Sponsor: MMI **Product: Symani system for microsurgical anastomosis** **Study: PRIMO**	statistical REVELATIONS *Transforming data into knowledge*
Statistical Analysis Plan Final 22 November 2024	

Statistical Analysis Plan title:

Integrated analysis of data collected prospectively in the PRIMO study[1] and retrospectively in the PRIMO study addendum.

[1] PRIMO study title:

Post-Market, Non-**R**andomized, Mult**i**centre PMCF Study To **Mo**nitor The Safety And Performance Of Symani System In Microsurgical Reconstructive Procedures In A Real Life Setting

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SIGNATURES

Statistical Analysis Plan title:

Integrated analysis of data collected prospectively in the PRIMO study[2] and retrospectively in the PRIMO study addendum.

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[2] PRIMO study title:

Post-Market, Non-**R**andomized, Mult**i**centre PMCF Study To **Mo**nitor The Safety And Performance Of Symani System In Microsurgical Reconstructive Procedures In A Real Life Setting

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADE	Adverse Device Event
AE	Adverse Event
BMI	Body Mass Index
CL	Confidence Limit
FAS	Full Analysis Set
OR	Operating Room
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
UADE	Unexpected Adverse Device Event

1. OVERVIEW AND INVESTIGATIONAL PLAN

1.1 Study design

The PRIMO study is a prospective, non-randomized, single arm, multicenter, post-market clinical follow-up (PMCF) study designed to evaluate the safety and effectiveness of the Symani System when used to assist microsurgical anastomoses in the real-world setting: i.e. it is a real world prospective observational data collection process. Patients selected will include adults (over 18 years) requiring microsurgical reconstructive procedures applied to arterial, venous, neural, or lymphatic anastomosis. Patients will be enrolled, undergo surgery, and have assessments made at regular intervals (day 1, day 4, day 14, day 30 (free flap), and 24 weeks (lymphatic anastomoses).

An addendum to the PRIMO study was prepared and approved in December 2022. The addendum describes the addition of retrospective data collection to the PRIMO study. This will include patients with the same profile as the prospective data collected in the PRIMO study (i.e. >= 18 years requiring microsurgical reconstructive procedures applied to arterial, venous, neural, or lymphatic anastomosis) and will collect as much data as possible (based on availability) using the same data collection process as for the prospective data collection. Accordingly, the PRIMO study describes two data sources (prospective data collection and retrospective data collection), both collected under a common protocol. There will be some case report forms defined for prospective data collection (in the PRIMO protocol), specifically nurse and clinician questionnaires, which will not be available for the data collected retrospectively (in the PRIMO addendum).

1.2 Purpose of this Statistical Analysis Plan (SAP)

This SAP describes endpoints to be analyzed for the PRIMO study, using data collected prospectively and retrospectively, where available, for all patients.

The purpose of this SAP is to provide a detailed description of the methods of analysis to be used for the PRIMO study endpoints.

1.3 Study Objectives

The objective of the PRIMO study is to monitor the safety, usability, performance, and long-term efficacy of the Symani System.

1.3.1 Endpoints

Primary endpoint

The primary endpoint is defined as the ability to complete the surgical task with Symani as intended by the surgeon. This endpoint will be referred to as “Procedure Robotic Success”.

Secondary endpoints

The main secondary endpoint will be the rating of the surgeon's experience of robot usability, which will be assessed using the usability questionnaire.

Further secondary endpoints will be assessed regarding the clinical outcome of the procedures (e.g. time for each anastomosis). Some of these endpoints may differ depending on the procedure performed (replantation, free flap surgery, lymphatic surgery or other).

Replantation

- Time for each anastomosis execution or nerve coaptation
- Warm ischemia time (minutes)
- Intraoperative need to redo the anastomosis (yes or no)
- Postoperative need to redo within 7 days (Complication and need to return to the operating room to explore anastomosis: yes or no)
- Complications
- Replantation Failure or Loss (subsequent amputation)

Free Flaps

- Time for each anastomosis execution
- Warm ischemia time (minutes)
- Intraoperative need to redo the anastomosis (yes or no)
- Postoperative need to redo within 7 days (Complication and need to return to the operating room to explore anastomosis: yes or no)
- Complications
- Flap Failure or Loss (yes or no)

Lymphatic Surgery

- Time for each anastomosis execution (in minutes)
- Intraoperative need to redo based on ICG Patency (yes or no)
- Postoperative need to redo based on ICG Patency (yes or no)
- Complications
- Limb volume reduction

1.3.2 Safety endpoints

The complications as indicated above, will be collected as adverse events (AE, SAE/ADE/SADE/ADE/DD) reported by patients or evaluated by the Surgeon from day 0 to either 30 days after surgery for free flaps, replantation and other procedures, or 24 weeks after surgery for the LVA procedures will be recorded.

1.4 Relevant study documents

- Protocol: CDC-00031 PRIMO Clinical Investigation Plan Rev. 03
- Addendum to protocol: CDC-00031 Rev03 - Addendum to PMCF Protocol for retrospective data collection Rev.01.pdf
- CRF Dendrite: CDC-00085 RASM PMCF Case Report Forms
- CRF Castor: CDC-00124 PRIMO Case Report Forms_Rev03

Note: Prospective patients enrolled prior to 01FEBRUARY2023 were collected in electronic data capture (EDC) Dendrite Clinical System (Dendrite). Prospective patients enrolled post 01FEBRUARY2023 were collected in the EDC Castor. All retrospective patients' data will be collected in the EDC Castor. Both EDC Case Report Forms contain the same data elements; however, the names and format of the CRFs have been revised in Castor for ease of use.

1.5 Modifications from the statistical section of the protocol

Modification to the definition of the FAS to only include patients who had at least one robotic suture placed.

Definition of a safety set to be all patients with at least one robotic suture attempted.

Amendment to the sample size section to note analysis at the anastomosis level and to remove notes about missing data as this is handled under data derivations.

Amendment to the sample size section to note that the total sample specified in the PRIMO study protocol can be achieved through prospective or retrospective patients. That is, the data of retrospective patients is now included in the target sample size.

Amendment to the analysis of the primary effectiveness endpoint to be at the anastomosis level rather than at the patient level.

Amendment to the analysis of anastomosis time to use a mixed model rather than a KM analysis. This change has been made since all anastomoses will have a time, so a specific 'time to event' analysis (eg KM) is not needed as there are no censored times. Using a mixed model will allow adjustment for the dependence in the data.

Definition of some additional efficacy endpoints namely:

- Free flap viability at 30 days
- Intra-operative anastomosis patency

Definition of some additional safety endpoints namely:

- Freedom from device related serious adverse events prior to discharge

- Freedom from device related adverse events prior to discharge
- All cause re-admission rates
- All cause re-operation rates up to 30 days
- All cause mortality rates up to 30 days

1.6 Modifications from the approved statistical analysis plan

N/A. This is the first version of the SAP.

1.7 Determination of sample size

The planned minimum sample size is 402 patients. The primary endpoint for the study is technical performance, assessed as a binary outcome procedural success Yes/No. Procedural success will be assessed at the anastomosis level; each patient may have > 1 anastomosis. Based on data published in the medical literature (see RASM Literature Review Report [5]), the traditional failure and complication rate for vascular anastomoses is 15%, implying a success rate of 85%. The study will have 85% power to conclude that a success rate using Symani of 89% (or higher) is better than the literature value if a minimum of 402 anastomoses operations are performed. The percentage success will be estimated and exact 95% confidence limits calculated. If the lower 95% confidence limit exceeds 85% then the conclusion can be reached that Symani is superior to manual surgical methods. As each patient may have more than one anastomosis operation, the number of anastomoses will be >= 402 from 402 patients, providing increased power. As the number of anastomoses/patient is unknown at the time of study design, the conservative approach of recruiting 402 patients has been followed.

