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# Prospective first-in-human clinical investigation to evaluate the safety of the fracture monitor T1 in patients with femur fractures treated with a locking compression plate: a study protocol

Benedikt J Braun ,[1] Michael J Raschke,[2] Konrad Schütze,[3] Tim Pohlemann,[4] Alexander Joeris ,[5] Manuela Ernst[6]

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For numbered affiliations see end of article.

**Correspondence to**
Professor Benedikt J Braun; bbraun@bgu-tuebingen.de

## ABSTRACT

**Introduction** An objective way to monitor bone healing in real time could provide major benefits for the rehabilitation of fracture patients. The fracture monitor T1 is a novel biofeedback sensor system designed to provide continuous data of the relative implant load, that is, a measure inversely correlated to bone healing progression as well as patient's physical activities. The primary objective of this first-in-human study is to evaluate the safety, that is, the incidence of adverse device effects (ADEs), of the investigational device fracture monitor T1 in femoral fracture patients within the first 6-months postsurgery. Secondary objectives are to collect information on clinical performance, other safety parameters and device handling and usability.

**Methods and analysis** 37 adult patients with femoral fractures to be treated with a plate, which is compatible with having the fracture monitor T1 mounted on it, will be prospectively enrolled in this multicentre, interventional first-in-human study. The fracture monitor T1 will be implanted together with the osteosynthesis plate for femoral fracture fixation as well as femoral instabilities, such as post-traumatic non-unions. Standard of care will be followed for femoral fracture treatment and patients will be followed up for 6-months. Demographic data, comorbidities, prior medication, prior treatment details, injury details, treatment details and outcome measures will be documented in a cloud-based database. The primary outcome measure is ADEs. Secondary outcome measures include clinical and functional outcomes, safety outcomes, device removal, patient-reported outcomes (pain, Numeric Rating Scale, EQ-5D-5L), device handling and usability, number of visits and radiographic assessments, radiographic outcomes, relative implant load and technical performance parameters. A statistical analysis plan will be prepared before final analysis.

**Ethics and dissemination** Ethics approval is obtained at each site before patient enrolment, which follows an informed consent process approved by the responsible ethics committee. Data from this first-in-human study will be compiled into a clinical evaluation report for the application of CE (Conformité Européenne, certification mark indicating conformity with European Union health, safety and environmental protection standards) marking of the device. The results of this first-in-human study will be published in a peer-reviewed journal.

**Trial registration number** NCT05410587

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first-in-human, interventional multicentre, prospective study to date designed to provide safety and performance data on the fracture monitor T1 device for monitoring femoral fracture healing over a 6-month postsurgical period.
⇒ The study will provide the necessary safety profile of fracture monitor T1 to be used for the conformity assessment of the device according to medical device regulation.
⇒ Outcome data collected may further our understanding of fracture treatment, fracture after-care and rehabilitation, and how this immediately relates to fracture healing.
⇒ Limitations of the study include the small sample size; studies with longer follow-up periods may be needed to capture the true clinical performance of the fracture monitor T1; there may also be a lack of generalisability of the results to other types of fractures, as this study is limited to femoral fractures.

## INTRODUCTION

Current methods to determine the state of fracture healing in the clinical setting are based on radiographic evaluation and clinical examination, both of which are highly subjective. Despite advancements in imaging techniques to assess fracture healing, plain radiography and CT evaluation remain the most used radiographic tools for monitoring bone formation, combined with the clinical assessment of the point of return to full load bearing. However, standard radiographic assessment may be insufficient when there are healing disturbances or if a more precise

evaluation of fracture healing is required. Early detection and treatment of healing disturbances could have a considerable impact on patient care and healthcare socioeconomics. A more objective method to assess healing is through fracture stiffness, a robust index of regained mechanical function. In the initial phase after surgical fracture fixation, the loads generated from weight bearing are carried primarily by the fixation material. As healing progresses, the bone and repair tissues increasingly share the weight-bearing, as their stiffness increases, and the fixation construct is gradually unloaded. While this principle of indirectly measuring fracture stiffness through the assessment of implant load has been demonstrated before, particularly with external fixators, no method or device is yet available to assess this in clinical practice.[1–5]

The fracture monitor T1 (AO Research Institute Davos (ARI)) is a novel biofeedback sensor system designed to provide relative implant load data for continuous long-term monitoring of bone healing progression[6 7] in plate osteosynthesis. Preclinical studies attaching the device to conventional locking plates showed a decline in the implant load signal as the fracture callus formed.[8] Additionally, a predecessor of the device was used non-invasively with external fixation in 10 patients and suggested good potential of the device to track the course of fracture healing and patient activity through measuring relative implant load.[9]

This prospective, interventional, multicentre first-in-human study aims to monitor fracture healing using the fracture monitor T1 in femoral fractures. The primary objective of this first-in-human study is to evaluate safety, that is, the incidence of adverse device effects (ADEs), of the investigational device fracture monitor T1 in patients with femoral fracture within the first 6-months postsurgery. The secondary objectives are to evaluate the clinical performance, other safety parameters, device handling and usability rated by the patients and investigators, and technical performance (TP) of the fracture monitor T1.

