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White Paper

Silhouette for Clinical Trials

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Contents

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Introduction

This white paper provides an overview of the use of Silhouette® for capturing information in a clinical trial. This document outlines the advantages Silhouette offers for evidence-gathering, data capture, and data sharing during wound-related clinical trials, compared with traditional methods of imaging and documenting wounds.

The intended audience for this document is relevant personnel in organizations that are considering organizing or participating in a clinical trial, either:

- a company intending to run a clinical trial to test a particular therapy (a sponsor);
- a contract research organization (CRO) that is working with a sponsor company to manage the data for such a study;
- an investigator site; or
- an individual or university with a specific research project in mind.

Although this document is written assuming a multicenter study, the information is also relevant for a trial at a single center.

Clinical Trials – the Critical Role of Information and Communication

A clinical trial is conducted to evaluate medical devices, pharmaceuticals, dietary supplements, and other enablers of health and wellbeing, or to study patterns and characteristics of disease. Clinical trials can vary in size from a single center in one country to large multicenter trials in multiple countries. A clinical trial may be managed by a project sponsor or an outsourced partner such as a contract research organization (CRO).

A significant amount of information is gathered during the clinical trial, including images of wounds, their measurements over time, and notes about the wound, the specific assessment, and the subject. Investigators recruit subjects with predetermined characteristics, administer the treatment(s), and collect information about the subjects for a defined time period. The investigators send this information to the trial organizer who analyzes the pooled data using statistical analysis. These methods should be designed to prove the endpoint/s as quickly and definitively as possible to avoid jeopardizing the primary endpoint evidence, and therefore the entire basis for the trial.

Each clinical trial has a protocol – a document that contains a precise study plan for executing the clinical trial. The protocol includes an exact template for trial conduct by investigators at multiple locations (in a multicenter trial) to standardize trial data collection.

The system of clinical research as described above is dependent on accurate data flowing from multiple investigator sites to the trial sponsor. Monitoring and data management/ statistics can cost up to one-third of a large trial's cost[i]. Therefore, data should be easy to gather and communicate. It should minimize the risk of variability, error and time wastage. Stakeholders such as auditors, peer reviewers, and regulatory authorities require clear documentation of trial activity, so that those making decisions based on the trial results can be confident that the trial results are replicable, reliable, and undistorted.

All assessment information should be securely and efficiently managed, organized, and stored. The sponsor should have wound assessment data available instantly, but traditional methods involve delays of days or even weeks, during which time inclusions/exclusions can be compromised, subjects can become unavailable or fall out of inclusion definition, images can turn out to be unusable, and evidence integrity can be compromised.

Silhouette Overview

Silhouette is a family of products for imaging, measuring and documenting wounds. It provides accurate and easily reproducible data across all investigator sites to a centralized database that can be accessed anywhere in the world.

Silhouette is designed to improve workflow in wound assessment, allowing an investigator to quickly image and accurately analyze a wound using Silhouette's portable, non-contact device. All measurements saved directly into an electronic database designed specifically for wounds that can be viewed via an Internet browser by the sponsor or CRO. All measurements are made without touching the subject. This eliminates discomfort and reduces risk of infection.

The principle components in the Silhouette product suite are:

- the SilhouetteStar™ wound camera;
- SilhouetteConnect™ software to drive the imaging, measurement and documentation functions;
- SilhouetteCentral™ centralized database;
- An optional Silhouette Protocol Engine, which aligns each wound assessment with the protocol of a specific clinical trial
- Auto-distribution of assessment reports via email.

Since its launch in 2007, Silhouette has been the wound assessment documentation choice for more than 70 clinical studies around the world – from small, single-center studies, to large multicenter trials with hundreds of sites and spanning several continents.

Silhouette is the preferred wound assessment solution and source documentation choice for a number of clinical studies in the United States – many of which are FDA approved – and more than 15 other countries worldwide. Characteristics of these studies include:

- Multicenter and multi-national studies;
- Pre-clinical to Phase III studies, but most commonly Phase II and Phase III;
- Ulcer research including Venous Leg Ulcers (VLU), Diabetic Foot Ulcers (DFU) and Pressure Ulcers (PU);
- Studies assessing ABSSSI (Acute Bacterial Skin and Skin Structure Infections);
- Assessing agents that include biological, pharmaceutical, dressing and medical device products;
- Clinical trials that range in size from 1 to 250 investigator sites;
- Human, porcine, equine and rodent subjects.