The number of patients missing a response for the primary endpoint will be monitored and additional patients may be recruited if deemed necessary.

There will be no predetermined limit to the number of sites that can participate in the study. Patients enrolled under the retrospective data collection protocol addendum will contribute to the planned sample size for the entire study (prospective plus retrospective).

2. STATISTICAL AND ANALYTICAL PROCEDURE

The study has a hierarchical structure as follows:

- There are three types of surgery: free flaps, replantations, and lymphatic. A patient may have more than one type of surgery (e.g flap and replantation).
- Within a type of surgery, e.g. free flaps, a patient may have more than one procedure during an operation.
- Within each procedure, anastomoses are performed. More than one anastomosis may be performed within a procedure.

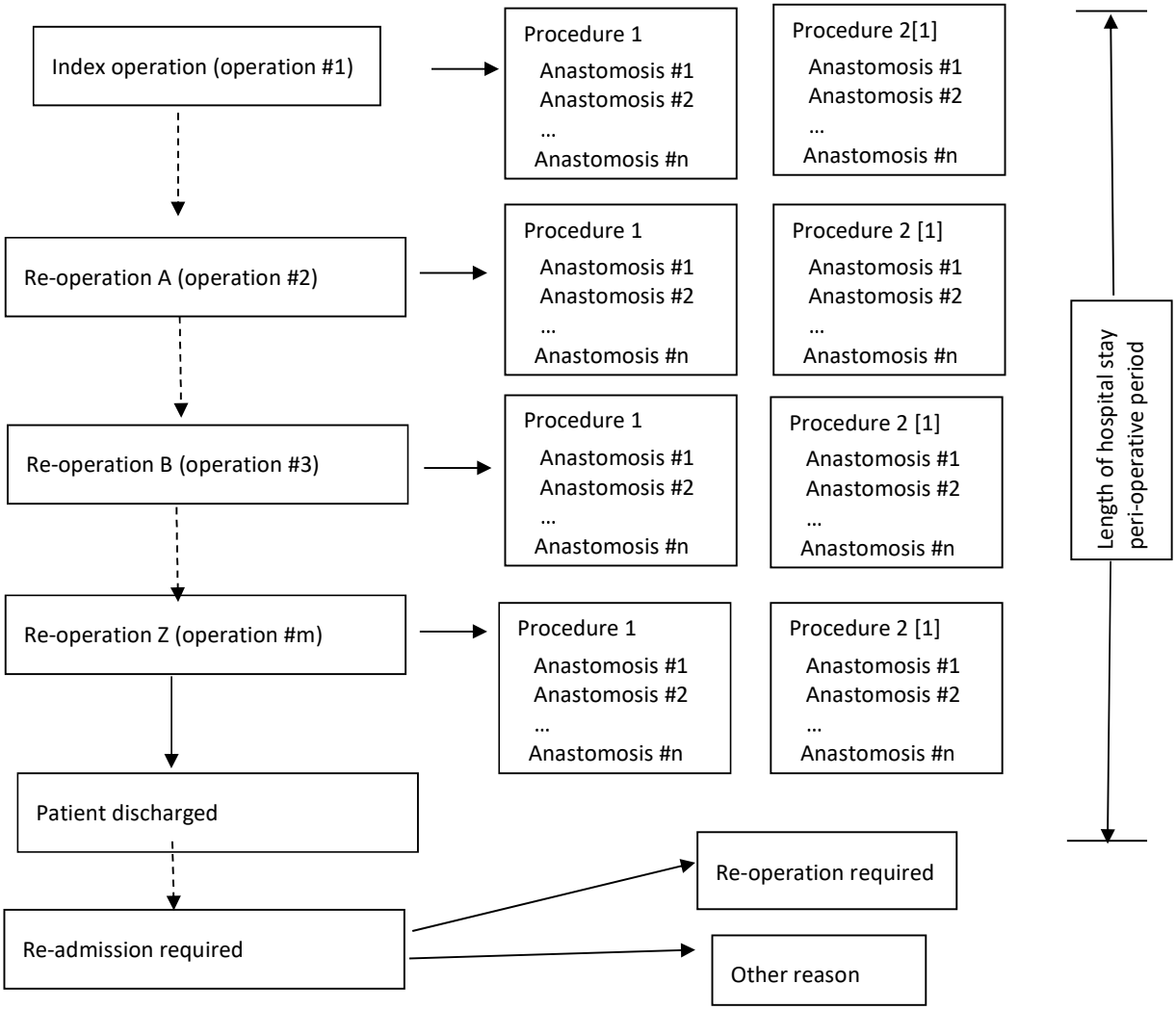
For the purpose of this SAP, endpoints may be defined at any of these levels, i.e. patient, surgery type, procedure within a surgery type, anastomosis within procedure. This hierarchy is described in Figure 1. The unit of analysis for each endpoint will be clearly defined in this SAP.

Figure 1 hierarchy of dependence in the endpoint data.

Level			
Surgery type within patient	Free flap	Replantation	Lymphatic
Procedure within surgery type	FF1, FF2, FF3 etc	R1, R2, R3 etc	LVA1, LVA2, LVA3 etc
Anastomosis within procedure	FF1A1, FF1A2, FF2A1, FF2A2, FF3A1, FF3A2, etc	R1A1, R1A2, R2A1, R2A2, R3A1, R3A2, etc	LVA1A1, LVA1A2, LVA2A1, LVA2A2, LVA3A1, LVA3A2, etc

In addition to this hierarchical structure regarding the initial attempt, for a particular anastomosis, there may be the need for an intraoperative redo within the same operation (a secondary endpoint), or the need for a re-operation on a subsequent date (a secondary endpoint). This patient flow is described in Figure 2.

Figure 2. Patient flow through study procedures



Note. Procedure = flap or replantation or lymphatic. [1] There may be > 1 procedure done. A second procedure may be the same type as procedure 1 (e.g 2 flaps procedures) or may be different. The figure suggests 2 procedures (due to space limitations) but there may be > 2 procedures.

2.1 Study variables

2.1.1 Demographic and baseline characteristics

Demographic assessments (age, gender, ethnicity, height and weight) are performed at the screening visit. Body Mass Index (BMI) will be derived from the height and weight entered, as follows:

BMI = weight (kg)/height (m^2)

Medical history items are also recorded at the screening visit using a defined list of conditions and recorded as never, past, or present. No derivation of data based on medical history will be undertaken.

A full physical examination is performed at the screening visit. No derivation of data based on physical examination findings will be undertaken.

Risk factors recorded at the screening visit will be collected. No derivation of risk factors will be undertaken.

For lymphatic surgery, lymphedema stage will be reported.

2.1.2 Operative variables

There are three types of procedure: free flap, replantation, and lymphatic procedures. A patient may have more than one type of procedure within the same operation. For each type of procedure, the relevant CRF forms will be completed.

The Dendrite eCRF forms for different types of procedure will be 'grouped' together into operations if the date of the operation recorded on form E is the same.

The Castor eCRF forms are grouped into the following options: Free Flap Procedure, Replantation Procedure, Lymphatic Procedure or Free Flap and Lymphatic Procedure. For patients who undergo both free flap and lymphatic procedures, they will be entered under the same participant ID.

For each type of procedure in Dendrite, the time of entering the operating room (OR) and leaving the OR is recorded on form E (patient in, patient out).

For each type of procedure in Castor, the time of entering the operating room (OR) and leaving the OR is recorded as follows:

Free Flap Operation Visit: Operation Data Form

Replantation Operation Visit: Replantation Operation Form

LVA Operation Visit: LVA Operation Form

This will be checked for consistency across different forms within the one operation since all types of procedure on the same day would be expected to be the same visit to the OR, so the same time of entering and leaving OR.

For each operation, the total time in OR will be derived using data on Dendrite's form D, or Castor's procedure specific visit, Operation Form as:

OR time (mins) = Patient out – patient in.