## METHODS AND ANALYSIS

### Study design and setting

This first-in-human study is a prospective, interventional, multicentre clinical investigation of the fracture monitor T1 device, which is in the premarket stage of clinical development. Four sites in Germany are included (table 1).

**Table 1** Current participating sites

| Name | Country |
|---|---|
| Berufsgenossenschaftliche Unfallklinik Tübingen, Tübingen | Germany |
| Universitätsklinikum des Saarlandes, Homburg | Germany |
| Universitätsklinikum Münster, Münster | Germany |
| Universitätsklinikum Ulm, Ulm | Germany |

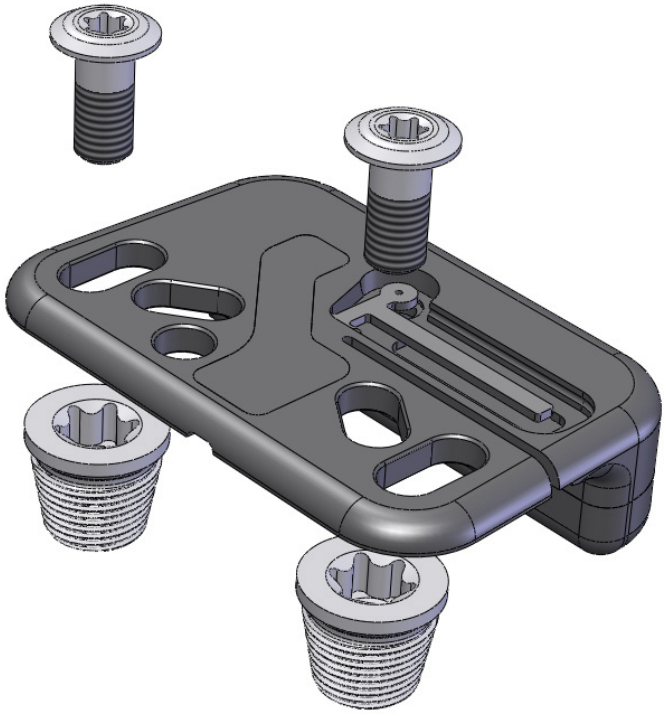

**Figure 1** The implantable data logger is attached to the bone plate. The implantable data logger (dimensions: length 32.8 mm, width 21.8 mm, height 8.6 mm) is fixed rigidly to a conventional bone plate with the corresponding inserts and screws.

### Study procedures

For this first-in-human study, the fracture monitor T1 implantable data logger (figures 1 and 2) will be implanted together with the fixation plate used for surgical treatment of femoral fracture requiring osteosynthesis. The fracture monitor T1 implantable data logger—powered by an internal battery—is rigidly attached to the bone plate through two inserts, which are screwed into the locking part of two adjacent combi holes and two non-locking screws pressing the implantable data logger against the inserts. The design of the hole pattern in the data logger took into account the hole patterns of the targeted plates, thus ensuring target plate compatibility.

For this study, the fracture monitor T1 will be implanted together with the fixation plate. Postoperatively, a patient-specific calibration of the implantable data logger will be done and the implant will be paired with the respective custom smartphone application for wireless data transmission. After the implantation, the patient receives the patient sheet with the implant card. Standard of care (SoC) will be followed for the femoral fracture treatment, including the surgeon's decision on

**Figure 2** The implantable data logger is attached to a conventional femoral plate.

the diagnostic procedure, choice of fixation constructs, surgical approach, postoperative care and follow-up visit scheduling. All subsequent visits after discharge related to care of femoral fracture or its treatment will be documented (only up to 6 months plus adverse events (AEs) and implant removal). If removal of the fixation plate (during which fracture monitor T1 will also be removed) is not planned within a maximum of 2 years, an additional surgery that is not part of SoC will be performed to remove only the fracture monitor T1. It is mandatory that the fracture monitor T1 implantable data logger be removed, as no long-term data is available, given that the present study is the first-in-human study. Table 2 provides a summary of procedures performed and data collected.

### Inclusion criteria

Patients fulfilling the following criteria will be included:

- Age 18 years or older.
- Patients with closed growth plates at the time of injury.
- Patients with femoral fractures requiring osteosynthesis and treated with one of the following plates:
  - DePuy Synthes LCP 4.5/5, Broad.
  - DePuy Synthes LCP 4.5/5, Broad Curved.
  - DePuy Synthes LCP Condylar Plate 4.5/5.0.
  - DePuy Synthes VA-LCP Condylar Plate 4.5/5.0.
  - DePuy Synthes LCP Distal Femur.
  - DePuy Synthes LCP Proximal Femoral Plate 4.5/5.0.
  - DePuy Synthes LCP Proximal Femur Hook Plate.
  - 41medical AG, Biphasic Plate DF.