Data Capture at Investigator Sites

ARANZ Medical has developed the Silhouette system to support the standardization and centralization of data capture at investigator sites – a critical and challenging aspect of any clinical trial.

SilhouetteStar+SilhouetteConnect

SilhouetteStar is a special "wound camera" that connects to a Windows computer using a USB cable. SilhouetteConnect is software that installs on that Windows computer and controls the SilhouetteStar camera, enabling imaging, 3D measurement, and documentation.

Key features of SilhouetteStar+SilhouetteConnect include:

- Multiple tools in one – wound imaging, measurement and documentation;
- Repeatable and accurate measurements of surface area, length, width, perimeter, maximum depth, average depth, volume, and percentage [area] change;
- Non-contact assessment;
- The ability to track wound healing over time, graphed on Silhouette's dashboard and in Wound Assessment Reports;
- Quick and easy to use.

Some of these aspects are considered in more detail below.

Wound Imaging – High Quality Images and Easy-to-Use Camera

SilhouetteStar includes a digital camera that is always in focus, with its own lighting system to provide consistent ambient background lighting, and a single button for image capture. Users are able to repeatedly obtain high quality and consistent images from week to week using a device that is perhaps the easiest-to-use digital camera available.

For a comparison of the advantages of using SilhouetteStar over a conventional digital camera, please refer to Appendix 1.

Measurements – Accurate and Repeatable

A study has shown that inter- and intra-rater repeatability of measurements of wound surface area using Silhouette is superior to those made using acetate tracings, the current clinical standard for such measurements[ii]. A study[iii] of SilhouetteStar+SilhouetteConnect has shown that inter-rater and intra-rater variability were less than 1% for both area and perimeter, and less than 2% for average depth and volume on wound models. This indicates that repeated measurements over time, even by different users, will detect small differences as a wound changes in size.

Another study on large skin features[iv] (for example areas of erythema) have also shown that Silhouette can accurately measure surface area of lesions as small as 2mm², and ranging to 900cm². In this study both the repeatability associated with the three raters and intra-rater variability for each of the three raters were less than 2%.

Wound Assessment Notes – Configurable and User-Friendly

Silhouette has a configurable data entry system called the Wound Assessment Notes. This part of the application asks the user to enter information about the subject or the wound, as dictated by the clinical trial protocol, through a series of input fields. These fields take the form of yes/no (Boolean) radio buttons, numeric (integer or decimal), selection from a drop down list (single or multiple selection), date/time, or free text fields. All data entered into the wound assessment becomes part of the record that is transferred to SilhouetteCentral database during synchronization.

The information that the user is prompted to enter is completely customizable for the organization. Configuration of the wound assessment notes occurs in SilhouetteCentral through a user interface on the Administrator tab. This is performed prior to the commencement of the clinical trial during the configuration of Silhouette, and can be done by the sponsor, CRO, or ARANZ Medical.

Silhouette Protocol Engine – Align Assessment Practice with the Clinical Trial Protocol

If the study is based on one assessment per visit, the Silhouette Protocol Engine can be programmed by ARANZ Medical to align the collection of data with the clinical trial protocol. It guides the user to enter data, capture images, or make measurements in a particular sequence. Depending on the answers provided, the Protocol Engine can branch down different paths.

The Silhouette Protocol Engine helps to ensure that data is collected consistently across all subjects and across all centers as per the clinical trial protocol. This is essential in ensuring the integrity of the clinical trial data. For example, the clinical trial protocol may require at different times (or under different circumstances) that images and/or measurements be taken before debridement, after debridement, without debridement, or in some combination. Knowing when to make such choices can be difficult for the site, and the Silhouette Protocol Engine can help take the uncertainty out of knowing what to do and when to take specific actions.

The Silhouette Protocol Engine reduces the amount of time required for study administrators to administer the SilhouetteCentral database, and reduces the recurrence of investigators' support requests.

SilhouetteCentral – Up-To-Date Information on Sites' Progress

SilhouetteCentral is both a data management system for storage and organization of subject and wound information, and a synchronization engine for exchanging data with and between any number of SilhouetteConnect instances. Figure 1 shows how SilhouetteCentral and SilhouetteConnect interact.