For each type of procedure, the incision start time and closure end time are recorded. The operative time will be derived as:

Operative time (mins) = closure time - incision time.

Note, this may be different for each type of operation conducted within the one operation (i.e. within one visit to OR).

Use of venous thromboembolism (VTE) prophylaxis, antibiotics, anticoagulants, and inotropes during the procedure is recorded using checkboxes. No derivations will be made.

Donor site

The donor site, side, type of tissue transfer (pedicled or free) and composition are recorded using checkboxes. No derivations will be made. In addition, the flap name is recorded using a numerical code. This is grouped by location (head and neck, trunk front, trunk back, upper limb, lower limb) and within location a name. The codes will be used to assign the location.

The requirement for a re-operation (at the donor site) is recorded. If a re-operation is required, the date and type of re-operation (collected using tick boxes) is recorded. Re-operation is a specific secondary endpoint, see below.

The time (in days) from initial operation to re-operation will be derived as:

Date of donor site re-operation – date of initial operation +1 days.

Free flap ischemia time is recorded.

Recipient site (free flaps)

Recipient site is grouped within the eCRF as:

- Head and neck
- Trunk
- Perineum
- Upper limb
- Lower limb
- Breast

For analysis, this will be collapsed into 4 categories; namely head and neck, extremities (upper and lower limb), breast and other (includes trunk and perineum).

For the recipient site, for each overall location (i.e. head and neck, trunk, perineum, upper limb, lower limb, breast) further details of location are collected using tick boxes.

In addition, details are recorded for the recipient arteries and veins (i.e. which vessels are involved), the reason for surgery (i.e. recipient indication), exposed anatomy, infection indications and tumor type are all recorded using tick boxes. No derivations are planned.

For all recipient locations, the requirement for re-operation is collected. If a re-operation is required, the date and type of re-operation (collected using tick boxes) is recorded. The side is also recorded. Re-operation is a specific secondary endpoint, see below.

The time (in days) from initial operation to re-operation will be derived as:

Date of recipient site re-operation – date of initial operation +1 days.

No further derivations will be made.

Lymphedema location (lymphatic surgery).

The lymphedema location is collected ((11 options). These will be combined for analysis as follows:

- Head and neck will include head, neck and face
- Upper limbs will include hand, forearm, arm, upper arm
- Lower limbs will include – foot, leg, thigh, calf.

Replantations

Replantations can be free flap or nerve.

In addition, recipient site has the same options as free flaps and will be collapsed into 4 categories as defined above for free flaps.

Anastomosis

Information is collected for each anastomosis, including type of vessel (artery, accompanying vein, superficial vein, nerve lymphatic, other), type of anastomosis (end-to-end, end-to-side, vein graft or flow through), vessel diameter, pedicle length and suture size. No derivations will be made unless some categories are sparsely populated in which case categories may be combined for data summaries.

The intended operation (manual or robotic) is recorded together with the number of robotic sutures used and the number of manual sutures used. The robotic and manual execution time is recorded.

Total procedure execution time will be derived where possible.

No further derivations will be made.

2.1.3 Effectiveness endpoints

Data collected from the operation(s) undertaken during the study will be used to define the effectiveness outcomes. As the timing of operations is important to assess the outcomes, the flow described in figure 2 will be used to assess the timing of procedures.

During the initial hospital stay, patients may undergo multiple operations as per standard of care. The date, start time, and end time of each operation will be recorded (Dendrite: form D, or Castor: Operation Form within procedure specific visit) and these will be used to sort the operations from earliest (index procedure) to latest. The date of discharge from hospital is recorded on Dendrite's form U1, or on Castor's Visit Forms (1-4). The time from the date of the index procedure to the date of discharge (inclusive) is defined as the perioperative period. Any operations recorded after the discharge date will be classified as a re-operation (after hospital re-admission).

Total hospital time (days) = peri-operative time = date of discharge – date of index procedure +1 (days).

2.1.3.1 Primary effectiveness endpoint – Procedure Robotic Success

Form R or Anastomosis Data Form will be completed for each anastomosis. If the answer to the question 'How did you intend to perform this anastomosis' is 'Robotic' then the anastomosis is included for this endpoint.

The endpoint will be derived for each anastomosis using the question "Did you experience any system technical issues resulting in unplanned return to conventional suturing".
If the response is 'No' and the number of robotic sutures is > 0 or the number of robotic redo sutures is > 0, the anastomosis will be classified as 'intra-operative change from robotic to manual '= 'no'.
If the response is 'yes' anastomosis will be classified as intra-operative change from robotic to manual '= 'yes'.
If there is no response to the question the anastomosis classification will be missing.

If the planned approach was manual the result will be N/A

The unit of analysis for this endpoint is the anastomosis.

2.1.3.2 Secondary effectiveness endpoints (All procedures)

2.1.3.2.1 Surgeon assessment of robotic usability.

From the usability questionnaire (to surgeons) the response to the final question: "Indicate whether the device performance met your expectation in procedural success" will be used. Three responses are available, complete procedure success, partial procedural success, no procedural success.
Patients will be classified as:

Success=”yes” if the response is ‘complete procedural success’

And success=’No’ otherwise. A sensitivity analysis will be performed with ‘partial procedural success’ included in success=Yes

Note, this endpoint will only be derived for the prospective subpopulation.

For this endpoint the patient is the unit for analysis.

2.1.3.2.2 Time for each anastomosis execution.

Robotic usage time and manual time are recorded for each procedure (free flap, replantation, lymphatic) and each anastomosis within a procedure within an operation on Dendrite’s form R, and Castor’s Anastomosis Data Form (procedure specific).

Total time will be derived (for each anastomosis) as robotic time + manual time.

For this endpoint, the anastomosis is the unit of analysis.

In addition to reporting the time per anastomosis, for each procedure the overall total robotic suturing time, the total manual suturing time and total suturing time will be derived as follows:

For each procedure within an operation, the total robotic usage time will be derived as the sum of the time recorded for each anastomosis within that procedure.

For each procedure within an operation, the total manual time will be derived as the sum of the time recorded for each anastomosis within that procedure.

For each procedure within an operation, the total suture time (robotic plus manual) will be derived as:

Total robotic time + total manual time within that procedure.

For this additional summary, the procedure is the unit of analysis.

2.1.3.2.3 Intraoperative need to redo the anastomosis (yes or no)

Castor’ and Dendrite’s anastomosis form has a question ‘timing of anastomosis’, with the options ‘first attempt’ and ‘subsequent attempt’. Subsequent attempt is a redo form.

Redo forms will be ‘aligned’ with first attempt forms by matching anastomosis type (free flap, replantation) according to the form completed and with surgery type by matching the responses to the questions:
Side, vessel type and vessel diameter.

For lymphatic surgery matching will be done using type (lymphatic anastomosis form completed), type of anastomosis and vein diameter.

Any anastomosis which has at least one redo form will be classified as redo=”yes”.
Any anastomosis which does not have a matching form for subsequent attempt will be classified as redo=’No”.
If there are subsequent attempt forms which do not directly align with a first attempt form, this will be resolved by clinical review so all subsequent attempt forms are aligned with a first attempt form.

For this analysis, the anastomosis is the unit of analysis.

2.1.3.2.4 Post-operative need to redo the anastomosis within 7 days (yes or no)

The need for a re-operation (yes/no) is recorded on several forms, namely Castor operation data forms contain the question ‘Any post-operative need to redo?” and all post-surgery visit forms (visit 1 (24 hours), visit 2 (4 days post-surgery), visit 3 (14 days post-surgery) and visit 4 (30 days post-surgery for free flaps and replantations, 24 weeks post-surgery for lymphatic operations) and the unplanned visit form have the question “Postoperative need to redo?”.

Note, the derivation of this endpoint is at the procedure level. Re-operation forms are by procedure (free flaps, replantation, lymphatic surgery) and will be ‘aligned’ to the index operation of the same type.