The decision to include a patient will be taken by the surgeon; whichever fracture in the femur the surgeon decides to treat with one of the compatible plates can be included.

- American Society of Anaesthesiologists score 1–3.
- Full weight-bearing capacity prior to the injury.
- The patient is foreseen to be capable of postoperative weight-bearing of at least 15 kg.
- Willingness to undergo an additional surgery to remove the fracture monitor T1 if removal of the fixation plate is not planned within 2 years.
- Ability to provide written informed consent.

### Exclusion criteria (preoperative)

Patients diagnosed with concomitant fractures in the contralateral leg or fulfilling any of the following criteria will be excluded:

- Electromagnetic hypersensitivity.
- Implanted electromagnetic bone stimulators.
- Pregnancy (determined by pregnancy test).
- Prisoner.
- Known history of substance abuse (eg, recreational drugs and alcohol) that would preclude reliable assessments.
- Participation in any other medical device or medicinal product study within the previous month that could influence the results of the present clinical investigation.

### Exclusion criteria (intraoperative)

Patients will also be excluded intraoperatively if any of the following criteria are fulfilled:

- Use of a compression lag screw across the fracture fragments.
- Compression osteosynthesis.
- Precontouring of the implant in the area of the attachment of fracture monitor T1.
- Double-plating technique.
- Soft-tissue coverage >6 cm above the data logger.
- Concurrent use of an intramedullary nail.
- Patient foreseen to require MRI scanning at any part of the body or shockwave therapy at the proximity of the fracture monitor T1.
- Fracture monitor T1 not functional according to the instruction for use and no functional replacement fracture monitor T1 available.

### Recruitment

A recruitment period of approximately 24 months is planned to enrol 37 patients. Each patient will be followed in the study for up to 6-months after the surgery with a safety follow-up on the day of device removal (at latest after 2 years postsurgery) if the device is not removed within 6-months postsurgery.

Each site will identify potentially eligible patients according to the preoperative inclusion and exclusion criteria. The assessment of preoperative eligibility includes an inquiry about the interest and willingness of the patient to be included in the study. A member of the research team will explain the nature of the study, its purpose, procedures involved, expected duration, potential risks and benefits, and any discomfort it may entail and the informed consent process to each patient using lay language. Patients will be informed that participation in the study is voluntary and that they may withdraw at any time, without affecting subsequent medical treatment, that their medical records may be examined by authorised individuals other than the treating surgeon, and that participation in the study involves removal of the fracture monitor T1 at the latest after 2 years. Potential participants will be provided with a specific patient information sheet and consent form. They will also be informed that participation in the study requires the use of a smartphone app installed preferably on their personal smartphone, but if not possible, on one provided by the sponsor.

Data collection for the study is not allowed without the written consent of the patient, and therefore, no data are collected in the electronic case report form (eCRF) before obtaining consent from the patient. Intraoperative inclusion criteria will be assessed before the fracture monitor T1 is implanted. Thus, patients are considered as enrolled when the fracture monitor T1 is implanted.

All consented patients will be given a unique patient number. Each site will keep an identification list linking the patient number with the patient identity. This identification list is always kept safe in a locked place. Sites are not allowed to share the identification list with any third

**Table 2** Study schedule and data collection at each visit

| | | | Postoperative visits* | | | |
|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3* | Visit 4 to x* | Final visit* | Safety FU† |
| Study procedures and assessments | Screening/baseline | Intraoperative (Day 0) | Postoperative day | FU X | 6-months visit | Removal of device |
| Patient information/consent | X | | | | | |
| Eligibility | X | X | | | | |
| Pregnancy test‡ | X | | | | | |
| Baseline characteristics§ | | | | | | |
| Demographics | | X | | | | |
| Comorbidities | | X | | | | |
| Medications | | X | | | | |
| Previous treatments | | X | | | | |
| Injury details | | X | | | | |
| Somatometrics | | | X | | | |
| Treatment details | | | | | | |
| Surgical details | | X | | | | |
| System test | | X | | | | |
| Fracture monitor T1 implantation | | X | | | | |
| Injury-related treatments | | | X | X | X | |
| Discharge | | | X | | | |
| Adverse events | | X | X | X | X | X |
| Installing app in smartphone | | | X‡‡ | | | |
| Implant registration | | | X‡‡ | | | |
| Implant load calibration | | | X‡‡ | | | |
| Bone healing | | | | X | X | X |
| Weight-bearing | | | | | | |
| Prescribed weight-bearing | | | X | X | X | |
| Use of walking aids | | X¶ | X | X | X | |
| FIX-IT score | | | X | X | X | |
| Incapacity for work | | | X | X | X | |
| Device deficiencies | | X | X | X | X | X |
| Device removal | | | X | X | X | X |
| Patient-reported outcomes | | | | | | |
| Pain NRS | | X¶ | X | X | X | |