During the synchronization process all wound data that has been collected on SilhouetteConnect (including images, measurements and wound assessment notes) is transferred to SilhouetteCentral via the internet (WiFi, 3G, etc).

The synchronization between SilhouetteConnect (running on a site's laptop, Windows Tablet or PC) and SilhouetteCentral (typically hosted in a secure data warehouse) is initiated by the user through the SilhouetteConnect software interface, and the data will be on the SilhouetteCentral database instantaneously. Furthermore, any number of SilhouetteConnect instances can synchronize simultaneously from around the world.

ARANZ Medical recommends synchronization after every patient visit, and at least at the end of every day on which subject data has been collected at the site. This ensures that the data is securely backed up and gives the clinical sponsor and/or CRO immediate access to all the collected data.

SilhouetteCentral can be configured to simplify administration by pushing new software releases to sites using SilhouetteConnect.

Centralized Data Storage – SilhouetteCentral

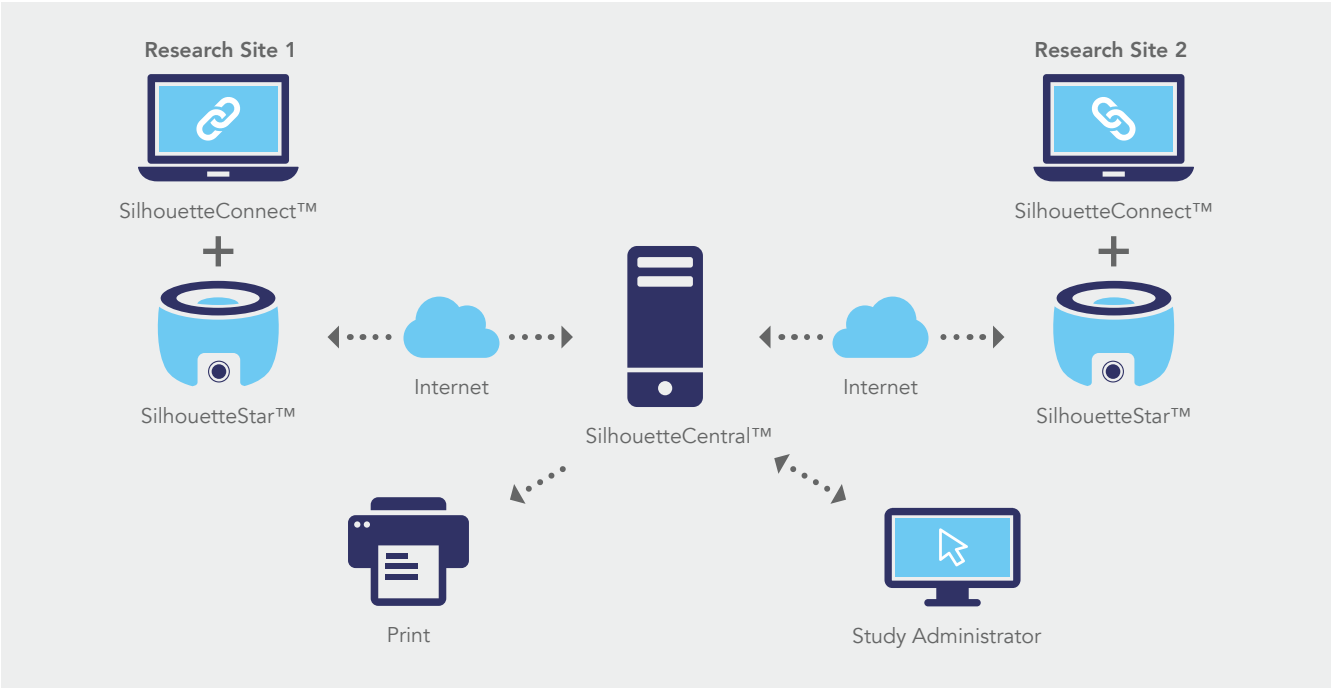

Fig 1 The Silhouette schema showing how wound assessment information can be accessed remotely.

Reviewing Data and Trial Management

The SilhouetteCentral database is accessed using a web browser (Figure 2) by authorized individuals, providing a number of additional administrative features and functionality:

- Create and manage user accounts, including usernames and passwords;
- Control access rights for different types of users (investigators, monitors, sponsors, etc);
- Configure the information users are authorized to access within SilhouetteConnect (such as which subjects, which features, what data);
- Define wound assessment notes;
- Export data for loading into other applications for further analysis.