If, for that procedure, the answer to any of the questions above is yes, there should be a re-operation form for that procedure

The date of re-operation is recorded on the re-operation form.

The time (in days) to re-operation will be determined as:

Date of reoperation – date of index operation.

If the time to re-operation is <= 7 days then the patient will be classified as reoperation within 7 days = Yes.

If there are no re-operation forms where the time to re-operation is <= 7 days then the procedure will be classified as re-operation within 7 days = No.

If there are no re-operation forms (and ALL questions above are No, for need for a re-operation) for that procedure type, then re-operation within 7 days = No.

If any of the questions suggest there was a re-operation but there is no accompanying re-operation form then the following approach will be used.

- If the answer to re-operation needed is “yes” on the index operation form or the form for visit 1 (24 hours) or visit 2 (4 days) is Yes, then re-operation = Yes.

- If the answer for re-operation on the unplanned visit form is "yes", then if the date of the unplanned visit is within 7 days of the date of the index procedure, then re-operation = "yes".
- If a clinical review of available data suggests there was a re-operation within 7 days then re-operation = "yes".
- In other circumstances re-operation within 7 days will be missing.

This analysis is at the procedure level.

2.1.3.2.5 Complications

All complications are recorded as adverse events. Derivation of adverse events and analyses is discussed under safety endpoints and analysis.

This endpoint is at the patient level.

2.1.3.3 Secondary Effectiveness Endpoints - Free Flap and Replantation

2.1.3.3.1 Ischemia time

Warm ischemia time is captured directly on the operation CRF (for free flaps and replantations).

2.1.3.3.2 Free flap failure or loss at discharge/replantation failure or loss (subsequent amputation).

This endpoint only refers to flap procedures or replantations.

The unit of analysis is the flap/replantation, i.e. at the procedure level.

Separate variables will be derived for flaps and replantations.

For each flap, Dendrite's form H and Castor's Free Flap Operation Visit operation visit: Operation Data Forms record the answer to the question 'Flap survival at recipient site at discharge', with options '100% - complete survival', 'partial survival', 'zero survival', 'buried flap' or' unknown. In Dendrite, the same form is used for replantations, so if the procedure is replantation, then the question will be interpreted as 'Replantation survival at discharge'.

Each flap will be classified as ''loss/failure' = yes if the response to the question is 'zero survival' and loss/failure = 'no' if the response is '100% complete survival' or 'Partial survival'. If the response is 'buried flap' or 'unknown' the response will be missing.

For replantations the options are:

Yes, No, partial failure, not applicable

Each replantation will be classified as ''loss/failure' = yes if the response to the question is 'yes' and loss/failure = 'no' if the response is No or 'Partial failure'. If the response is not applicable the response will be missing.

For both variables, if the question is not answered the variable will be missing.

2.1.3.4 Secondary Effectiveness Endpoints - Lymphatic surgery – limb volume reduction

Limb volume is recorded on the pre-operative limb assessment form and at each follow-up visit.
The change in limb volume will be calculated as:

limb volume at visitx – limb volume pre-op.

Where x is visit 1 (24 hours post-op), visit 2 (4 days post-op), visit 3 (14 days post-op) or visit 4 (24 weeks post-op). This represents limb volume reduction.

This endpoint is at the procedure level.

2.1.3.5 Additional Effectiveness Endpoint (not defined in protocol)

2.1.3.5.1 Free flap viability at 30 days

For Castor, separate forms are used for free flaps and for replantations. At all follow-up forms for flaps, there is a question 'flap loss/failure', with the options Yes or No. For replantations the question relates to replantation failure with the options 'Yes', "no', 'N/A' or 'Other'.

To derive the endpoint

For all follow-up forms, the date of follow-up and the date of surgery will be used to determine the time post-surgery. I.e.
follow-up time = date of follow-up visit – date of operation +1 days.
All forms will be considered.

If there is a form where the visit is at least 23 days post index operation, this will be used as the 30 day follow up form.

The following hierarchy will be used to derive the endpoint:

If there is a 30-day follow-up form with a non-missing answer to the question, this response will be used.

Otherwise, if the study termination form (form z in dendrite, termination visit: termination form in castor) indicates the patient did not complete the study and the reason for study exit was patient death, the last recorded flap survival status will be used, regardless of when this was recorded. Note, the reason for withdrawal on form z or termination visit: termination form is free text. However, form u1 or all visit forms record the patient status at

discharge (alive/dead) and date of discharge/death. If there is a form u1 or any visit forms (1-4) where status at discharge is dead, the patient will be regarded as died during the study.

Otherwise, if the study termination form notes the patient did not complete the study and the reason for study exit was anything other than death, the last recorded flap survival status will be used, provided the status was recorded ≥20 days since the index procedure.

Otherwise, in all other circumstances the endpoint will be set to missing.
For replantations the same approach will be used, hover if the response to the question is 'N/a' or 'Other' then failure/loss will be missing.

2.1.3.5.2 Intra-operative anastomosis patency

For each anastomosis, Dendrite form R or Castor Anastomosis Data Form asks the question 'Success of anastomosis'. If the response is 'Patent' then intraoperative patency = Yes.

If response = 'failed' or 're-done' then intraoperative patency = No.

Note, this endpoint will only be assessed using the index operation where the timing of anastomosis = 'First attempt'.

The unit of analysis is the anastomosis.

2.1.4 Questionnaires

For each patient, the surgeon will complete two questionnaires:

The exoscope/Symani questionnaire – this comprises 19 questions with a 5 point Likert scale response (Strongly disagree, disagree, neither agree nor disagree, agree and strongly agree), 5 questions with a binary response (yes/no) and 2 questions with a 5 point response (awful, negative, neutral, positive, fantastic).

In this questionnaire, all questions are phrased so that agree and strongly agree represent positive responses, as does 'positive' and 'fantastic'. In addition, for the binary responses all questions except 1, a 'yes' is a positive response. For the question "I needed to switch from robotic suturing to manual suturing because I was not comfortable with 3D vision", a 'No' is a positive response.
All questions will be classified accordingly as positive 'yes' or 'no'. The total number (and percentage) of positive responses will be derived.
If a question is not answered it will not be classified.

The usability questionnaire – this comprises 7 questions using a 5 point Likert scale (from strongly disagree to strong agree), one binary response question (yes/no), one question assessed on a scale of 1-10 and one question with 3 options (this question is used for the key secondary endpoint).

As above, all 5 point Likert scale questions 'agree' and strongly agree' represent a positive response.

For the binary response question 'yes' is a positive response and for the scale of 1-10, a high number is a positive response. For classification of positive (yes/no) a value of >=6 will be classified as positive.

For the 3 option question (the primary endpoint), responses of 'complete procedural success' and 'partial procedural success' will be classified as positive.

As for the exoscope questionnaire, the number (and percentage) of positive responses will be derived.

In addition, for each patient, the circulating nurse will complete a questionnaire with 6 questions on a 5 point Likert scale, one question on a 1-10 scale and the same question (as for the surgeon) rating the overall performance with 3 options.

As above, each question will be classified as positive (yes/no) and the number and percentage of positive responses derived.

The scrubbed nurse/sterile assistant will also complete a questionnaire with 5 questions on a 5 point Likert scale, one question on a 1-10 scale and the same question (as for the surgeon) rating the overall performance with 3 options.

As for the circulating nurse, the number (and percentage) of positive responses will be derived.

2.1.5 Safety endpoints

All adverse events (AE, SAE/ADE/SADE/ADE/DD) reported by patients or evaluated by the Surgeon from day 0 to either 30 days after surgery for free flaps, replantation and other procedures, or 24 weeks after surgery for the LVA procedures will be recorded.

All adverse events will be recorded on an adverse event form in the CRF (form U2 in Dendrite or Repeating Data: Adverse Events in Castor). Adverse events will be coded using MedDRA to obtain system organ class (SOC) and preferred term (PT).

