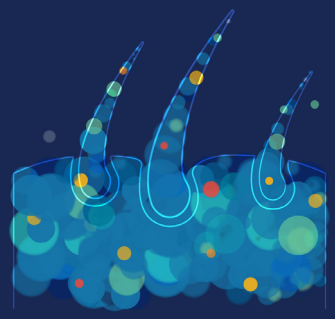
Whitepaper:

DERMATOLOGY CLINICAL TRIALS: BEST PRACTICES IN DIGITAL PHOTOGRAPHY



THE ROLE OF PHOTOGRAPHY IN DERMATOLOGY CLINICAL TRIALS

Given the visual nature of skin diseases, digital photography can be an integral component of clinical trials in many dermatology indications, including inflammatory skin disease (e.g. psoriasis, atopic dermatitis, and hidradenitis suppurativa); autoimmune disorders (e.g. alopecia areata and vitiligo); venous leg ulcers and diabetic foot ulcers; autoimmune bullous diseases (e.g. bullous pemphigoid and pemphigus vulgaris); and infectious conditions such as onychomycosis.

The use of photography in dermatology clinical trials has become more prevalent in the last few years in part due to advances in the quality and affordability of digital cameras and external light sources for flash photography. In addition, several companies manufacture proprietary camera systems designed for specific skin imaging indications such as wounds or facial aesthetics.

The Use Of Digital Photography In A Clinical Trial May Provide The Following Benefits:

- Development of internal training programs to provide education to investigators, site staff, and sponsor team members on the indication and on the clinical outcome assessments.
- Incorporation of images into scientific presentations and publications.
- Utilization for endpoint assessments during review by a central reader or by computer software analysis.
- Documentation of a biopsy site or other area of interest.
- Confirmation of eligibility criteria based on the skin examination.
- Capture of image data in a decentralized clinical trial.

It is important that both the investigator and site staff as well as the trial sponsor have a clear understanding of the goals for use of digital photography in the clinical trial so that the optimal camera device, camera device settings, and image series can be obtained. As most clinical trial sites will not have access to a dedicated medical photographer, it is important that the site staff responsible for capturing digital images receive thorough training on their responsibilities, are comfortable using the camera device, and can reliably capture high quality images.

SKIN IMAGING DEVICES FOR PHOTOGRAPHY

There are several options when choosing a camera device for use in a clinical trial. Regardless of the device used, it is recommended NOT to use a personal device for clinical trial purposes as doing so may jeopardize patient privacy laws. Important considerations when choosing a camera device for digital photography include the following:

- Will the images be used to perform a clinical outcome assessment or determine a study endpoint?
- Will total body photography or macrophotography be required?
- Will sites be permitted to use their own camera device, or will the sponsor provide standardized equipment?
- What is the budget for photography equipment?
- How will the image files be transferred and stored?

Standard Camera Device Options Include The Following:

- DSLR/mirrorless: The most expensive option but can accommodate special lenses such as a macro lens for close-up photography and external flashes such as a ring flash. DSLR/ mirrorless cameras have multiple customizable

settings and produce high quality images but require a higher level of training for the user.
- Compact ("point and shoot"): Available in a range of price points and typically the most affordable option. Compact cameras offer some customization with regards to camera settings but are less versatile than a DSLR/ mirrorless camera and do not accommodate external flashes or special lenses. They require much less training to use than a DSLR/ mirrorless camera and typically produce images of sufficient quality for most uses.
- Smartphone or tablet with built-in camera: The least versatile with regards to camera settings but many offer some limited setting customization; depending on the model they may be more expensive than a compact camera but are simple to use. Image quality is variable and generally the lowest.

Several higher-end proprietary digital imaging systems are available for highly specialized use in dermatology trials for indications such as facial aesthetics, cutaneous ulcers and wound care, and acne/rosacea. These include both 2D and 3D imaging systems that may incorporate laser-guided focus, volumetric and planimetry measurements, and colorimetric assessments.