Continued

**Table 2** Continued

| Study procedures and assessments | Visit 1<br>Screening/baseline | Visit 2<br>Intraoperative (Day 0) | Postoperative visits*<br>Visit 3*<br>Postoperative day | Visit 4 to x*<br>FU X | Final visit*<br>6-months visit | Safety FU†<br>Removal of device |
|---|---|---|---|---|---|---|
| EQ-5D-5L | | X¶ | X | X | X | |
| Device handling and usability | | | | | | |
| Surgeon evaluation | | X | | | | X** |
| Patient evaluation | | | | | X | |
| Medical attention outside of the study site | | | | X | X | |
| Return of sponsor's smartphone by patient† | | | | | X | |
| Images (X-ray/CT scan)†† | X | X | X | X | X | |

*Postoperative FU visits will be calculated from the day of surgery (ie, Day 0) and will be done according to the standard of care for femoral fracture at the study site. Outcome measures and images will be collected at every FU visit performed by the study site related to the care for the femoral fracture or its treatment. At the 6-month visit, the treating surgeon will discuss with the patient the timing of removing the fracture monitor T1 if it has not been removed.
†The purpose of this visit is to document the removal of fracture monitor T1 as per the instructions for use. This visit will take place at the time point when the fracture monitor T1 is removed as per instructions for use, if it has not been removed within the 6-months. This visit is also applicable for patients who withdraw from or cease to participate in the study within 6-months and in whom the fracture monitor T1 has not been removed.
‡If applicable.
§Data collection for these assessments should be done (i) earliest when intraoperative eligibility criteria are assessed, and the patient is confirmed enrolled (ie, with signed informed consent form and with the Fracture Monitor T1 implanted) and (ii) latest at the postoperative visit.
¶Refer to the pre-injury status and should be collected earliest on day of surgery (when intraoperative eligibility criteria are assessed, and the patient is confirmed enrolled, ie, with signed informed consent form and with the Fracture Monitor T1 implanted) or latest on the postoperative day.
**Or at the time when the Fracture Monitor T1 is removed (regardless of the reason of removal).
††All images (X-rays, CTs, etc) taken as part of the standard of care (routine) procedures or due to adverse events will be collected.
‡‡Must be done within 3 days of surgery.
CT, computed tomography; FIX-IT, Function IndeX for Trauma; FU, follow-up; NRS, Numeric Rating Scale.

party except for the sponsor representative, legal authorities and ethics committees, who may have access during on-site monitoring or auditing activities.

All enrolled patients should be followed up within the study, except if their study participation is prematurely terminated.

### Data collection

#### *Baseline information*

Baseline parameters to be recorded are sex, year of birth, height, weight, body mass index, smoking status, limb circumference above the device and comorbidities according to the Charlson Comorbidity Index.[10 11] Additionally, the presence of rheumatoid arthritis, diabetes mellitus (dietary management and/or physical activity alone) and osteoporosis (yes/no) will be recorded. Medications taken before the injury and previous treatment related to the injury will be documented.

#### *Injury details*

Injury details recorded are the date of injury, injured side, fracture classification according to the AO/OTA fracture classification and dislocation classification,[12] types of fracture (closed[13] and open),[14 15] types of injury, traumatic vascular injury and infected fracture (preoperatively).

#### *Treatment details*

Surgical details documented include the following:

- Date of surgery.
- Duration of surgery (skin-to-skin time).
- Surgical procedure.
- Plate details.
- Fracture monitor T1 details.
- Injury-related medications.

The date of discharge will be documented.

### Intervention

The intervention under investigation in this first-in-human study is femoral fracture fixation (bridge plating aiming at secondary bone healing) using a locking plate with the attached investigational device fracture monitor T1 (implantable device class III). Fracture monitor T1 is an implantable sensor system designed to measure the local deformation of bone plates under functional weight bearing as a surrogate measure of the progression of fracture healing. It is composed of an implantable data logger (containing a strain sensor to measure the bone plate deformation under patient loading as a measure of implant load), which can be attached to conventional locking plates, a smartphone app and a cloud-based web application for central data storage. Investigators will not have access to the platform where the recorded data is stored and can be visualised; the device data is to be prepared by ARI and forwarded to the investigators for blind retrospective evaluation. Data will be unblinded during the analysis phase.

The fracture monitor T1 is to be removed together with the bone plate in the following circumstances:

- The plate is planned to be removed within 2 years after implantation as per the local SoC.
- The plate needs to be removed for medical indications such as implant failure, revision surgery, wound infection and implant-related symptoms.

Alternatively, the fracture monitor T1 shall be removed separately without removing the bone plate, at the latest 2 years after implantation under the following conditions:

- Severe pain, swelling, irritation or warming of the soft tissue in the proximity of the device.
- Symptoms or signs indicating device damage.
- If the plate is not planned to be removed according to Soc.
- If the plate is planned to be removed beyond 2 years after implantation.