Subjects' data can be corrected (for example, move a wound assessment to the correct subject if it was collected against the wrong subject). Audit logs showing user access and changes made to subjects' records can be viewed.

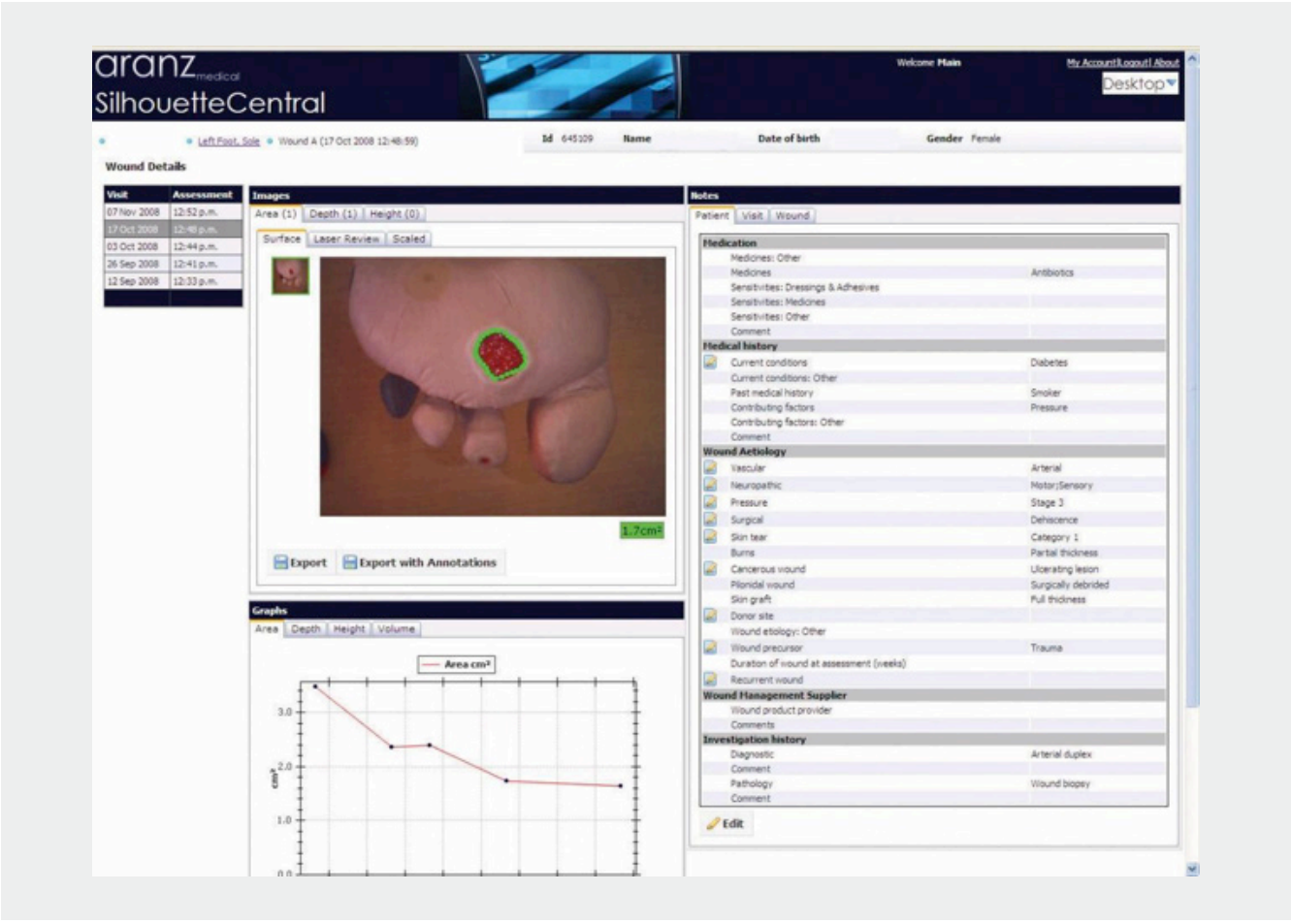

Fig 2 SilhouetteCentral Wound Details Screen.

Data Security

SilhouetteCentral allows for best-practice information storage and communication between authorized practitioners. The system is governed by username and password permissions, data encryption and an audit log of all access and changes made to the patient record.

