Infrared Thermography in Trauma and Orthopaedic Patients

Protocol

Acronyms and Abbreviations:

AHP – Allied Health Professional

AI – Artificial Intelligence

CDC – Center for Disease Control and Prevention (United States)

CRF – Case Report Form

CRP – C-Reactive Protein

HTU – Hull Trials Unit

IAFF – Infection after Fracture Fixation

IRT – Infrared Thermography

MCA – Mental Capacity Act 2005

MDT – Multidisciplinary Team

ORIF – Open Reduction Internal Fixation

PCR – Polymerase Chain Reaction

ROI – Region of Interest

SSI – Surgical Site Infection

Tsk – Skin Temperature

TBC – To be concluded

UK – United Kingdom

WCC – White Cell Count

Scientific Title

Assessment of skin temperatures (Tsk), as a predictor for infection, using infrared thermography (IRT) in Orthopaedic Patients – A Pilot Study.

Background

Despite advances in surgery, surgical site infection (SSI) remains one of the most feared complications. SSIs have great psychological and financial costs to the patient, surgeon and society. SSI is the third most costly type of healthcare-acquired infection with estimated costs of $20,000 per case, associated with direct medical costs, prolonged hospitalisation and reoperation, as well as loss of earnings and increased mortality (Zimlichman et al., 2013). These costs increase to up to $60,000 in the United States for periprosthetic joint infections (Hernández-Vaquero., 2013).

With SSI becoming more difficult to treat due to antimicrobial resistant pathogens, an early diagnosis combined with microbiological diagnostics is a key component of clinical care and aids early appropriate intervention (Dicks et al., 2014). The Musculoskeletal Infection Society (MSIS) provides gold standard criteria for periprosthetic joint infection (PJI) diagnosis including clinical, microbiological and serum assessment. However many of these are non-specific and detect infection at a late stage.

Infrared radiation, discovered by Herschel in 1800 (Ring, 2007), can be used to measure the energy emitted from the human body surface. Infrared in the range of 7 to 14μm is converted into a digital image (Langemo et al., 2017). Cameras are now cheap, portable and able to detect temperatures to about 0.05°C (Lahiri et al., 2012).

Romano et al. (2011, 2012), using IRT, showed temperature peaks at days 3 to 4 (like CRP), and reduced over 90 days, following knee arthroplasty. Only one old study (Lambiris, 1981) has used thermography following fracture fixation; of the forearm and lower leg. Measurements were only taken after thread pull and every 2 weeks up to 6 weeks. The authors reported normothermic values returning at the 5^{th} to 6^{th} week. A thermography scan that had not returned to normal values by this time therefore, or showed higher than normal values within the early healing period, may indicate the presence of infection.

There are no recent studies following ankle or wrist fixation and IRT. There are large potential benefits and savings to patients, hospitals and wider society from early treatment of infection following identification with IRT. Patients could have reduced morbidity and mortality from early identification and early appropriate management of infections following IAFF. Patients could avoid unnecessary hospital admission (e.g. in the case of a hot red knee and thermography out of keeping with infection) or tests or interventions (e.g. in the case of a fracture with thermography not suggestive of deep infection). There could also be reduced personal costs to patients through loss of work and providing for families, as well as less psychological impact from the sequelae of significant infections. Early infection identification using IRT could also impact hospitals through reduced length of stay, efficiency savings and reduced testing. Earlier return to work could benefit society and the local economy.

Rationale

- Surgical site infection (SSI), including infection after fracture fixation (IAFF), has great financial and psychological costs to patients, surgeons and society.
- Currently there is no rapid, non-invasive, inexpensive test that can be used to facilitate diagnosis.

- Infrared thermography has been shown to have the potential to provide early detection of infection as a rapid bedside test that could be performed in the outpatient clinic by an allied health professional (AHP)/doctor.
- There are few studies available of infrared thermography following arthroplasty to assess for prosthetic joint infection, but none in the field of trauma to assess IAFF.
- We propose a pilot study over 6 months to help identify baseline values, and clarify operational protocols and feasibility to inform a larger future study.