Photography Systems Of Interest In Dermatology Indications Include The Following:

- Canfield Scientific produces a suite of 2D and 3D imaging systems, including facial aesthetics imaging systems, total body photography systems, and DSLR/mirrorless cameras for a range of dermatologic and aesthetic indications.
- The ARANZ Medical SilhouetteStar is a laser-guided wound imaging medical device that provides 3D wound measurements and imaging for multiple indications, including venous leg ulcers and other chronic wounds.
- Quantificare produces a suite of laser-guided 2D and 3D camera systems that provide measurements, imaging, and colorimetric assessments for a broad range of general and aesthetic dermatology indications.

OPTIMIZING AND STANDARDIZING PHOTOGRAPHY FOR DERMATOLOGY INDICATIONS

The importance of high-quality images cannot be understated. Images that are out of focus, over- or underexposed, poorly white balanced, or otherwise suboptimal may lead to difficulty with interpretability and result in poor data quality. Therefore, it is of paramount importance that the photographer understands how to correctly operate the camera device, most importantly with regards to focus and lighting. As such, comprehensive written guidelines should be provided to investigators and site staff; a live or recorded video demonstration is recommended if a proprietary device will be used for imaging or if there are specific recommendations regarding the camera settings, image requirements, or other expectations that may be confusing or very detailed. Ideally, the user should be able to demonstrate competency in capturing reproducible and consistent images of sufficient quality for the intended purpose.

Basic Principles With Regards To Using Appropriate Camera Device Settings And Lighting For Medical Imaging In Dermatology Include The Following:

Patient Positioning

Appropriate positioning of the patient improves the image quality and standardization. The patient should be positioned comfortably such that the area of interest is easily visualized. When larger body regions or the entire skin surface need to be photographed, it is usually best to place the patient in a standing position. Halpern, et al. defined a series of 15 poses that can be used to provide adequate images of the entire body surface area for the purpose of total body photography.[1] Selected poses can be utilized, depending on the body regions of interest.

Remove, reposition, or minimize the placement of jewelry, glasses, hats, clothing, tattoos, and other distractions within the field of view or cover with a drape. If possible, use a plain blue or grey backdrop or drape to provide contrast and eliminate background elements such as the floor or examination table from the field of view.

Lighting

Adequate lighting is critical; options include the use of a properly angled ceiling-mounted examination light, an internal flash on the camera device, or an external flash such as a ring flash or speedlight; use of an external flash usually provides the best illumination.

Image Orientation

Position the camera lens perpendicular (90°) to the area of interest and orient the body region vertically or horizontally within the frame of view and not on an angle.

Obtain one image of the area of interest from such a distance as to permit identification of the body region; use an anatomical identifier such as the umbilicus if possible. Next, obtain a closer image of the area of interest such that this area accounts for about 50-75% of the field of view.

Additional General Tips

If measurements are needed, disposable paper rulers can be used; avoid partially covering or obscuring the area of interest. Use of a paper ruler can also aide in ensuring correct focus.

To stabilize the device and prevent blurring from motion artefact, either place the device on a tripod on a stable surface or hold the device with two hands and place one or both arms on a stable surface. Alternatively, using the camera timer can help to minimize movement of the camera when the shutter button is pressed by delaying the image capture by several seconds.

Camera Settings

A detailed discussion of appropriate camera settings is beyond the scope of this discussion; please refer to the manufacturer instructions for using the camera on the specific smartphone, tablet, compact camera or DSLR/mirrorless camera model to ensure an understanding of how to adjust the camera settings.

Key Points With Regards To Basic Principles Of Photography For Clinical Trials In Dermatology Include The Following:

Smartphone and Tablet Camera Settings:

Mode: Select the PHOTO mode; do not use PORTRAIT mode.

Autofocus: Use the touch focus option to facilitate autofocus.

Zoom: All smartphones and tablets have fixed lenses and true optical zoom can only be performed with certain devices that have multiple lenses. In general, use of digital zoom is discouraged as use will degrade the image quality. The best practice is to move closer to the patient.

DSLR/mirrorless or Compact and Shoot Camera Settings:

JPEG Compression: Set the camera to the lowest level of JPEG compression possible to preserve image quality.

Mode: While AUTO mode may produce images of sufficient quality, the use of MANUAL mode may be required to address issues with lighting or other constraints.