Silhouette products have numerous technical and design features to enhance data security and the privacy of patient information stored within Silhouette.

Silhouette supports a variety of protocols and functionality, including:

- HL7/DICOM patient demographic information exchange or transfer;
- HL7/DICOM image transfer;
- HL7/DICOM Encapsulated PDF report creation and transfer.

Silhouette is designed to support HIPAA and HITECH compliance.

Report Generation

For a particular subject, Silhouette can generate a clinical report about each wound assessment. This Wound Assessment Report provides a concise and complete summary of the status of the wound at a particular visit. The PDF report includes the digital images of the wound, the graphs of wound healing, and any relevant wound assessment notes that may have been entered.

Time can be saved by having reports generated automatically, although these reports can also be created manually (through SilhouetteConnect or SilhouetteCentral). SilhouetteCentral can be configured to generate the Wound Assessment Report any time new data is received at the SilhouetteCentral database; this report can then be automatically emailed (e.g. to the investigator and/or monitor), attached to a third party electronic medical record, or printed and stored in the clinical research form (CRF).

Information Transfer

SilhouetteCentral can be configured to coordinate the transfer of information from Silhouette to other information systems. Some examples are given below.

Example 1: Automatically Generate and Email Wound Assessment Reports

As discussed above, SilhouetteCentral has the ability to automatically generate a Wound Assessment Report when a new assessment is synchronized from a site's SilhouetteConnect. The system can be configured so that this report is automatically emailed to the investigator at the center at which the subject is enrolled. This is particularly useful when a third party reviewer is employed. This is also useful when subjects enrolled in clinical trials are also patients at the investigators' facility, meaning the report can be easily added to patients' files.

This feature can also be used to file source documentation for the study and to distribute updates to stakeholders. Any number of individuals can be included on the list of email recipients such as the CRA (Clinical Research Associate) who is overseeing the site and/or the medical monitor overseeing the study.

Example 2: Email Custom Information

For some clinical trials it may be useful for the organization managing the data to have information sent in a specific format for entry into a particular data management system. SilhouetteCentral can be configured so that when a new assessment is synchronized, an email is generated in a configurable format which is then emailed to an address that has been configured in the system.

Example 3: Notification of New Trial Data

For some clinical trials it may be useful for the representatives of the organization managing the data to be notified when new data arrives. This is typically achieved via email notification automatically generated by SilhouetteCentral. The system can be configured so notification events are sent to different recipients based on specific information, such as the site where the subject is enrolled, or at screening visits.

ARANZ Medical services

In addition to devices for data capture at investigator sites, ARANZ Medical provides a variety of services for organizations conducting clinical trials including data hosting, training, customer support and product configuration.

Secure Data Hosting

ARANZ Medical provides secure data hosting for clinical trial data gathered using Silhouette. This allows the sponsor or CRO to concentrate on the clinical aspects of the study, with ready access to the trial data at any time through the internet. Under this scenario, ARANZ Medical manages the IT aspects of the data, including database maintenance and back up. ARANZ Medical can also assist with data reporting and image management.

Training

Clinical Training

As part of the installation process, ARANZ Medical provides a clinical training session on the use of Silhouette for clinical trials. This works best if ARANZ Medical provides a trainer at the investigators' meeting(s). The trainer can then provide a hands-on training session (typically two hours), to investigators and other staff involved in the trial such as CRAs.

A clinical trial training session works best with smaller groups of trainees. For larger trials, we recommend splitting the trainees into more than one group and running a separate training session for each group at the investigators' meeting.

The training session is customized to the requirements of the trial protocol, and topics covered in such a training session include:

- Basic concepts of SilhouetteStar+SilhouetteConnect;
- Capturing the images;
- Making the measurements;
- Introducing the protocol engine (if used);
- Synchronizing data with SilhouetteCentral;
- Basic troubleshooting
- Quality control/best practice advice.

Detailed Technical Training

ARANZ Medical can also provide detailed technical training on Silhouette, which covers all parts of the Silhouette Product Suite. The typical time for this detailed technical training is 4-6 hours and would be attended by technical and clinical support staff responsible for supporting Silhouette users during the clinical trial.

ARANZ Medical recommends that technical training be scheduled for the day before the investigators' meeting. This equips them with knowledge of the system that can be used at the investigators' meeting and after implementation.