We propose a prospective observational cohort study to obtain thermographic reference values for patients who have undergone wrist/ankle fixation and to identify and measure values in those who develop infection.

Thermographic reference values will also be taken from a third group of patients who present with a red, hot swollen joint(s). Thermographic values will be correlated with requirement for joint washout, microbiological findings and final diagnosis.

This pilot study on a small group of patients will determine the feasibility of collecting thermographic data in this cohort, as well as the numbers required in a larger study to use IRT to identify infection in the target population.

<table>
<tr><td colspan="4">Table 1: Study Summary Table</td></tr>
<tr><td>Health condition studied</td><td colspan="3">Wrist fractures, ankle fractures, red hot swollen Joints</td></tr>
<tr><td>Groups</td><td>Group 1: Distal Radius fractures fixed with volar plate</td><td>Group 2: Ankle fractures post ORIF</td><td>Group 3: Patients presenting with red, hot, swollen joints: Shoulder, elbow, wrist, hip, knee and ankle.</td></tr>
<tr><td>Key Inclusion and Exclusion Criteria</td><td colspan="3">Inclusion Criteria

• Wrist fractures treated with volar plate
• Ankle fractures treated with plate and screws
• Patients with painful, red, hot, swollen joints (shoulder, elbow, wrist, hip, knee and ankle) attending the emergency department or who have been admitted

Exclusion Criteria

• Children (less than 18 years)
• Prior fixation to ipsilateral or contralateral ROI (Region of Interest)
• Concurrent skin condition over ROI
• Peripheral neuropathy or vasculopathy
• Pathological Fracture
• Inflammatory Arthropathy
• Open fracture
• Significant concomitant injuries, or other joints or limbs affected Conditions that will prevent the participant from having capacity, giving consent or following instructions</td></tr>
<tr><td>Study Design</td><td colspan="3">Prospective observational cohort study</td></tr>
</table>

Planned Sample Size	TBC after pilot study	
Follow up duration	- 0, 1 to 2, 4, 6, 12 and 24 weeks following wrist or ankle fracture fixation - Day 0 (i.e. admission and consecutive days up to washout) following presentation with red, hot swollen joint(s) and whilst in hospital and 1, 2, 4, 6, 12 and 24 weeks (aligned with outpatient clinic review)	
Outcomes	Primary	Secondary
	• Skin Temperature differences between ipsilateral and contralateral regions of interest • To determine numbers required to power a larger study to identify infection using IRT in these patient groups • To inform the design and feasibility of any future larger study	• To define thermographic reference values in orthopaedic conditions • To store thermographic data in a way that allows future analysis using an AI or machine learning or similar approach • To correlate Tsk with inflammatory markers e.g. CRP, WCC • To determine the effect of fracture pattern, comorbidity and wound length on Tsk

Aims and Objectives

Aim

- Feasibility study to investigate the use of thermography in orthopaedic patients after fracture fixation and who present with red, hot, swollen joints.
- To determine whether IRT can be used to accurately identify patients with infection after fracture fixation (IAFF) and septic arthritis

Objectives

Primary

- To determine baseline normal Tsk values using IRT for wound healing following wrist and ankle fracture fixation relative to the unaffected contralateral limb.
- To determine whether thermographic Tsk differences exist in those patients who go on to develop IAFF or wound healing problems.
- To determine baseline normal Tsk values using IRT for patients with a red, hot swollen joint(s).
- To determine whether thermographic Tsk differences exist in those patients who go onto develop septic arthritis, versus other conditions e.g. crystal arthropathy, cellulitis.
- To determine the feasibility, operational protocols and numbers required for larger, follow-up study.