All events are assessed by the surgeon for severity (mild/moderate/severe) and seriousness (serious/not serious). In addition, for each event, the surgeon will answer three questions regarding relationship to the device:

- Related to the device
- Related to device malfunction
- Related to device misuse

For each of these assessments, the response is on a 5 point 'scale', namely:

- Not related
- Unlikely
- Possible
- Probable

- Definite OR
- Unassessable

They are also asked to note whether there was a different (not device related) cause.

Treatment initiated (if any) and outcome (resolved, resolved with sequalae, ongoing or death) are also recorded.

Event details are recorded as verbatim text.

A separate form will be completed for each event.

Adverse events of special interest, namely, the AEs cited in the literature (e.g., arterial insufficiency, venous congestion) will be flagged based on MedDRA coding.

No further derivations of adverse events data will be undertaken.

2.1.5.1 Additional safety endpoints not defined in the protocol.

2.1.5.1.1 Freedom from device related serious adverse events prior to discharge.

Dendrite's Form U2, and Castor's Repeating Data Form: Adverse Events, is used to collect adverse event data. If there are any adverse events marked as serious where ANY device related question (see note below) is 'possible', 'probable' or 'definite' the event will be classified as a device related SAE = yes.

If ALL AE forms have full responses to the required questions and the AE is not classified as 'device related SAE'=yes then the patient will be classified as device related SAE=No.

If there is a device related SAE but the onset date is after the date of discharge, and the patient has no other event to classify them as having a device related SAE prior to discharge, then they will be classified as free from device related SAE prior to discharge = yes. Otherwise, if there is a SAE that is define as device relates SAE = Yes, then the patient will be classified as free from device related SAE prior to discharge = No.

If it is not possible to classify the event, the patient's classification will be missing. A supporting analysis will use freedom for device related SAE prior to discharge = No for all unclassified patients.

2.1.5.1.2 Freedom from device related adverse events prior to discharge

As described above for freedom from device related SAEs, but any AE which is classified as device related in the intra-operative period would see the patient classified as free from device related adverse events=No.

2.1.5.1.3 All cause re-admission rates

Dendrite's Form U1, and Castor's Visit Forms (1-4), is used to collect follow-up information. If all forms have the response to the question 'Any unplanned re-admission'=No, then the patient will be classified as any re-admission within 30 days = no.
If any form has the response to the question 'Any unplanned re-admission to hospital' = Yes, the patient will be classified as 'yes' to any re-admission.

For each form reporting a re-admission, the time to re-admission (in days) will be derived as

Date of re-admission – date of index operation +1.

If there are multiple forms for the same patient where any re-admission = Yes, the time of the earliest re-admission will be used to determine the time to re-admission.

For patients with no re-admissions, time to re-admission will be determined as follows:
In Dendrite, date of follow-up is recorded on form U1 (a follow-up visit form), form U2 (the adverse event form, here it can be recorded twice, once for an AE and once for an adverse device effect) and on form U3 (protocol deviation form).
In Castor, data of follow-up is recorded on Visit Forms (1-4), Repeating Data: Adverse Events, and on Repeating Data: Protocol Deviation Form.
All forms (there may be multiple of each type of form) will be inspected. The latest date will be used to determine time to re-admission.
Time to re-admission (in days) will be calculated as latest follow-up date – date of index operation +1. The patient will be censored in analysis.

2.1.5.1.4 All cause re-operation rates up to 30 days.

Dendrite's Form H, and Castor's Free Flap Operation Visit: Operation Data Form, collects information on whether a donor site re-operation was required, and if so, the data and type of re-operation. In Dendrite, forms J, K, L, M, N and P ask whether a recipient site re-operation was needed (each form collects data for a different recipient site). Form Q collects information on the date and type of recipient site re-operation. In Castor, the repeating data forms: Breast, Head & Neck, Lower Limb, Perineum, Trunk, and Upper Limb Recipient Data ask whether a recipient site re-operation was needed (each form collects data for a different recipient site). The last two questions on each repeating data form for the recipient site collect information on the date and type of recipient site re-operation.

In Dendrite, if all relevant forms (i.e H and the relevant form out of J, K, L, M, N and P) indicate 'no' to re-operation, then the anastomosis will be classified as 'no' for the variable 'any re-operation'. In Castor, if all relevant forms (i.e Free Flap Operation Visit: Operation Data Form and the relevant form out of the repeating data forms: Breast, Head & Neck, Lower Limb, Perineum, Trunk, and Upper Limb Recipient Data) indicate 'no' to re-operation, then the anastomosis will be classified as 'no' for the variable 'any re-operation.

Otherwise, if ANY of the forms indicate 'yes' to 'any re-operations' then the patient will be classified as any re-operation=Yes.

For both donor site re-operations and recipient site re-operations, the time to re-operation (in days) will be derived as

Date of re-operation – date of index operation +1.

If there are multiple anastomosis operations forms for one operation where any re-operation = Yes, the time of the earliest re-operation will be used as the time to re-operation.
If there are no re-operations recorded, the time to re-operation will be determined as follows:
In Dendrite, date of follow-up is recorded on form U1 (a follow-up visit form), form U2 (the adverse event form, here it can be recorded twice, once for an AE and once for an adverse device effect) and on form U3 (protocol deviation form).
In Castor, data of follow-up is recorded on Visit Forms (1-4), Repeating Data: Adverse Events, and on Repeating Data: Protocol Deviation Form.
All forms (there may be multiple of each type of form) will be inspected. The latest date will be used to determine time to re-admission.
Time to re-operation (in days) will be calculated as latest follow-up date – date of index operation +1. The patient will be censored in analysis.

2.1.5.1.5 All cause mortality rates up to 30 days.

Dendrite's Form U1, and Castor's Visit Forms (1-4), is used to collect follow-up information. The patient status at discharge is asked. If the response is 'dead' then the date of death is collected.

Dendrite's Form U2, the adverse event form, and Castor's Repeating Data: Adverse Events, also asks the status at discharge and the date of death (if status is dead). Consistency between forms will be assessed.

For any form where the patient is noted to be dead, the time (in days) to death (i.e. survival time) will be calculated as:
Date of death – date of index operation +1.

For patients who do not have a date of death, survival time will be calculated as follows:
In Dendrite, date of follow-up is recorded on form U1 (a follow-up visit form), form U2 (the adverse event form, here it can be recorded twice, once for an AE and once for an adverse device effect) and on form U3 (protocol deviation form).
In Castor, data of follow-up is recorded on Visit Forms (1-4), Repeating Data: Adverse Events, and on Repeating Data: Protocol Deviation Form.
All forms (there may be multiple of each type of form) will be inspected. The latest date will be used to determine survival time.
Survival (in days) will be calculated as latest follow-up date – date of index operation +1. The patient will be censored in analysis.

2.1.5.1.6 Length of hospital stay

The length of hospital stay (in days) will be calculated as :
Date of discharge – date of index operation +1.
If the patient does not have a date of discharge but has a date of death, the date of death will be used as the end date.
Otherwise the result will be missing.

2.2 Analysis populations

2.2.1 All Enrolled set (AES)

The All Enrolled Set includes all patients enrolled, i.e., all patients who are assigned a study specific patient ID number and for whom informed consent has been obtained (relevant to prospective enrollments only). For the retrospective data collection if the patient has been assigned an ID they will be included in the AES. This population will be used to describe patient flow through the study.

2.2.2 Effectiveness populations

2.2.2.1 Full Analysis Set (FAS)

The FAS will comprise patients in the All Enrolled Set for whom a robotic anastomosis has been performed. A robotic anastomosis is defined as having received at least 1 robotic suture as part of a study procedure. To assist in this determination, for the index procedure, for each anastomosis attempted, the number of robotic sutures will be classified as follows from CRF data:

0 (zero) robotic sutures

>=1 robotic sutures (minimum requirement for inclusion in the Safety Analysis Set (SAS) and the FAS)

If the number of robotic sutures is missing, then the anastomosis will be classified as robotic provided the following criteria are met:

The response to the question 'How did you intend to perform the anastomosis? = 'Robotic **and**

The response to the question "Did you experience any system technical issues resulting in unplanned return to conventional suturing"? = "No".