Site investigators and treating surgeons will be extensively trained on the use of the fracture monitor T1.

### Follow-up

Patients will be followed up for 6-months. ‘Day 0’ is the intraoperative visit which is when the verification of intraoperative exclusion criteria before implantation of the fracture monitor T1 takes place. At the 6-month visit, the surgeon will discuss the timing of removal of the fracture monitor T1 during an additional surgery if it has not yet been removed. The safety follow-up is defined as the day of device removal, at the latest, 2 years postsurgery.

The schedule for data collection at each visit is summarised in table 2.

### Termination of participation

Patient participation in the study may terminate for reasons such as withdrawal of informed consent, at the discretion of the investigator, loss to follow-up, death and termination of participation by the sponsor. Detailed information explaining the circumstances leading to the termination will be recorded in a dropout form in the CRF. If the patient withdraws from or ceases to participate in the study within 6-months and the fracture monitor T1 has not been removed, the investigator must discuss removal of the device, which is to be performed in an additional surgery. The patient will be informed about the risks related to the additional surgery and a separate written informed consent form will be collected. Data collected from these patients will be censored as of the day of termination. No further data will be collected from these patients. Censored data may be used to obtain meaningful study results.

## Outcome measures

Outcome measures will be assessed according to the schedule shown in table 2.

### Primary outcome measure

The primary outcome measure is the occurrence of a subgroup of AEs deemed as related, possibly related or probably related to the investigational device ADEs.

Anticipated ADEs are:

- Local soft tissue damage.

- Infection.
- Allergic reaction to the device substance or materials.
- Damage of device—toxic reaction causing tissue necrosis or sepsis, chemical burn causing necrotic tissues or pain.
- Overheating or thermal burn causing local pain.
- Device/component loosening.
- Device/component migration.
- Other ADEs.

### Clinical and functional outcomes

Bone healing status will be assessed by the treating surgeon following the local SoC based on clinical and/or radiographic assessments. It will be documented as either not assessable, no signs of healing, healing in progress (normal but slow or normal) or healed.

### Weight bearing

Weight bearing will be assessed through different measures. The time to partial weight-bearing and full weight-bearing prescribed will be analysed at the end of the study. The weight-bearing regimen prescribed by the treating surgeon will be documented as either no weight-bearing, partial weight-bearing or full weight-bearing. Changes in weight-bearing prescription between visits will also be documented. Further, the use of walking aids for patients who are allowed partial or full weight-bearing will be documented.

The Function Index for Trauma score (FIX-IT score)[16] is a way to standardise and combine the assessment of weight-bearing and pain into one score. The FIX-IT score ranges from 0–12 points in two domains: the ability to bear weight (maximum six points) and pain at the fracture site (maximum six points). Only patients who are allowed to do full weight-bearing by their treating surgeons will perform the 'single leg stand' part of the score. For patients prescribed with partial or no weight-bearing, the 'single leg stand' score will be 0, and there shall be no attempts to perform the test.

### Incapacity for work

Working status or duration and percentage of incapacity per medical certificate at time of injury, and time to return to work will be recorded.

### Adverse events

The occurrence of any AEs will be documented starting from the day of treatment (Day 0). Anticipated AEs related to the procedure under investigation are of special interest in the study, such as soft-tissue problems, mechanical failure and bone healing complications. Plate removal and/or exchange will be specifically documented along with the removal of the fracture monitor T1.

### Device deficiencies

The number and type of device deficiencies will be documented.

### Device removal

Date of removal, implants removed, reason(s) for removal and surgeon's opinion on handling will be recorded.

### Patient-reported outcomes

Local pain will be assessed using the numeric rating scale, where 0 is no pain and 10 is the worst imaginable pain. Quality of life will be assessed using the EQ-5D-5L.[17] In this study, the EQ-5D-5L self-complete German version will be used.

### Device handling and usability

A surgeon evaluation questionnaire will be answered by the treating surgeons to provide their evaluation of device handling and usability. It comprises five questions specific to placement, compatibility with instruments and bone plate, ease of skin closure, plate insertion in cases where the fracture monitor T1 was attached to the plate before bone fixation, and whether the device impairs radiographic assessment. The patient evaluation comprises sections on smartphone use, the app handling and usability, and the comfort of the fracture monitor T1, complaints or reportable events related to it.

### Total number of visits and X-rays/CT per patient

All images and visits will be done per SoC except for removal of fracture monitor T1 alone. The total number of visits and X-rays/CT scans within the 6-months from surgery will be documented. All follow-up visits and non-study site medical visits for the femoral fracture will be documented.