Secondary

- To define normal thermographic reference values in orthopaedic populations and over what time frame Tsk returns to normal.
- To confirm or refute whether contralateral Tsk temperatures during fracture healing follow a similar pattern to fractured limb as previously suggested.
- To store and analyse data in a way compatible with an AI/machine learning (advanced data analytical methods) model.
- To establish the effect of fracture severity and comorbidity on Tsk IRT readings in orthopaedic patients.
- To establish the effect of wound length on Tsk IRT readings

Study Design

The proposed study will be a multi-centre observational pilot study with three groups. The study will take place at Hull University Teaching Hospitals NHS Trust and Aalborg University Hospital, Denmark.

The total maximum sample size will be 30 patients at each centre. We will aim for a minimum of 10 patients taken from each group (wrist fractures, ankle fractures, and red, hot swollen joints) across all centres. This will leave a total of 30 to 60 patients.

Inclusion and Exclusion Criteria are as stated above.

Eligible and consenting patients will be identified in the emergency department and during trauma meetings/orthopaedic MDTs/ward rounds. The surgery itself will take place as per routine practice. However, images will be taken in addition to usual care.

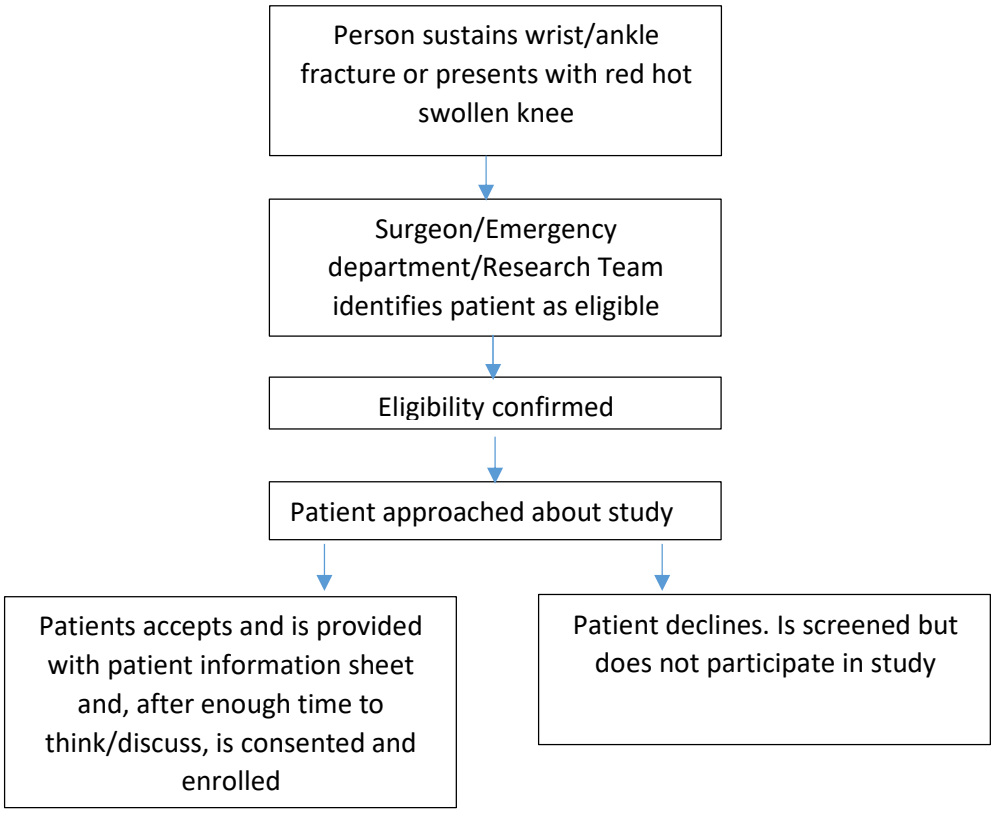
Following fixation, wrist and ankle fractures routinely undergo follow-up with one appointment at 1 or 2 weeks and another at 4 or 6 weeks, and occasionally a third appointment at 12 weeks. The study protocol will require images immediately following surgery, in the operating room to provide a baseline temperature reading. Patients will then be imaged at their routine follow-up appointments at 1 or 2 weeks, and 4, 6 and 12 weeks. We will invite the patients to be imaged after the operation at 1 or 2 weeks, 4, 6, 12 and 24 weeks. Therefore patients will require two extra hospital visits (if these were not already part of their individualised routine follow-up).