If at least one anastomosis is classified as robotic (as defined above) the patient will be considered treated robotically and will be included in the FAS for assessment of effectiveness.

The FAS will form the basis of all summarization and analysis of effectiveness variables. However, for each effectiveness variable, the data summary and analysis will only include patients that have non-missing data for the effectiveness outcome being analyzed. The number of patients included in the analysis/summary will be clearly indicated in each tabular presentation.

2.2.2.2 Subpopulations of the FAS.

Two distinct sub-populations will be defined based on the FAS.

- The prospective patient sub-population

- The retrospective patient sub-population.

All summaries and analyses will be presented using all data combined and by sub-population.

2.2.3 Safety populations

2.2.3.1 Safety Analysis Set (SAS)

The SAS will include all patients in the AES that had at least one robotic suture placed or attempted. Note that this definition will include all patients in the FAS as well as any other patients outside of this set (but in the All Enrolled Set) where robotic anastomosis is attempted but no robotic sutures placed. To classify as 'robotic anastomosis attempted' there will be a robotic time recorded on the CRF for at least one anastomosis.

As for the SAS, two sub-populations will be defined based on the SAS.

- The prospective patient sub-population
- The retrospective patient sub-population.

All summaries and analyses will be presented using all data combined and by sub-population.

2.3 Disposition of patients

The number of patients eligible for inclusion in the study, treated and completing the study will be summarized and presented graphically in a CONSORT style diagram using the All Enrolled Set.

For all patients in the FAS not completing the study, the reason for early termination will be summarized and included in the diagram.

2.4 Statistical methods

2.4.1 Reporting conventions

All summary tables will be presented overall and by subpopulation (prospective/retrospective). In addition, three distinct cohorts will be identified depending on the type of surgery performed: free flaps, replantation, or lymphatic surgery. Note, as described in figure 1, a patient may have more than one type of procedure and/or an operation may include more than one of a type of procedure (e.g. two flap operations). On all tables the unit of analysis will be clearly indicated. The number of patients involved as well as the number of units with non-missing data will be clearly indicated in summary tables. In addition, the number of units with missing data will also be included to aid data interpretation.

Continuous variables (such as age) will be summarized using descriptive statistics (n (the number of observations), mean, median, standard deviation (SD), minimum and maximum). Categorical variables (such as gender) will be summarized using frequency tables (frequencies and percentages). All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value. All percentages will be rounded to one decimal. The number and percentage of responses will be presented in the form XX (XX.X%), where the percentage is in parentheses.

All patient data listings will be sorted by patient ID number, sub-population (prospective/retrospective) and time point (if applicable).

All analysis and summary tables will have the analysis population sample size in the column headers in the form of N=XXX.

2.4.2 Demographics and baseline characteristics

Demographics (age, sex, race) will be presented using descriptive statistics. Height, weight, and BMI will be presented using descriptive statistics. All data will be listed.

Frequency tables for risk factors collected as part of the screening procedures and for lymphedema stage (LVA operations only) will be produced.

Medical history data will be listed.

Physical examination information will be listed.

2.4.3 Operation information

Information recorded for use of medications will be presented with frequency tables.

The time in OR and duration of procedure will be presented with descriptive statistics.

Details of donor site and recipient site will be presented using frequency tables.

All data will be listed.

The number of procedures performed during the index operation will be presented using frequency tables. In addition, the number of each type of procedure (ie flaps, replantations, lymphatic) in the index operation will be presented using frequency tables.

The number of anastomoses in the index procedure will be determined and presented using frequency tables.

Information collected for each anastomosis will be presented using appropriate summary tables (descriptive statistics or frequency tables), where n is the total number of anastomoses, which will be >= the number of patients.

2.4.4 Analysis of effectiveness variables

Note on analysis models/approach.

For all binary outcomes a simple frequency table presenting number and percentage (with confidence limits) will be produced, where the denominator will be the unit of analysis (patient, surgery type, procedure or anastomosis). The confidence limits produced will be biased as they assume independent observations whilst repeat assessments on the same patient (ie > 1 anastomosis/procedure, >1 procedure/patient) are not independent.

To explore the extent of dependence in the data, a table will be produced to describe the hierarchy in the data (as per fig 1), namely:

- Number of patients.
- Number of surgery types (flap, replantation, lymphatic)/patient (i.e. 1, 2 or 3 different types of surgery).
- Within surgery type, number of procedures/patient (i.e. number of flaps, number of replantations, number of lymphatic procedures).
- Within each procedure, number of anastomoses/procedure and also number of anastomoses/patient.

In the simplest scenario there will be one surgery type/patient, one procedure/patient and for that procedure only one anastomosis (so at all levels there is one/patient).

The most complex structure is each patient has all three surgery types, with multiple procedures of each type and for each procedure there are multiple anastomoses.

In addition to these levels of dependence due to repeated observations on the same patient, the results are expected to be influenced by surgeon. Accordingly, for the main analysis of all effectiveness endpoints, a mixed model will be employed where surgeon will be included as a random term.

All models will be fitted separately for each surgery type (free flaps, replantations, lymphatic).

In all models fixed effects for subpopulation (prospective/retrospective) and recipient site/location will also be included to facilitate estimation by subpopulation and recipient site/location. For analysis of replantations a further fixed effect will be included for procedure type (free or nerve).

The analysis models described below (where the unit of analysis is not the patient), allows for the most complex structure of data dependence/repeated measures; namely recipient site/location will be included as a fixed effect (as noted above), but procedure number (within type) and anastomosis number (within procedure for analyses where the unit of analysis is at the anastomosis level) will be included as random terms as required to acknowledge the repeated measures in the data. A decision will be made on production of the initial summary table on the level of complexity required for each analysis. Note, for all endpoints (unless otherwise specified) separate models will be fitted for each surgery type and all models for replantations will include the additional fixed effect of procedure type (free or nerve).

2.4.4.1 Analysis of primary effectiveness variable – procedure robotic success

As per section 2.1.3.1 each anastomosis for each patient in the FAS will be assigned to 'Yes' or 'No' for procedure robotic success. This represents a binary outcome. The analysis of this variable is at the anastomosis level.

For each surgery type (replantation, free flap or lymphatic surgery) stratified frequency tables will be presented stratified by subpopulation (prospective/retrospective) and recipient site/location. The denominator is the number of anastomoses. The proportion of anastomoses classified as a robotic success by stratum and overall for each surgery type will be presented with 95% confidence limits. Results will also be presented on a forest plot.

For replantations a further stratifying variable will be included, namely procedure type (free/nerve).

For each surgery type, a generalized linear mixed model (GLMM) will be used to estimate the percentage of anastomoses classified as robotic success. In SAS, PROC GLIMMIX will be utilized to analyze the data. Subpopulation (prospective/retrospective), recipient site/location and surgeon experience will be included as fixed effects, and surgeon as a random effect. Procedure number (within a surgery type) and anastomosis number (within a procedure) will be included as random terms to acknowledge the dependence in the data (see note above). From the model the adjusted rate of robotic success will be obtained, with 95% confidence limits, for each type of surgery overall and by recipient site/location, by surgeon experience and by subpopulation. (Model 1).

Fixed effects

For free flaps, recipient site will be head and neck, extremities, breast or other.

For lymphatic surgery location will be heads and neck, upper limbs or lower limbs

For replantations there will also be a factor for procedure type (free or nerve), as well as recipient site (as for free flaps) (Model 1a) and results also obtained by procedure type (free/nerve).

For all types of surgery, surgeon experience is classified as microsurgeon, fellow, resident.

