ADMAIORA

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D5.2
Preliminary brace skeleton

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PP	Restricted to other programme participants (including the Commission Service)	
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CO	Confidential, only for members of the consortium (including the Commission Service)	

Document History

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2	25/11/2019	Erik Dumont, IGT	First version of the Deliverable
3	27/11/2019	Leonardo Ricotti, Irene Bernardeschi, SSSA	First revision of the Deliverable draft
4	29/11/2019	Erik Dumont, IGT	Second revision of the Deliverable draft
5	30/11/2019	Leonardo Ricotti, Irene Bernardeschi, SSSA	Final revision and upload of the Deliverable

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1 Executive summary

In this deliverable, a prototype of a knee brace for treatment monitoring and LIPUS stimulation is presented.
The purpose of the knee brace is double:

1. To enable the monitoring of the cartilage healing process through different direct (US imaging of the cartilage), and indirect means (temperature measurements, maximum bending angle of the knee).
2. To enhance the treatment efficacy by exposing the cartilage to a mechanical stimulus through Low-intensity pulsed ultrasound stimulation (LIPUS) that has been shown to promote stem cell differentiation in chondrocytes.

The required LIPUS exposure time is assumed to be compatible with a session in which the patient is seated, i.e. a completely wearable stimulation gear is not required since the stimulation does not need to be applied for extended period of time in dynamic conditions. This means that the brace needs to accommodate the ultrasound transducers for LIPUS but not the external power signal generator to drive them. The generator can be embedded in a seat specifically designed to provide the correct knee positioning for the LIPUS stimulation.
The brace design is determined by the constraints of the US imaging examination which needs to be thorough, as shown in a preliminary study performed with a professional US radiologist, and by the placement of the ultrasound transducers for the LIPUS stimulation. The clinical examination was performed with a TELEMED echography system with a linear probe. However, due to the limited acoustic window to the condyles, it is not possible to have simultaneously the TELEMED US probe and the LIPUS transducer in place at the same time. Therefore two different accessories have been added to a commercial brace to enable:

1. a complete US imaging examination (with 8 probe arrangements and 3 different positions of the leg) thanks to a positioning guide;
2. LIPUS session in a comfortable position with a transducer holder fixed to the brace.

The maximum angulation of the articulation (the angle closest to 180° between the femur and the tibia) is a good indicator of patient condition improvement over time. It has therefore been decided to include a goniometer on the brace to enable a precise measurement of the joint angle.
A second important measurement concerns inflammation, which is related to the joint temperature. A pocket has been added to the brace to fit in a skin temperature probe.
The brace prototype is still a preliminary design and needs to be further engineered, integrated and validated in real usage on volunteers. A second iteration will be made on the brace design once the results of T6.2 (Bioeffects of LIPUS on the nanocomposite construct) and T4.3 (Investigation of acoustic parameters for in vivo translation) will provide the optimal size, shape and position of the LIPUS transducers.

2 Design of the stimulation and monitoring brace

2.1 Introduction

The design of the stimulation and monitoring brace is based on three main requirements:

- The brace should guide the multiple placements of the US probe to provide the referring physician with a thorough and precise US imaging examination, if possible performed solely by the patient, without external help.
- The brace must maintain the LIPUS transducers in an optimal position for proper ultrasound stimulation of the damaged cartilage for the whole duration of the treatment session (between 15' to 1 hour per session depending on results of T6.2).
- The brace should be easy to wear without the US probe or the LIPUS probes holders in place because other measurements (knee temperature and maximum angulation of the articulation) should be monitored dynamically during extended periods.

2.2 Signal generator for LIPUS

It is assumed that it is not necessary to have a wearable LIPUS generator. Indeed this would be necessary if the exposure time had to be very long (hours) or if the exposure had to be done in dynamic conditions (like during walk or physical exercise), which is not the case. Preliminary observations, based on 3D MRI images of the knee, show that two ultrasound transducers for LIPUS stimulation should provide a good exposure of the cartilage to ultrasound. Optimal number, shape and position of LIPUS transducers will be further evaluated using numerical simulations within T4.3.
A prototype multiple channels phased array generator has been designed and tested for electrical performance for radiofrequency power output of up to 80W. The actual power output necessary to produce the required acoustic field in patient will be refined within task T4.3. A second prototype will then be designed, according to refined specifications for tighter integration into a customized chair (that will also be necessary for treatment monitoring with US imaging).

2.3 Positioning and acoustic coupling mechanism for US transducers

A first design of the brace skeleton has been developed with holders for both the two LIPUS transducers and the imaging probe, and is shown in Figure 1. The design is a prototype which is very flexible in term of positioning of the LIPUS transducers and ultrasound probe, while providing some guidance to reach the correct orientations for imaging.