Shutter Speed: The shutter speed controls the length of time that the shutter is open and therefore the amount of light that is permitted. A slow shutter speed may result in a blurry image. For MANUAL settings, start with a shutter speed of 1/125 or 1/250.

ISO: The ISO controls the sensitivity of the camera to light and thus the exposure. For MANUAL settings, start with an ISO 200; increase the ISO if needed but avoid using a high ISO as this will degrade image quality.

Aperture: The aperture controls the amount of light that enters the camera; the higher the f-stop, the less light that is permitted. Aperture also controls the depth of field, and use of a large aperture will reduce the depth of field such that not all areas of the image are in focus. For MANUAL settings, use a starting aperture of f8 and to adjust the aperture as needed.

White Balance: Correct use of white balance will ensure that all colors are correctly calibrated. If using a camera with a flash, set the flash settings to AUTO and the white balance setting to FLASH. If not using a flash and you are in an examination room, set the white balance to AUTO, INCANDESCENT, or FLUORESCENT depending on the type of lighting present in the room.

Metering: Use spot metering as opposed to center-weighted or matrix in order to set an appropriate exposure for the area of interest.

Focus: It is often difficult for the camera to focus on the skin due to a lack of contrast between normal skin and the area of interest; use of a small black and white disposable paper ruler can be helpful in assisting the autofocus feature. Use of autofocus is recommended unless you are comfortable with using manual focus.

Macro: Close-up images are best captured with the camera set to MACRO, if available, or with the use of a macro lens.

DATA PRIVACY COMPLIANCE: HIPAA AND GDPR

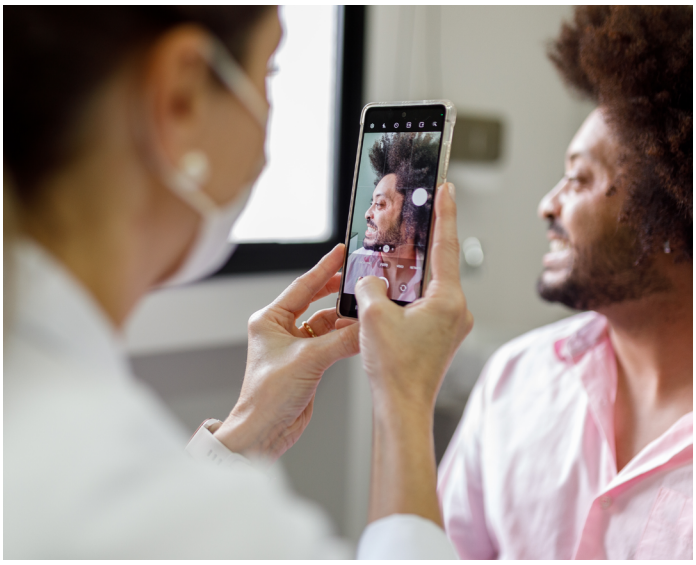
Data privacy laws, including the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule in the United States and the General Data Protection Regulation (GDPR) in the European Union and the European Economic Area, apply to photography as these images are considered data related to an identifiable person. As such, the use of photography should be justified and limited to only those images required to appropriately execute the protocol. Furthermore, informed consent is mandatory and should include detailed information regarding the patient's data privacy rights and the justification for including photography in the clinical trial. Finally, safeguards must be implemented to maintain data privacy throughout the trial, which includes de-identification through masking of images and removal of metadata (i.e. exchangeable image file format (EXIF) data such as date, time, and location) as well as data file transfer considerations.

While images of the face can easily and obviously be used to identify individual patients, images of other body areas that contain identifiable physical features such as injuries, anatomic anomalies, scars, tattoos, piercings, birthmarks, jewelry, and any other distinguishing features that are considered soft biometric data should also be de-identified. De-identification practices for soft biometrics per the National Institute of Science and Technology (NIST) include redaction through the placement of masking with an opaque bar, cropping the image file, blurring, and coarse pixelation.

Deletion of metadata and masking of images should be performed in an irreversible manner and can be subcontracted to specialized vendors or performed through image processing tools provided directly to sites.