2.4.4.2 Analyses of secondary efficacy variables

2.4.4.2.1 Surgeon assessment of robotic usability.

This endpoint is derived from one question on the surgeons usability questionnaire, as defined in section 2.1.3.2.1. This analysis is at the patient level. Frequency tables will be used to present the number of patients where the surgeon classified the procedure as 'success', with 95% confidence limits. Results will be presented overall and by surgery type.

Note, this endpoint is for the prospective subpopulation only.

The data will be collapsed to surgeon level. For each surgeon the number of patients will be counted (N), as will the number of patients that were classified by the surgeon as 'success'. A generalized linear mixed model (GLMM) will be used to estimate the percentage of patients classified by surgeons as successful. In SAS, PROC GLIMMIX will be utilized to analyze the data. Surgery type (see note below) will be included as a fixed term and surgeon will be included as a random effect.

Surgery type will be included as a fixed term. For patients who had more than one type of surgery, they will be classified as surgery type = 'multiple'.

From the model the overall success rate and success rate by surgery type will be obtained with 95% confidence limits. Model 2.

In addition, results by surgeon (with confidence limits) will be obtained and presented on a forest plot.

2.4.4.2.2 Anastomosis execution time

Robotic usage time, manual suture time and total suture time are derived as described in section 2.1.3.2.2. This analysis is at the anastomosis level.

For each surgery type, results for each variable will be summarized using descriptive statistics overall and by subpopulation (prospective/retrospective) and by recipient site. The denominator for all calculations will be the number of anastomoses.

For each surgery type, a general linear mixed model (GLMM, using SAS proc mixed) will be fitted with time as the outcome and recipient site/location and subpopulation as fixed effects. Procedure number (within a surgery type) and anastomosis number (within a procedure) will be included as random terms to acknowledge the dependence in the data (see note above). For each type of surgery, from the model the adjusted mean time will be obtained, with 95% confidence limits, overall and by recipient site and subpopulation. Model 3.

For replantations an additional fixed effect for procedure type (free or nerve) will be included and results obtained by procedure type (free/nerve). Model 3a.

Separate models will be fitted for robotic time, manual time and total time for each surgery type.

2.4.4.2.3 Intra-operative need to redo the anastomosis.

As per section 2.1.3.2.3 each anastomosis for each patient in the FAS will be assigned to 'Yes' or 'No' for intra-operative redo. This represents a binary outcome. The analysis of this variable is at the anastomosis level.

Summary and analysis will be as described for the primary effectiveness endpoint (model 1/1a).

2.4.4.2.4 Post-operative need to redo within 7 days.

As per section 2.1.3.2.4 each patient in the FAS will be assigned to 'Yes' or 'No' for post-operative redo within 7 days for each surgery type. This represents a binary outcome. The analysis of this variable is at the procedure level.

For each surgery type (replantation, free flap or lymphatic surgery) stratified frequency tables will be presented stratified by subpopulation (prospective/retrospective) and recipient site/location. For replantations an additional stratum, procedure type (free or nerve) will be included. The denominator is the number of procedures. The proportion of procedures needing a post-operative redo by stratum and overall for each surgery type will be presented with 95% confidence limits. Results will also be presented on a forest plot

For each surgery type a generalized linear mixed model (GLMM) will be used to estimate the percentage of procedures needing a post-operative redo within 7 days. In SAS, PROC GLIMMIX will be utilized to analyze the data. Recipient site/location and subpopulation (prospective/retrospective) will be included as fixed effects, and surgeon as a random effect. Procedure number (within a patient) will be included as a random term to acknowledge the dependence in the data (namely that each patient may have > 1 procedure and any number may require post-operative redo). From the model the adjusted rate of post-operative redo can be obtained, with 95% confidence limits, for all procedures combined and by procedure type and subpopulation. Model 4.

For replantations, an additional fixed effect of procedure type (free nerve) will be included and results obtained by type. (Model 4a).

If most patients have only one procedure for a given surgery type, then the model will be simplified and the random term for procedure number will be dropped.

2.4.4.2.5 Warm ischemia time (flap and replantations only).

Warm procedure time (see section 2.1.3.3.1 for derivation) will be summarized and analyzed as described for anastomosis time.

2.4.4.2.6 Free flap failure/loss (free flap procedures only)

As per section 2.1.3.3.2 each patient in the FAS who underwent a free flap operation will be assigned to 'Yes' or 'No' for flap loss/failure for each flap (a patient may have > 1 flap operation). This represents a binary outcome. The analysis of this variable is at the procedure (flap) level.

Stratified frequency tables will be presented stratified by subpopulation (prospective/retrospective) and recipient site. The proportion of flaps which failed overall and by stratum will be presented with 95% confidence limits.

Model 4 will be fitted.

2.4.4.2.7 Replantation loss/failure (replantation procedures only)

As per section 2.1.3.2.2 each patient in the FAS who underwent a replantation operation will be assigned to 'Yes' or 'No' for replantation loss/failure for each replantation (a patient may have > 1 replantation operation). This represents a binary outcome.

Stratified frequency tables will be presented stratified by subpopulation (prospective/retrospective), type (free or nerve) and recipient site. The proportion of flaps which failed overall and by stratum will be presented with 95% confidence limits.

Model 4a will be fitted.

If all (or most) patients have only one replantation operation then the model will be simplified and the random term for procedure number will be omitted.

2.4.4.2.8 Limb volume reduction (lymphatic procedures only)

Each patient in the FAS who underwent a lymphatic operation will have limb volumes measured pre-operation and at each post-operation visit. The change from baseline will be calculated (see section 2.1.3.4).

The analysis of this variable is at the procedure level.

Descriptive statistics for limb volume and change from baseline by timepoint will be presented.

A general linear mixed model (GLMM) will be fitted using SAS Proc mixed, with change in limb volume as the outcome and timepoint as a fixed term. Pre-operative limb volume will be included as a covariate. Surgeon will be included as a random term. Procedure number (within patient) will be included as a random term to acknowledge dependence in the data. From the model the adjusted mean change in volume (with 95% confidence limits) will be obtained. If most patients have only one procedure, the random term for procedure number will be omitted. Model 6.

Patients undergoing prophylactic procedures will be summarized separately.

2.4.4.3 Analysis of additional secondary endpoints (not defined in the protocol).

2.4.4.3.1 Free-flap survival rate at 30 days

As per section 2.1.3.5.1 each flap for each patient in the FAS will be assigned to 'Yes' or 'No' for free flap survival at 30 days. This represents a binary outcome. The analysis of this variable is at the procedure (flap) level. Summary and analysis will be as described above for flap loss/failure (Model 4).

In addition, the effectiveness of the Symani System will be evaluated for consistency with the free flap success rates reported in the UK National Flap Registry [1], where the overall free flap survival rate was 96.0% (95% confidence limits, 95.4%, 96.6%)."

2.4.4.3.2 Intraoperative anastomosis patency

As per section 2.1.3.5.2, each robotic anastomosis conducted on each patient in the FAS during their index procedure will be assigned to 'Yes' or 'No' for intraoperative anastomosis patency. This represents a binary outcome at the anastomosis level.

Methods for summarization and analysis will be as described for the primary effectiveness endpoint (Model 1/1a).

2.4.5 Analyses of questionnaire data

All questionnaire results will be summarized using frequency tables, where the number (and percentage) of respondents selecting each response option will be presented by question.

In addition, the number of positive responses per questionnaire and the percentage of positive responses (see section 2.1.4 for derivation) will be presented using descriptive statistics. The number of missing responses per questionnaire will also be presented.

2.4.6 Analyses of safety data

2.4.6.1 General analyses of adverse events

Summary tables displaying both incidence and number of adverse events (AE) overall, by severity, by relationship to study device, by relationship to study procedures, and by seriousness will be produced. The incidence of AE which are device deficiencies will also be shown. Subset incidence tables will be produced for anticipated AE, and for unanticipated AE.