### Radiographic outcomes

The following outcomes will be assessed:

- Screw configuration and fracture monitor T1 position on the first available postoperative image.
- The modified radiographic union scale for tibia score (mRUST).[18 19]

mRUST subdivides the cortical assessment into the presence of bridging callus. The lowest score indicates no callus, and the highest indicates remodelling.[18] The mRUST score ranges from 4–16 as the four cortices assessed in two orthogonal planes have a score range from 1–4. mRUST will be centrally assessed in post-operative images taken at follow-up visits at 6 and 12 weeks, and 6-months postsurgery. The methodology for assessing cortices obscured by the plate has been assessed using available literature.[20–22] In addition, the study by Brodke *et al*[23] provides valuable insights on score progression; although this study discusses nail fixation, which may perform differently to plate osteosynthesis, its data on mRUST progression remain relevant for contextual comparison. Even though a low number of non-assessable cortices which, are not visible due to the plate is expected, the handling of missing assessments is defined as follows: while a total score will be calculated for patients with all four cortices assessed, for patients with missing values, a corresponding scenario-based RUST score will be calculated. Accordingly, for each patient, only one score will be

calculated based on the number of assessed cortices. This results in the following four options:

- mRUST score (exactly four cortices assessable, range 4–16).
- 3-cortex RUST score (exactly three cortices assessable, range 3–12).
- 2-cortex RUST score (exactly two cortices assessable, range 2–8).
- 1-cortex RUST score (exactly one cortex assessable, range 1–4).
- Osteoarthritis is to be centrally assessed in the hip and knee joints using the preoperative image.

### Implant load curve analyses

The strain sensor in the implantable data logger of the fracture monitor T1 device measures the bone plate deformation under patient loading as a measure of implant load. This specific output from the fracture monitor T1 device is used in the implant load curve analyses. The relative implant load will be used to generate the loading curves using a defined algorithm. Relative implant load is defined as the load generating elastic deflection of the bone plate relative to the maximum measured elastic deflection over time. Summary statistics will be used to analyse loading curves according to the following parameters:

- Time to a 50% drop in the signal.
- Timing between drop in the loading curve (50%) versus timing of the first visible sign of healing, defined as the presence of callus (mRUST ≥2) in at least one cortex on the postoperative follow-up visit radiographs taken as SoC.
- Other percentages of curve drop may be analysed if deemed clinically relevant.

Additionally, surgeons will be provided with the anonymised implant load curves of all patients and of different time points to perform a qualitative assessment of the curve profile.

Further parameters were collected by the implantable data logger.

In addition to the relative implant load, the following patient-related (PR) and TP parameters will be automatically collected and continuously transmitted by the fracture monitor T1 device to the secure cloud environment:

- Average minimum sensor strain per loading event PR.
- Daily active time of implant (patient activity triggers recording of implant) PR.
- Number of daily activations (implant switches from idle to recording) PR.
- User calibration range (patient-specific calibration on stiffness of fixation construct) (PR.
- Data down and upload frequency (TP.
- Number of Bluetooth adverts (TP.
- Bluetooth signal strength (dBm) TP.
- Bluetooth connection time (s) TP.
- Battery voltage after each month (TP
- Power consumption (device lifetime) TP.
- Internal device temperature TP.
- Initialisation and daily system test results TP.
- Internal clock accuracy TP.

## Hypothesis and statistical considerations

### Sample size determination

The aim of the clinical investigation is to detect ADEs; there is no formal hypothesis. The target sample size was calculated by setting a 95% CI for observing a rare event occurring with a probability of 10%. Accordingly, to detect at least one possibly/probably/definitely related ADE occurring with an incidence of at least 10% (1 in 10 patients) with a probability of 95%, 29 patients are needed. Assuming a 20% dropout rate, 37 patients will be enrolled. The sample size calculation was performed using nQuery, Statistical Solutions.

### Statistical analysis

In this study, categorical variables will be summarised using frequency and percentage for each category; continuous variables will be summarised using mean, SD, median, IQR, and minimum and maximum values and, if appropriate, according to clinically relevant categories. Continuous variables with both baseline and follow-up measurements available will be summarised as changes between baseline and follow-up at the individual patient level. Definition of the analysis populations, the handling of missing data and protocol violations will be specified in the detailed statistical analysis plan, which will be prepared before the final analysis. For the primary analysis, the risk of experiencing any ADEs within 6-months after surgery will be reported at the patient level. Risk estimates plus 95% Clopper-Pearson CI will be presented. For calculating the incidence of ADEs for the primary analysis, only patients with sufficient follow-up data will be included, that is, patients who drop out from the clinical investigation or for whom the fracture monitor T1 is removed before the 6-month follow-up and who do not experience an ADE during the available follow-up will be excluded from the denominator. The aim of this conservative approach is to ensure that the ADE rate is not underestimated by including patients with unknown or not applicable safety status in the denominator. For the secondary analyses, simple summary statistics will be used to present clinical and functional outcomes, additional safety parameters, patient-reported outcomes, device handling and usability, as well as radiographic outcomes. Patient-reported outcomes, which are measured repeatedly over follow-up will be analysed using mixed models for repeated measures (MMRM). The MMRM uses all available data, including subjects with partial data (ie, with missing values at some time points). Time to partial/full weight-bearing and time to return to work will be graphically presented using Kaplan-Meier plots. Inter-rater agreement on the assessment of implant load curves will be analysed using Fleiss' Kappa. Analysis of the fracture monitor T1 data, including graphical presentation of loading patterns, will be done by ARI.