Patients will need to be managed in a removable cast or splint to allow for image capture. As per standard procedure, patients who are managed in a back slab postoperatively will have this removed at wound check at 1 or 2 weeks and their limb placed in a removable orthosis (e.g. removable cast or boot) for the duration of their immobilisation. This will be either weightbearing or non-weightbearing at the discretion of the surgeon as per routine practice.

Patients attending with red, hot swollen joints will be imaged during admission and consecutive days up until washout and daily until discharge. Patients will then be pragmatically imaged during routine follow-up, which will be directed by their surgeon. This will likely be at 1, 2, 4, 6 and 12 weeks. We will invite the patients to be imaged after the operation at 1 or 2 weeks, 4, 6, 12 and 24 weeks. Therefore patients in this group will require one extra hospital visit. Patients who present with a red, hot swollen joint but who do not undergo washout will be imaged during routine follow-up.

Several factors have been shown to influence skin temperatures including NSAIDs, caffeine, medication, alcohol, nutrition, menstrual cycle, massages, circadian rhythm, age and sex. Many of these factors are difficult, or impossible, to control and therefore in this pragmatic study we will attempt to record these data using questionnaires at each visit. However, we will not attempt to control these factors.

Recruitment Flow Chart



Interventions and Risks

All patients will undergo routine surgical care, performed by surgeons as part of their everyday practice. As such, the study would not deviate from routine care protocols and no new interventions will be studied. Therefore risk will not be increased in these patients.

Patients will be managed in removable casts. Casts are often removed or changed in fracture clinic for a number or reasons. Fractures after being fixed with metal work may or may not routinely be managed with a plaster cast. Therefore, removing the cast for the taking of a photograph will not increase the risk of displacement.

There will be a theoretical increased risk of infection due to dressing changes for photographs at both 1 and 2 weeks. The National Institute for Clinical Excellence advises that wounds should be untouched for only 48 hours after surgery (NICE, 2020). Wound epithelisation usually is completed in 1 to 3 days in acute wounds that are primarily closed (Hopf et al., 2008). Therefore by one week wounds would have sealed and the risk of infection due to dressing change would be minimal. Often, dressings are changed routinely in fracture clinic to inspect wounds, especially if there is any leakage. Furthermore, some surgeons routinely will change the dressing and inspect wounds. During the surgical procedure wounds will be closed using skin glue, to provide a water tight seal, prior to dressing to help mitigate this potential risk.

Outcomes

Primary Outcome

The primary outcome is to determine skin temperature (Tsk) differences using Infrared thermography (IRT) immediately post-operatively and at 1 to 2, 4, 6, 12 and 24 weeks following wrist and ankle fracture fixation. Images will be taken as per the infrared camera manufacturer's instructions, using predefined protocols of the ROI (see 'Imaging Position' below) in outpatient clinics. The maximum temperature differences (Tmax) and average temperatures differences (Tmean) between ipsilateral and contralateral side will be recorded.

IRT images to determine Tsk will be recorded on day 0 (i.e. admission and consecutive days up to washout) following presentation with red, hot swollen joints and daily whilst in hospital and during the patient's routine clinical follow-up (approximately 1, 2, 4 , 6, 12 and 24 weeks).

Data for those who develop IAFF and delayed wound healing will be compared with non-infected patients.