The overall incidence of any adverse event will be presented with exact 95% confidence limits. The result will be compared descriptively with the 30 day complication rate of 31.6% (95% confidence limits 27.5, 36.0%) reported by Veith et al [2]. The paper by Veith et al has been selected as the literature value for descriptive comparison as it describes complication rate in the 30 day post-operative period; which is the period of observation in the current study. Other than this paper there is limited published information on 30 day complication rates.

For serious AE, frequency tabulations of the reasons for the event being an SAE will be produced. A subset incidence table will be produced for anticipated SAE, and a second subset table for unanticipated SAE.

Tables will be produced for the SAS and by subpopulation (prospective/retrospective).

All adverse event data will be shown in patient data listings.

2.4.6.2 Additional safety endpoints not defined in the protocol

2.4.6.2.1 Freedom from device related serious adverse events prior to discharge.

Derivation is described in section 2.1.4.1.1. Results will be summarized using frequency tables for the SAS and by subpopulation (prospective/retrospective) and by procedure type. Exact 95% confidence limits will be presented.

2.4.6.2.2 Freedom from device related adverse events prior to discharge.

Derivation is described in section 2.1.4.1.2. Results will be summarized using frequency tables for the SAS and by subpopulation (prospective/retrospective) and by procedure type. Exact 95% confidence limits will be presented.

2.4.6.2.3 Re-admission within 30 days

As per section 2.1.4.1.3, each patient in the SAS will be assigned to 'Yes' or 'No' for re-admission and the time to re-admission derived.

Patients classified as re-admission = "Yes" will be classified as events, and other patients will be censored. A Kaplan Meier plot will be produced for time to re-admission, overall, by subpopulation (prospective/retrospective) and by procedure type (flap, replantation, lymphatic). From the Product Limit Estimator (PL estimator), an estimate of re-admission rate within 30 days will be obtained.

2.4.6.2.4 Re-operation within 30 days

As per section 2.1.4.1.4, each patient in the SAS will be assigned to 'Yes' or 'No' for re-operation and the time to re-operation derived.

Patients classified as re-operation = "Yes" will be classified as events, and other patients will be censored. A Kaplan Meier plot will be produced for time to re-operation, overall, by subpopulation (prospective/retrospective) and by procedure type (flap, replantation, lymphatic). From the Product Limit Estimator (PL estimator), an estimate of re-operation rate within 30 days will be obtained.

Re-operation rate will be evaluated for consistency with the re-operation rates reported in the UK National Flap Registry (UKNFR), where the overall re-operation rate was 10.7% (95% confidence limits 9.8%, 11.7%). The re-operation rate within 30 days for the Symani system will be presented with 95% confidence limits.

2.4.6.2.5 Death within 30 days

As per section 2.1.4.1.5, survival time for each patient will be determined. Patients noted to be dead will be classified as events, and other patients will be censored. A Kaplan Meier plot will be produced for survival time, overall, by subpopulation (prospective/retrospective) and by procedure type (flap, replantation, lymphatic). From the Product Limit Estimator (PL estimator), an estimate of death within 30 days will be obtained.

2.4.6.2.6 Length of hospital stay

As per section 2.1.5.1.6 the length of hospital stay (in days) for each patient in the SAS will be derived. Results will be summarized using descriptive statistics for the SAS overall, by subpopulation (prospective/retrospective) and by procedure type (flap, replantation, lymphatic).

2.5 Statistical/ Analytical Issues

2.5.1 Adjustments for covariates

Surgery type (flap, replantation, lymphatic) and subpopulation (prospective/retrospective) are included as fixed factors where applicable in the primary and secondary efficacy modelling. Results by these factors are included in tables and forest plots produced for the study.

Surgeon is included as a random effects term in each of the models.

Procedure number/anastomosis number (within patient) are included in models where relevant to acknowledge dependence in the data.

2.5.2 Handling of Dropouts or missing data

For all outcomes, if there is insufficient information available to determine the outcome (including for the continuous measure of length of hospital stay), the patient will be excluded from the analysis in question.

2.5.3 Interim analyses and data monitoring

No interim analysis is planned.

2.5.4 Multiple comparisons/ multiplicity issues

There are no multiplicity issues in this study.

2.5.5 Windows for time points

All data are expected to be collected within a timeframe of 30 ±7 days from the initial study procedure (or 24 weeks +/- 2 weeks for lymphatic surgery). If a patient has a revision procedure where the revision is to a robotic anastomosis, then the timeframe for data collection will be 30-days from the date of the last revision procedure (revision to a robotic anastomosis), where the date of re-operation is prior to the date of discharge. However, for the retrospective data collection, available data will be used whenever possible. Data may not be available at 30 days post-operation.

2.5.6 Statistical technical issues

The models noted in the efficacy analyses propose a default covariance structure of type=VC, which is a simple diagonal matrix with equal variances across all levels of the surgeon ID variable. This will be examined to determine if the structure is appropriate, or whether an alternative structure is more appropriate. The use of the GROUP= option in the random statement may also be investigated if type=VC does not adequately explain the variance observed across surgeons (that is, including GROUP=surgeon in the random statement). This will be done as part of normal model checking procedures and described as part of the reported statistical analysis results.

The retrospective data collection may have a reasonable amount of missing data. All data available will be used as much as possible and the derivation of the effectiveness endpoints defines how to obtain a result if possible. All data summaries will clearly indicate the amount of missing data.

3. SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher. All figures will be generated using SAS 9.4 or higher.

4. REFERENCES

[1] The British Associative of Plastic Reconstructive and Aesthetic Surgeons. First UK National Flap Registry Report. 2019. https://bahno.org.uk/_userfiles/pages/files/uknfr_first_report_4dec_2019.pdf

[2] Veith, Donato, Holoyda, Simpson and Agarwal. Variables associated with 30-day postoperative complications in lower extremity free flap reconstruction identified in the ACS-NSQIP database. Microsurgery 2019; 39:621-628.

Appendix 1. Summary of endpoints, unit of analysis and analysis method

Endpoint	Level	analysis
Robotic success	Anastomosis	GLMM. Bernouilli form by stype Fixed: recipient site/location, subpop For replantations also include procedure type (free or nerve) Random surgeon, procedure number anastomosis number, subject=patient. Model 1/1a.
Robotic usability	Patient	GLMM Binomial form as nsuccess/npats by stype Fixed: recipient site/location. For replantations also include procedure type (free or nerve) Random surgeon. Model 2./2a
Anastomosis time	Anastomosis	GLMM normal by stype Fixed: recipient site/location, subpop For replantations also include procedure type (free or nerve) Random surgeon, procedure number anastomosis number, subject=patient. Model 3/3a
Intra-operative redo	Anastomosis	Model 1/1a
Post-op redo	Procedure	GLMM Bernouilli form by stype Fixed: recipient site/location, subpop For replantations also include procedure type (free or nerve),

		Random surgeon, procedure number subject=patient. Model 4/4a
Complications	Patient	Safety endpoint. Summaries of AEs
Warm ischemia time		
Flap loss/failure	Procedure	Model 4/4a
Limb volume reduction	Procedure	GLMM normal Fixed timepoint. Cov baseline vol. Random surgeon, procedure number subject=patient. Model 5.
Free flap viability at 30 days	Procedure	Model 4/4a
Intra-operative anastomosis patency	Anastomosis	Model 1/1a
Rate of intra-operative approach change	Anastomosis	Model 1/1a
Freedom from device related SAE at discharge	Patient	Simple frequency and exact CL
Freedom from device related AE at discharge	Patient	Simple frequency and exact CL
All cause re-admission rate	Patient	KM. Use PL to get rate within 30 days
All cause re-op rate	Patient	KM. Use PL to get rate within 30 days
All cause mortality rate	Patient	KM. Use PL to get rate within 30 days
Length of hospital stay	Patient	Descriptive stats

PRIMO Statistical Analysis Plan

Final Audit Report 2024-12-13

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