Descriptive analysis of TP parameters will be done by ARI. Descriptive analysis of the relationship between implant load and clinical, functional and patient-reported outcomes over time will be done at the patient level. The safety analysis summary tables will be produced on the ADE/AE level and according to clinically relevant categories.

### Current study status

The protocol in operation is V.5.0 dated 6 November 2024 as reflected in the manuscript, with protocol changes (extension of the recruitment period) from the previous version. There are four participating sites in Germany. All sites have ethics approval, and currently, 14 patients have been enrolled from three sites. The first patient was enrolled in October 2023, and the data analysis is planned for December 2026.

### Ethics and Dissemination

Patient data are documented in eCRFs and captured in the REDCap Cloud Electronic Data Capture system (https://www.redcapcloud.com/).[24 25] CRFs are to be completed in a timely manner and are password protected, and only authorised personnel have access. After the termination of the study, each site will receive an electronic copy of its own data. Images collected during the study will be de-identified and sent to the sponsor digitally. The data security concept for the fracture monitor T1 includes anonymity with no personalised patient data saved on the system. For data completeness, data remains in the memory of the implantable data logger. Data encryption is used for all data transfer and storage. Data logger access, the secure cloud environment and the database is passkey/two-factor authentication protected with access only to specific individuals.

Ethics approval was obtained from the local ethics committee or institutional review board before patient enrolment (Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen, Approval ID 799/2022MP1, EudraCT nr.: 00014142/CIV-22-12-041649). The study is designed and implemented according to current valid international standards (ISO 14155 and the EU Regulation 2017/745 on medical devices (Medical Device Regulation (MDR)) and based on the ethical position of the Declaration of Helsinki to guarantee optimal protection of patient interests. It is envisioned that the results of this study shall be published in a peer-reviewed journal.

## DISCUSSION

This study protocol describes a first-in-human, prospective, interventional, multicentre clinical investigation of the fracture monitor T1 device, which is in the premarket stage of clinical development. Its primary purpose is to analyse safety data when the device is applied internally attached to a locking plate at the femur for up to 2 years. The results are going to serve the completion of the clinical evaluation report for subsequent Conformité Européenne (CE) certification of the fracture monitor T1.

Traditionally, fracture healing is monitored in a discontinuous fashion through radiographic assessment and clinical evaluation. As a novel biofeedback sensor system, the fracture monitor T1 allows for long-term monitoring, taking into account biomechanics and load bearing of the implant, and thus provides an objective parameter of fracture healing. The use of the implantable sensor also means that fracture healing can be monitored free from radiation exposure. The fracture monitor T1 aims at identifying patients at risk of delayed union or non-union earlier than with the current SoC, through identifying the absence of or slow healing. This can facilitate taking further treatment decisions in a timely manner. Additionally, in patients with normal healing, the number of regular, planned clinical follow-ups could potentially be reduced, thereby allowing for a more thoughtful use of healthcare resources.

In this first-in-human study, the investigators and the patients will not have real-time access to the data collected by the fracture monitor T1, and no clinical decisions will be made by the investigators based on this information during the clinical investigation, thus not influencing SoC treatment. This increases patient safety by preventing misdiagnoses, as clinical device performance has not yet been proven. A drawback is that the patients enrolled in the first-in-human study do not benefit from the potentially improved healing assessment method.

This first-in-human study is limited by the relatively small sample size (37 patients); yet it was chosen because this first-in-human study's primary aim is to provide safety data to support the regulatory approval of the investigational device. Thus, close monitoring of AEs through post-market surveillance activities is necessary to confirm the results obtained from this first-in-human study and to evaluate long-term efficacy. While in principle, all femur fractures treated with the above-mentioned plates can be enrolled, we acknowledge that it is highly likely that mostly distal femur fractures will be included in the study. Additionally, while the 6-month follow-up period is a common practice for assessing early bone healing, fracture healing can sometimes take much longer for complete recovery. Studies with longer follow-up periods will be important to capture the true performance of the device. Finally, there may be a lack of generalisability of these first-in-human study results to other fracture types, as this first-in-human study is limited to femoral fractures. It is possible that healing dynamics may be different in different fractures.

Additionally, data from this first-in-human study may provide preliminary data to acquire a better understanding of fracture treatment, fracture after-care and rehabilitation, and how this immediately relates to fracture healing. There could be future potential applications of the technique and principles to other fracture settings with similar, but also different, biological challenges.

Nevertheless, the focus of this first-in-human study is on the safety aspects of the fracture monitor T1, which must first demonstrate a sufficient safety profile for regulatory approval.