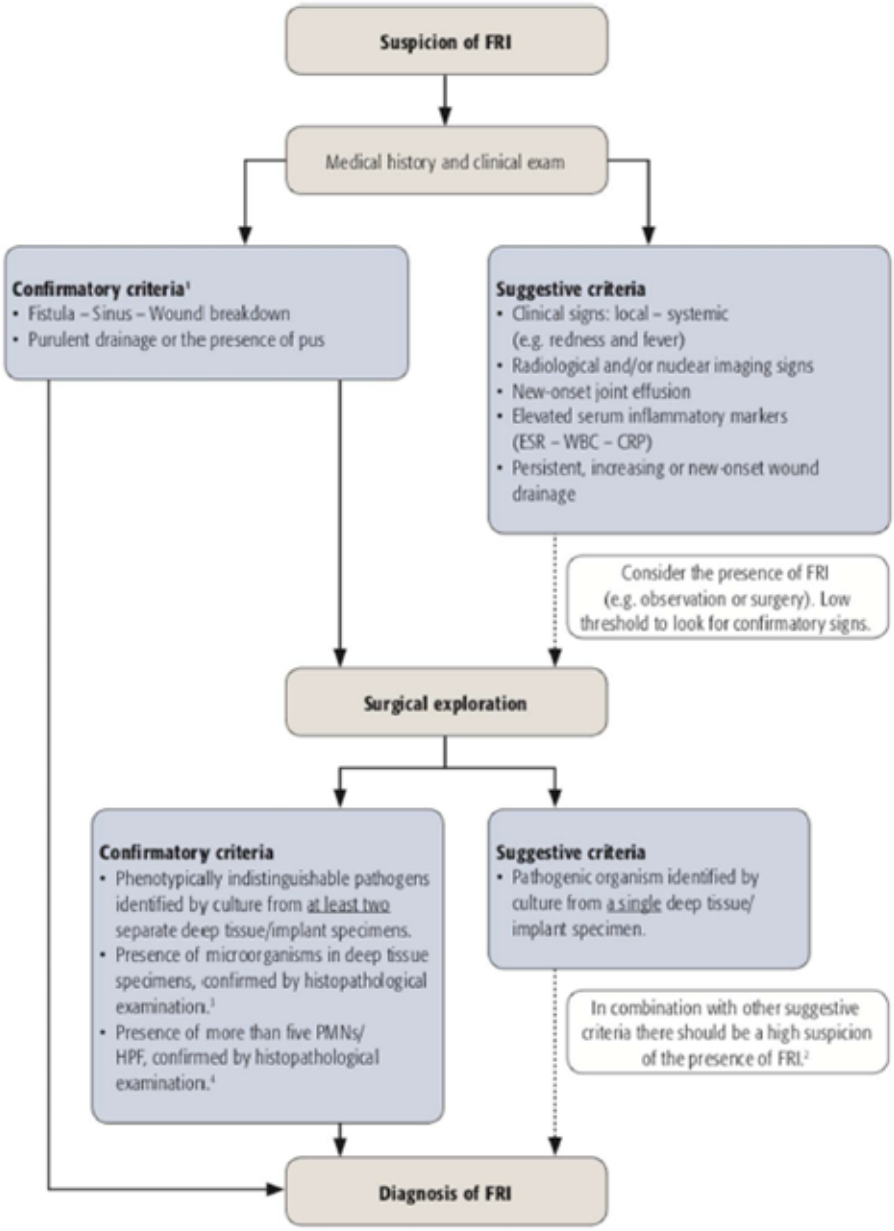
Definition and Classification of Infection and wound healing problems

For wrist and ankle fracture patients: IAFF is defined as per the CDC definition of SSI i.e. either superficial or deep as stated in tables 2 and 3 below. IAFF will also be defined as per confirmatory criteria as per Govaert et al., (2020) – see algorithm below. This is either confirmatory clinical signs or confirmatory criteria at clinical exploration; or the presence of suggestive criteria when the patient is commenced on antibiotic treatment.