CHALLENGES WITH USING PHOTOGRAPHY IN DERMATOLOGY CLINICAL TRIALS

Although high-quality images can usually be captured with the use of an appropriate camera device, adequate lighting, and appropriate training of site staff, there are several indications in which it can be challenging to obtain high quality images. With an understanding of the principles of optical physics and some ingenuity, creative solutions to address these issues have been developed.



DARKER SKIN TYPES

Dark skin tones create significant challenges with regards to skin photography. The use of flash lighting can create a flash artefact that results in a glare or shine on the skin, and use of standard room lighting (i.e., fluorescent or incandescent lighting) may influence color tones and create shadows. Use of an external light source is preferred; external LED light sources are relatively inexpensive and will produce less glare. It may also be helpful to adjust the angle of the external light source to an approximately 45° angle from the area of interest, which will minimize glare by reducing the amount of light reflected directly back towards the camera lens. The use of a light grey or blue drape can not only hide distracting background details but will also reflect some light back onto the patient, improving exposure.

Originally described by Rox Anderson in 1991, the use of cross-polarized light photography using two polarizers placed perpendicularly – one on the light source and one on the camera lens – reduce glare and enhance visualization of dermal structures such as blood vessels and melanin, thus enhancing visualization of erythema and skin pigmentation on dark skin.[2-5] Simple modification of a smart phone to provide cross-polarization has been reported using plastic linear polarizer sheets affixed in front of the camera lens and the flash.[6]

ERYTHEMA

Inflammatory skin conditions such as acne and rosacea are characterized by variable degrees of erythema, which typically reflect disease severity and/or status; however, subtle changes in erythema levels may not be visible to the naked eye. The use of cross-polarized light photography, in addition to reducing glare, will enhance the visualization of erythema in disorders such as acne and psoriasis. It should be noted that this occurs at the expense of reduced visualization of epidermal morphologic features such as scaling. It may be helpful to capture separate images with both non-polarized light and cross-polarized light in order to provide a comprehensive assessment of the lesion morphology if assessment and documentation of epidermal features is important.

Sophisticated multi-spectral imaging systems such as the VISIA and VISIA-CR systems, the latter which is designed for clinical research (Canfield Scientific, Parsippany, NJ, USA), capture images under white light, UV light and polarized light and then use a quantitative software analysis to enhance or reduce reflected light in either the red space, defined by the light absorption pattern of hemoglobin, or the brown space, defined by the light absorption pattern of melanin.[7] Use of this technology to enhance the red light space has been evaluated in inflammatory skin conditions such as rosacea and acne.[8,9]

VITILIGO

The ability to discriminate between affected and unaffected areas of skin in patients with vitiligo may be challenging, particularly in fair-skinned patients. In clinical practice, examination with the aid of a Wood's light or other light source that produces ultraviolet light is commonly used to accentuate the affected areas of skin. Interestingly, Robert Williams Wood, the creator of the Wood's lamp – a barium sodium silicate and 9% nickel oxide filter that significantly reduces emission of light in the visible spectrum while permitting UV light emission in the 320 – 400 nm range – originally used his invention for UV photography.[10,11] However, naturally occurring phosphors in the skin such as collagen and elastin absorb light in the UV range and through the process of electron excitation and relaxation emit photons in the visible light range. Depigmented areas of skin such as seen in vitiligo, lacking melanin, fluoresce brightly under UV light. This phenomenon can be used to facilitate photography of depigmented skin.

Capturing enhanced images of UV-induced fluorescence requires use of a UV camera flash, high output UV flash, or Wood's lamp; while the use of a Wood's lamp is the simplest option, the presence of shadows may be an issue.[12,13] Any camera and camera lens can be used for this purpose. It is important to note that unless a high output UV flash is used, images must be captured in a dark room as the fluorescent light emission will otherwise be obscured by visible light. It may be necessary to use a tripod and a high ISO in order to adequately capture images of sufficient quality.

The use of cross-polarized light can also enhance the visualization of areas of skin affected by vitiligo by reducing glare, minimizing the appearance of distracting epidermal morphology, and accentuating pigmentary differences between affected and unaffected skin.

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