**Author affiliations**
[1]Klinik für Unfall- und Wiederherstellungschirurgie an der Eberhard Karls Universität Tübingen, BG Klinik Tübingen, Tübingen, Germany
[2]Klinik und Poliklinik für Unfall-, Hand- und Wiederherstellungschirurgie, Universitätsklinikum Münster, Münster, Germany
[3]Klinik für Unfallchirurgie, Hand- und Wiederherstellungschirurgie, Universitätsklinikum Ulm, Ulm, Germany
[4]Klinik für Unfall-, Hand- und Wiederherstellungschirurgie, Universitätsklinikum des Saarlandes, Homburg, Germany
[5]AO Innovation Translation Center, AO Foundation, Davos, Switzerland
[6]ARI Biomedical Development, AO Research Institute Davos, Davos, Switzerland

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**ORCID iDs**
Benedikt J Braun https://orcid.org/0000-0001-7575-0568
Alexander Joeris https://orcid.org/0000-0002-7748-7115

## REFERENCES

1 Burny F, Donkerwolcke M, Bourgois R, *et al*. Twenty years experience in fracture healing measurement with strain gauges. *Orthopedics* 1984;7:1823–6.
2 Claes L, Grass R, Schmickal T, *et al*. Monitoring and healing analysis of 100 tibial shaft fractures. *Langenbecks Arch Surg* 2002;387:146–52.
3 Richardson JB, Cunningham JL, Goodship AE, *et al*. Measuring stiffness can define healing of tibial fractures. *J Bone Joint Surg Br* 1994;76:389–94.
4 Richardson JB, Kenwright J, Cunningham JL. Fracture stiffness measurement in the assessment and management of tibial fractures. *Clin Biomech (Bristol)* 1992;7:75–9.
5 Seide K, Weinrich N, Wenzl ME, *et al*. Three-dimensional load measurements in an external fixator. *J Biomech* 2004;37:1361–9.
6 Ernst M, Richards RG, Windolf M. Smart implants in fracture care - only buzzword or real opportunity? *Injury* 2021;52 Suppl 2:S101–5.
7 WindolfM, ErnstM, SchwynR, *et al*. *A biofeedback system for continuous monitoring of bone healing. proceedings of the international joint conference on biomedical engineering systems and technologies - volume 1*. SCITEPRESS - Science and Technology Publications, Lda, 2014:243–8.
8 Windolf M, Varjas V, Gehweiler D, *et al*. Continuous Implant Load Monitoring to Assess Bone Healing Status-Evidence from Animal Testing. *Medicina (Kaunas)* 2022;58:858.
9 Ernst M, Baumgartner H, Döbele S, *et al*. Clinical feasibility of fracture healing assessment through continuous monitoring of implant load. *J Biomech* 2021;116:110188.
10 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
11 Quan H, Li B, Couris CM, *et al*. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. *Am J Epidemiol* 2011;173:676–82.
12 Meinberg EG, Agel J, Roberts CS, *et al*. Fracture and Dislocation Classification Compendium-2018. *J Orthop Trauma* 2018;32 Suppl 1:S1–170.
13 Tscherne H, Oestern HJ. A new classification of soft-tissue damage in open and closed fractures (author's transl). *Unfallheilkunde* 1982;85:111–5.
14 Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *J Bone Joint Surg Am* 1976;58:453–8.
15 Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. *J Trauma* 1984;24:742–6.
16 Bhandari M, Wasserman SM, Yurgin N, *et al*. Development and preliminary validation of a Function IndeX for Trauma (FIX-IT). *Can J Surg* 2013;56:E114–20.
17 EuroQol research foundation. EQ-5d-5l 2019. 2019. Available: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/
18 LitrentaJ, TornettaP, MehtaS, *et al*. Determination of Radiographic Healing: An Assessment of Consistency Using RUST and Modified RUST in Metadiaphyseal Fractures. *J Orthop Trauma* 2015;29:516–20.
19 Seide K, Aljudaibi M, Weinrich N, *et al*. Telemetric assessment of bone healing with an instrumented internal fixator: a preliminary study. *J Bone Joint Surg Br* 2012;94:398–404.
20 Graf RM, Shaw JT, Simske NM, *et al*. Distal femur nonunion: Risk factors and validation of RUST scores. *OTA International* 2023;6:e234.
21 Plumarom Y, Wilkinson BG, Marsh JL, *et al*. Radiographic Healing of Far Cortical Locking Constructs in Distal Femur Fractures: A Comparative Study With Standard Locking Plates. *J Orthop Trauma* 2019;33:277–83.
22 Wang A (Wei T, Stockton DJ, Flury A, *et al*. Radiographic Union Assessment in Surgically Treated Distal Femur Fractures. *JBJS Rev* 2024;12.
23 Brodke D, Devana S, Hernandez A, *et al*. Timing of Radiographic Healing for Distal Femur Fractures Treated With Intramedullary Nails. *J Orthop Trauma* 2024;38:661–7.
24 Harris PA, Taylor R, Minor BL, *et al*. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
25 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.