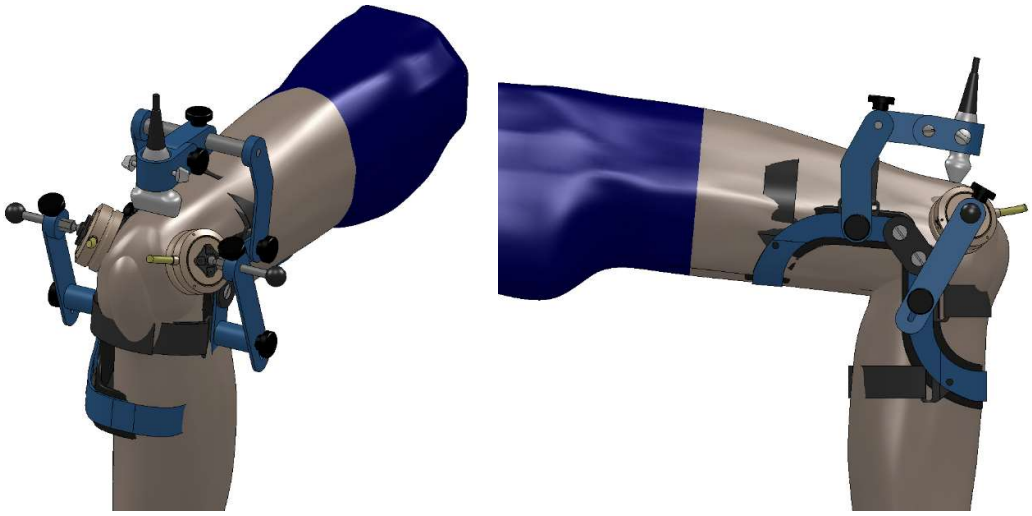

Figure 1: The first design of the brace skeleton includes adjustable holders for the two LIPUS transducers (brown, on both sides of the knee) and the US imaging probe (grey, above the knee).

This first design is used to test the LIPUS transducer positioning and the acoustic coupling mechanism to ensure a proper acoustic path to the cartilage and in order to get the prescribed ultrasound exposure *in-situ*.

However, this design cannot be used as it is, because the acoustic window to reach the diseased cartilage is quite limited, and it is therefore impossible to have the US imaging probe and the LIPUS transducers assembled at the same time, since they need to share the same acoustic window.

The acoustic coupling is realized through a gel filled membrane fixed to the transducer (Figure 2). In the first prototype (Figure 3), the gel was degassed and injected through a small opening in the back of the transducer which is then sealed to avoid any bubble. The membrane is chosen to be acoustically transparent and preferably latex free to avoid allergic reactions. A thin (50 µm) polyurethane membrane proved to be perfectly adequate for the purpose.

Figure 2: LIPUS transducers with the acoustic coupling made through a degassed gel filled membrane.