Additional refresher/new user training is available on request.

Product Configuration

Silhouette software offers flexible configuration of Notes and fields. ARANZ Medical is able to configure the Silhouette product suite to suit the needs of a particular clinical trial.

Data Curation Services

ARANZ Medical can assist with various data curation activities. ARANZ Medical recognizes the need for high quality images and are able to provide a quality control service to review images.

It is common for trials to require wound images and notes to be edited and deleted. ARANZ Medical can offer this service, and are also able to develop reports during the trial to track healing rates and other statistics.

Customer Support

ARANZ Medical offers phone support and an email address for Silhouette customer support around the world. This supports customers within their respective working hours (Asia/Pacific, United States, Europe/UK). If support outside these hours is required, this can be offered as an additional service. Different levels of support are available depending on needs.

Regulatory Considerations

ARANZ Medical is an ISO 13485 certified manufacturer of medical devices.

Device Approvals

Silhouette has the following regulatory approvals:

- FDA 510(k) approval
- CE Mark
- Health Canada – Therapeutic Products Directorate
- TGA approval (Australia)
- WAND registration (New Zealand)

CFR

The US Code of Federal Regulations (CFR) applies to clinical trials that are being conducted in the United States, particularly 21CFR11. Silhouette supports compliance with 21CFR11. However, systems like Silhouette cannot address all aspects of 21CFR11 – for example, specific training and documentation of the processes to which the system is being applied. ARANZ Medical can assist a sponsor and/or a CRO in ensuring that Silhouette is configured and used in a manner consistent with the requirements of 21CFR11.

Summary: Advantages of Silhouette for Clinical Trial Use

Using Silhouette, organizations conducting clinical trials in wound care can capture comparative wound healing data in a way that is quick, efficient, accurate, user-independent, secure and accessible. Data is collected at one or more sites using SilhouetteStar+SilhouetteConnect and data from each of these sites is synchronized to a SilhouetteCentral database customized to that clinical trial. All the data in the study can be accessed and exported for further analysis from anywhere in the world through the web interface to SilhouetteCentral.

Silhouette has a number of advantages when used in clinical trials:

- Easy to set up – Silhouette is easy to install and configure for a specific clinical trial;
- Training is minimal – In less than two hours, users are confident in operating SilhouetteStar+SilhouetteConnect;
- Data collection is quick and efficient – In under three minutes an investigator can capture an image, make measurements (area, depth, etc), and have all this information automatically tagged against a particular subject and anatomical site;
- Measurements are repeatable and accurate – Providing confidence in the wound healing information tracked over time, even with different users;
- Repeatable evidence supports the achievement of the endpoint/s;
- 3D accuracy – With SilhouetteStar's smart calibration technology, Silhouette is able to correct for the camera position and orientation, and the curvature of the wound and the surrounding skin, resulting in measurements that are significantly more accurate than other methods;
- Protocol compliant – The Silhouette Protocol Engine can be configured to ensure that all users are stepped through the required steps the same way, every time, ensuring consistency and integrity of the collected data;
- Data is secure – Information in Silhouette is encrypted and access is protected via a username and password;
- Robust, automated and seamless information transfer – At the touch of a button, information is sent via the internet to SilhouetteCentral for long-term storage. Data is immediately accessible for study administrators via the internet;
- Study data is easily exported into a standard format for further analysis and statistical processing;

Support is provided for CFR Title 21 Part 11 compliance including system access password, data encryption and audit logging of user activities.

Appendix 1: Wound Imaging using Silhouette

The following table presents a comparison of the advantages of using SilhouetteStar for the capture of wound images, compared with an off-the shelf digital camera.

