriction	Complete disability
<i>Emotional</i>		
Read to the patient the following statements and record the score that pertains to the one they choose that closely describes how he/she feels about the result of the surgical treatment for his/her tumor.		
<u>Score</u>	<u>Description</u>	<u>Clarification</u>
5	Enthused	I am enthusiastic and would recommend to others with the same problem.
4	Intermediate	I like it and would do it again.
3	Satisfied	I am satisfied and would do it again.
2	Intermediate	I accept it and would do it again.
1	Accepts	I accept it but would not do it again if there was another choice.

0	Dislikes	I dislike it and would not do it again.
<i>Hand Positioning</i>		
<u>Score</u>	<u>Description</u>	<u>Clarification</u>
5	Unlimited	180° elevation
4	Intermediate	
3	Not above shoulder or no prosupination	90° elevation
2	Intermediate	
1	Not above waist	30° elevation
0	None	0° elevation
<i>Manual Dexterity</i>		
<u>Score</u>	<u>Description</u>	<u>Clarification</u>
5	No limitations	Normal dexterity and sensibility
4	Intermediate	
3	Loss of fine movements	Cannot button, etc. or minor loss of sensitivity (specify)
2	Intermediate	
1	Cannot pinch	Major sensory loss (specify)
0	Cannot grasp	Anesthetic hand
<i>Lifting Ability</i>		
<u>Score</u>	<u>Description</u>	<u>Clarification</u>
5	Normal load	Matches normal
4	Intermediate	Less than less normal
3	Limited	Minor load
2	Intermediate	Gravity only
1	Helping only	Cannot overcome gravity
0	Cannot help	Cannot move

Appendix 4: Activities of Daily Living Score - EORTC-QLQ-BM22

The activities of daily living will be assessed by EORTC-QLQ-BM22, which is a 22-item questionnaire assessment composed of multi-item measures. It has been divided into the following categories: Painful Sites (PS), Pain Characteristics (PC), Functional Interference (FI), and Psychosocial Aspects (PA) (Table 1).

Scale Name	Number of Items	Items Numbers	Item Range*
Symptom scales			
Painful Sites (PS)	5	1-5	3
Pain Characteristics (PC)	3	6-8	3
Functional scales			
Functional Interference (FI)	8	9-16	3
Psychosocial Aspects (PA)	6	17-22	3

*Range is defined as the maximum and minimum scale values for a particular item. Since all items in BM22 questionnaire have maximum of 4 and minimum of 1, the range for all items are 3. All of the scales will be transformed to range in score from 0 to 100. A high score for the symptom scales represents a high level of symptomatology or problems, whilst a high score for the functional scales represents a high level of functioning.

With regards to the positive phrasing of questions 21 and 22, the scoring must be reversed prior to statistical analysis.

The detailed scoring procedure for the EORTC QLQ-BM22 is outlined below:

PS: Painful Sites Scale (items 1-5)

- Compute the raw score (mean scale score) if at least 3 of the items have a valid score.
 $XPS = \text{Mean of } (Q1 - Q5)$
- Carry out a linear transformation to convert to a 0-100 scale: $PS = \{(XPS - 1) / 3\} * 100$
- If fewer than 3 of the items have a valid score treat the scale as missing.

PC: Painful Characteristics Scale (items 6-8)

- Compute the raw score (mean scale score) if at least 2 of the items have a valid score.
 $XPC = \text{Mean of } (Q6 - Q8)$
- Carry out a linear transformation to convert to a 0-100 scale: $PC = \{(XPC - 1) / 3\} * 100$
- If fewer than 2 of the items have a valid score treat the scale as missing.

FI: Functional Interference Scale (items 9-16)

- Compute the raw score (mean scale score) if at least 4 of the items have a valid score.
 $XFI = \text{Mean of (Q9 – Q16)}$
- Carry out a linear transformation to convert to a 0-100 scale: $FI = \{1 - (XFI - 1) / 3\} * 100$
- If fewer than 4 of the items have a valid score treat the scale as missing.

PA: Psychosocial Aspects Scale (items 17-22)

- Reverse observed score for item 21-22 by 5 subtracted by Q21 or Q22
- Compute the raw score (mean scale score) if at least 3 of the items have a valid score.
 $XPA = \text{Mean of (Q17 – Q22)}$
- Carry out a linear transformation to convert to a 0-100 scale: $PA = \{1 - (XPA - 1) / 3\} * 100$
- If fewer than 3 of the items have a valid score treat the scale as missing.

Observed values and changes from baseline for the EORTC-QLQ-BM22 two symptom scales (PS, PC) and two function scales (FI, PA) will be summarized by visit.