Table 2: Superficial Infections must meet the following criteria:
Date of event occurs within 30 days after operative procedure (where day 1 = the procedure date) AND involves only skin and subcutaneous tissue of the incision AND patient has at least one of the following: a. purulent drainage from the superficial incision. b. organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or nonculture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment. c. superficial incision that is deliberately opened by doctor/AHP and culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed. AND Patient has at least one of the following signs or symptoms: localised pain or tenderness; localised swelling; erythema; or heat. d. diagnosis of a superficial incisional SSI by a doctor/AHP.
The following do not qualify as criteria for superficial infection: • Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet superficial infection criterion 'd'. • A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration). • A localised stab wound or pin site infection; depending on the depth, these infections might be considered either a skin (SKIN) or soft tissue (ST) infection.

Table 3: Deep Infections must meet the following criteria:
The date of event occurs within 90 days after the operative procedure (where day 1 = the procedure date) AND involves deep soft tissues of the incision (for example, fascial and muscle layers) AND patient has at least one of the following: a. purulent drainage from the deep incision. b. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a doctor/AHP. AND organism(s) identified from the deep soft tissues of the incision by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment or culture or nonculture based microbiologic testing method is not performed. A culture or non-culture based test from the deep soft tissues of the incision that has a negative finding does not meet this criterion. AND patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. c. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

Confirmatory criteria for Infection after Fracture Fixation (IAFF) as per Govaert et al., (2020):



[1] In cases of purulent drainage or fistula/sinus/wound breakdown, the presence of pathogens identified by culture is not an absolute requirement (e.g. in the case of chronic antibiotic suppression).
[2] If the positive culture is from sonication fluid, it is highly likely that FRI is present. This is especially true when virulent bacteria (i.e. *Staphylococcus aureus*) are present.
[3] The presence of microorganisms is confirmed by using specific staining techniques for bacteria and fungi.
[4] The presence of an average of more than five PMNs/HPF on histopathological examination should only be considered diagnostic of FRI in chronic/late-onset cases (e.g. fracture nonunion).
ESR: erythrocyte sedimentation rate, WBC: white blood cell count, CRP: C-reactive protein, PMN(s): polymorphonuclear neutrophil(s), HPF: high-power field.

Wound healing problems, for wrist and ankle fracture patients, will be defined as per criteria for leaky wounds as per International Consensus Meeting on Prosthetic Joint Infection (Wagenaar et al., 2017). This will be wounds that leak, greater than 2x2cm for more than three days following surgery that do not fulfil the above criteria for infection.

For joint infection patients: infection is defined as patients who have a clinical presentation consistent with septic arthritis plus a positive microbiological culture for a recognised pathogen or suggestive histology or a positive non-culture based test (e.g. PCR) from intraoperative or aspirate samples and/or are treated as septic arthritis (if culture/PCR negative) with at least 4 weeks of antibiotic therapy having had an arthroscopic or open surgical washout. Cases will be reviewed independently by at least two members of the study team to confirm whether the diagnosis was likely or unlikely to be septic arthritis based on the clinical presentation, imaging performed, microbiological results, and operative findings (e.g. pus clearly seen).

The feasibility and protocols will be optimised and the numbers needed to power a study to use IRT to detect infection in these cohorts will be determined.

Imaging Position

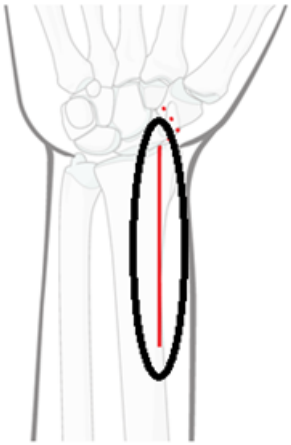
Ankle patients will be positioned supine and wrist patients seated with elbows resting on table (flexed to approximately 90° and supinated) to avoid dependency. The affected and contralateral limbs or joints, where possible, will be placed on a black acrylic/polystyrene board or similar, to improve image quality. Casts, dressings and clothing will be removed whilst the areas of interest are allowed to equilibrate for 15 minutes with the environment. Images taken of patients in theatre will not require further acclimatisation as the wound has already been exposed throughout the procedure.