Issue with standard digital photography solutions	SilhouetteStar Feature(s)	Silhouette Benefit
Most standard digital cameras have many controls which often confuse clinical users and also lead to selection of inappropriate settings on camera.	SilhouetteStar has no operator adjustable controls for image capture. There is simply a shutter release button.	Users are confident in their ability to use SilhouetteStar, and there is no chance of inappropriate settings being selected on the camera
Different lighting conditions and inconsistent application of camera auto color balance cause different color casts in different images.	SilhouetteStar provides its own lighting of a known color temperature. Only one standard "fixed" color correction is required and this is applied automatically by the software to every image captured.	Every image captured can be compared with every other image without variance in color cast.
Often images are captured that are out-of-focus due to operator issues with camera.	SilhouetteStar has a camera lens of a fixed focal length. The lasers in the camera provide guidance for the operator to ensure that the operator holds the camera the correct distance from the subject to ensure the image is in focus.	Every image is in focus even when taken by users with little understanding of photography.
With standard digital camera, the images need to be manually transferred from the camera and assigned to the subject / assessment. This is time consuming and often errors occur.	Every SilhouetteStar image is captured directly into the subject record and automatically assigned to the appropriate assessment.	Assuming the correct subject is selected in the application software there is no chance of the images being assigned to the incorrect subject, ensuring integrity of the collected data.
Standard digital cameras store unencrypted data on the card in the camera, usually in a standard format e.g. jpeg. Anyone who can access that memory card can access the protected health information (PHI) it would contain. This can lead to breaches of PHI.	SilhouetteStar does not store subject data on the camera.	There is no opportunity for inadvertent release of PHI because data is either not stored on the camera or stored in encrypted format on a computer.

Issue with standard digital photography solutions	SilhouetteStar Feature(s)	Silhouette Benefit
Photographs taken from a standard digital camera can be modified by the user in a program like Adobe Photoshop. This means images can be modified without the modification being noted in the audit log.	Silhouette stores information in formats that are not editable by users. Thus image modification can only be performed by the Silhouette application software by authorized users with corresponding changes noted in the audit log.	Guaranteed integrity of study data.
Standard digital cameras are difficult to clean.	SilhouetteStar was designed as a medical device, for easy cleaning with standard medical wipes.	Minimizes risk of cross-infection.
Standard digital cameras often become obsolete requiring sourcing and validation of a new (replacement) model.	ARANZ Medical controls the design and production of SilhouetteStar to ensure that there will be supply of validated cameras.	Surety of supply of cameras that meet the validated specification.
Standard digital cameras are not robust and often have to be replaced. They are also desirable as consumer items for theft.	SilhouetteStar was designed for medical environments and cannot be used without the appropriate software. The products also look less like consumer products than standard digital cameras so are less of a theft target.	Long camera life.

Appendix 2: Information Requirements for a Clinical Trial using Silhouette

Answers to the following questions will assist ARANZ Medical to create a solution that best meets the needs of a clinical trial.

General Questions

1. Describe the study (phase, aims, arms, protocol ID number etc)
2. What are the end-points (primary, secondary, other)
3. How many sites are there?
4. What countries and time zones are the sites in?
5. What are the key dates? (eg first subject in, last subject in, last subject out, etc)
6. Number of subjects required for the study?
7. When, where and how many Investigator Meeting(s) are planned?
8. How will data be reviewed, analyzed, and presented at the completion of the trial?

Measurement Specific Questions

1. What wound types are being measured?
2. At which anatomical sites?
3. What is the range of wound sizes that are being measured?
4. Do any other relevant inclusion / exclusion criteria apply regarding wound sizes?
5. What measurements parameters are required? (eg surface area, depth, volume)
6. How many measurements are being performed per subject over what time frame? If a variable number per subject, what is the anticipated average number of assessments per subject? (A sample response: Screening assessment at week -1, and then weekly assessments from week 0 until closure or until week 16 if closure not achieved. The range of assessments per subject is 3 (i.e. healed at week 1) to 18 (healed or unhealed at week 16), with anticipated average of 9.5 per subject.)
7. Does more than one assessment need to be made during some or all visits? If so which ones, and why? (A sample response: There are pre and post debridement measurements taken at screening (week -1), and then only one measurement thereafter unless debridement is clinically indicated (occasionally) in which case there will be two).

Extended Services

1. Will your study require the automatic emailing or archive of reports?
2. Will it be desirable to align each wound assessment with the trial protocol?
3. Are customized instructions for each visit required?
4. Would this study benefit from ARANZ Medical reviewing wound imaging and measurements?
5. Will it be necessary to hold spare SilhouetteStar wound cameras in stock, to mitigate the risk of lost or damaged cameras? If so, how many replacements would be required?
6. Is 24-hour, five-day, or seven-day support coverage required from ARANZ Medical?

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Next Steps

To find out more, contact ARANZ Medical:

www.aranzmedical.com

sales@aranzmedical.com

+1 866 467 0934 or +64 3 374 6120 (head office)

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