For wrist patients the region of interest will be defined as an ellipse. Longitudinally (from distal to proximal) this will be from points 2cm distal and proximal to the wound edges. Horizontally (from medial to lateral) this will be from points 2cm medial and lateral at the distal and proximal wound edges.

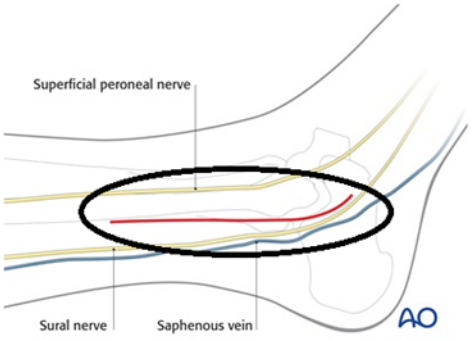
Similarly, for ankle patients the region of interest will be defined as an ellipse. Longitudinally (from distal to proximal) this will be from points 2cm distal and proximal to the wound edges. Horizontally (from anterior to posterior) this will from points 2cm anterior and posterior at the distal and proximal wound edges.

For joints an ellipse will be created as described by Romano et al., (2012) which is 20cm long in the longitudinal axis and the full width of the joint.

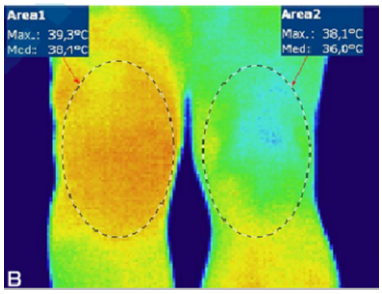
ROI Wrist



ROI Ankle



ROI Knee Joint



Secondary Outcomes

1. Thermographic Reference Values: Thermographic reference values of operated and contralateral sides for orthopaedic patients following wrist and ankles fractures will be determined at 1, 2, 4, 6 12 and 24 weeks. This will include the temperature patterns following normal bone healing following fracture fixation as detected by IRT.
2. Contralateral Tsk Temperature Patterns: Contralateral Tsk temperature patterns following wrist fractures have previously been reported to increase in a similar pattern to the injured limb (Haluzan et al., 2015). We will determine whether this is the case following fracture fixation.

3. Automated learning: Automated learning has been used to analyse IRT images in breast cancer screening. We will store images securely in a way that they can be retrospectively analysed by an AI/machine learning or similar algorithm (advanced data analytical techniques.
4. Comorbidity and Fracture Severity: Fractures are known to impact blood supply to the fracture site and therefore may have an impact on Tsk IRT readings. We will determine the relationship between fracture severity and temperature differences over the 24 week period.
5. Non-infected Non-union: Any cases of non-infected non-union will be identified and correlated with Tsk IRT readings.
6. Wound length: The effect of wound length on IRT readings will be established.

Data Management

Study data will be recorded for the patient, which will be completely anonymised for purposes of analysis and any subsequent reports or publications. For the purposes of ongoing data management, individual patients will only be identified by study numbers.

Each site will hold data according to the Data Protection Act 1998 and data will be collated in case report forms (CRFs) identified by a unique identification number (i.e. the Study number) only. A Study Enrolment Log at the sites will list the ID numbers. HUTH will maintain a list of study numbers for all study patients at each site.

All the data will be kept on the trust computers and offices. It will be only accessible to the research team.

IT Services Department has a backup procedure approved by auditors for disaster recovery. Servers are backed up to disk media each night. The disks run on a 4-week cycle. Files stay on the server unless deleted by accident or deliberately. Anything deleted more than 4 weeks previously is therefore lost. Additional 'archive' backups are taken for archived data, so data should not be lost from this type of system e.g. File Vision which stores Medical Records. Disks are stored in a fireproof safe.

Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. All essential documents will be stored in hard copies for 5 years and electronic data will be stored for 15 years on trust computers. A sticker stating the date after which the documents can be destroyed will be placed on the inside front cover of the case notes of study participants.

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