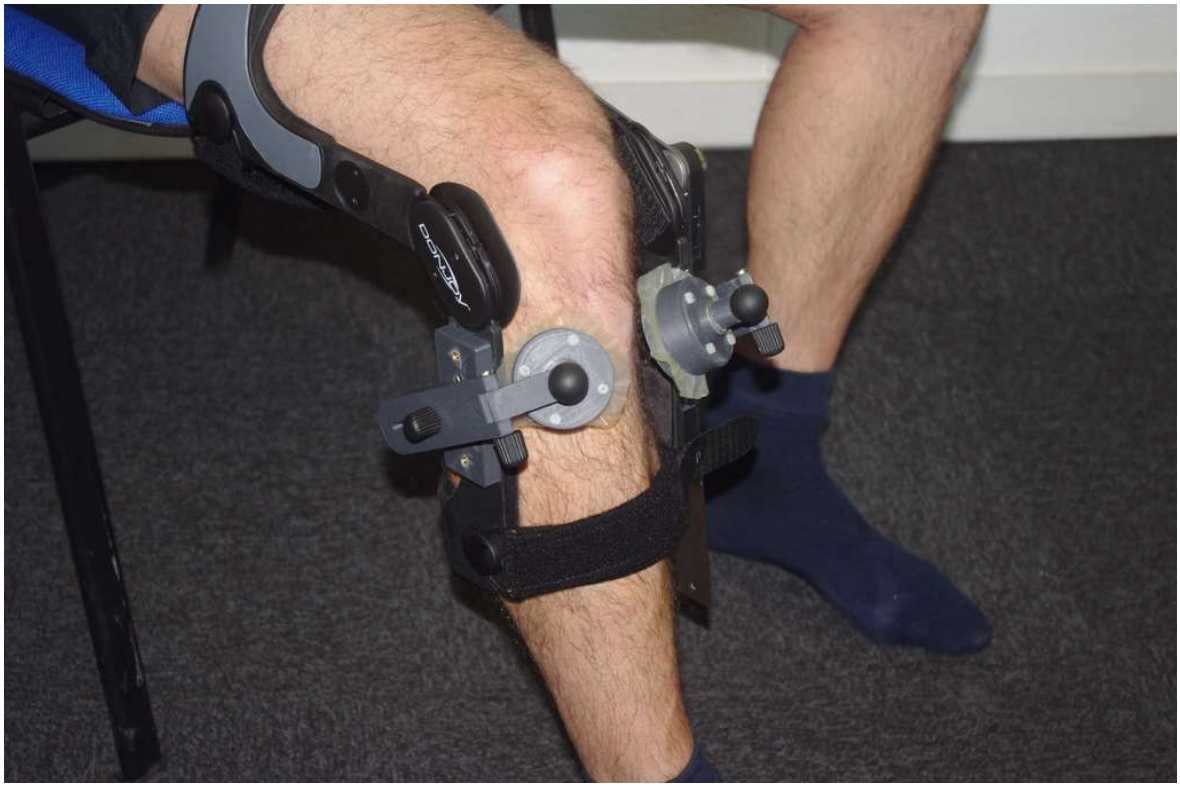

Figure 3: first prototype of the LIPUS transducers holders.

2.4 US imaging to monitor cartilage repair

The clinical examination of the cartilage using US imaging is rather complex and needs to be performed reliably and with great precision to enable the referring physician to assess the healing process in the cartilage. The SSSA team acquired a TELEMED ultrasound imaging system (ARTUS EXT-1H with linear probe L15-7H40-A5, http://www.telemedultrasound.com/artus-ext-1h/?lang=en, Figure 4) for the purpose of testing its imaging performance. The device proved perfectly suitable for this kind of examination with very good, diagnostic image quality. An added advantage of the TELEMED ARTUS system is its compact size and a PC-based interface which will make image transmission to the clinician through a cloud service much easier.

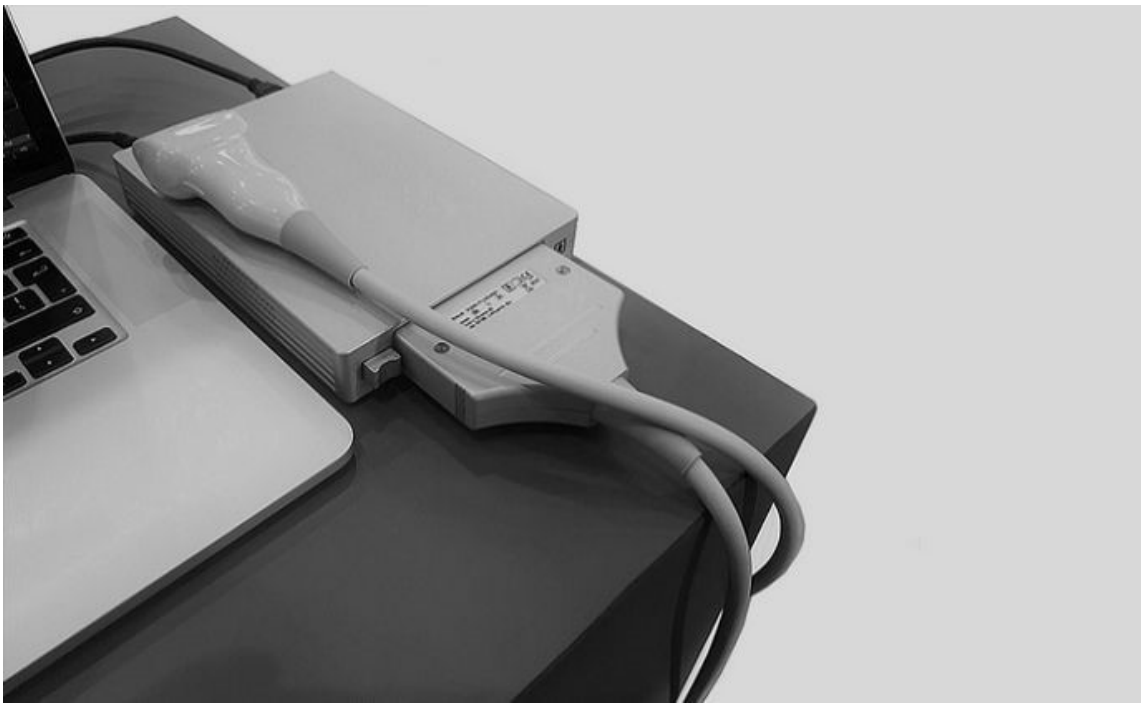

Figure 4: TELEMED US imaging system with a linear probe.

The system was tested on two volunteers, both to validate the image quality but also to determine the best imaging parameters and imaging planes for an optimal assessment of the cartilage state, the presence of inflammation and synovial fluids in the joint.

The examination should consist of 8 images taken at well-defined orientations, as shown in Figure 5.

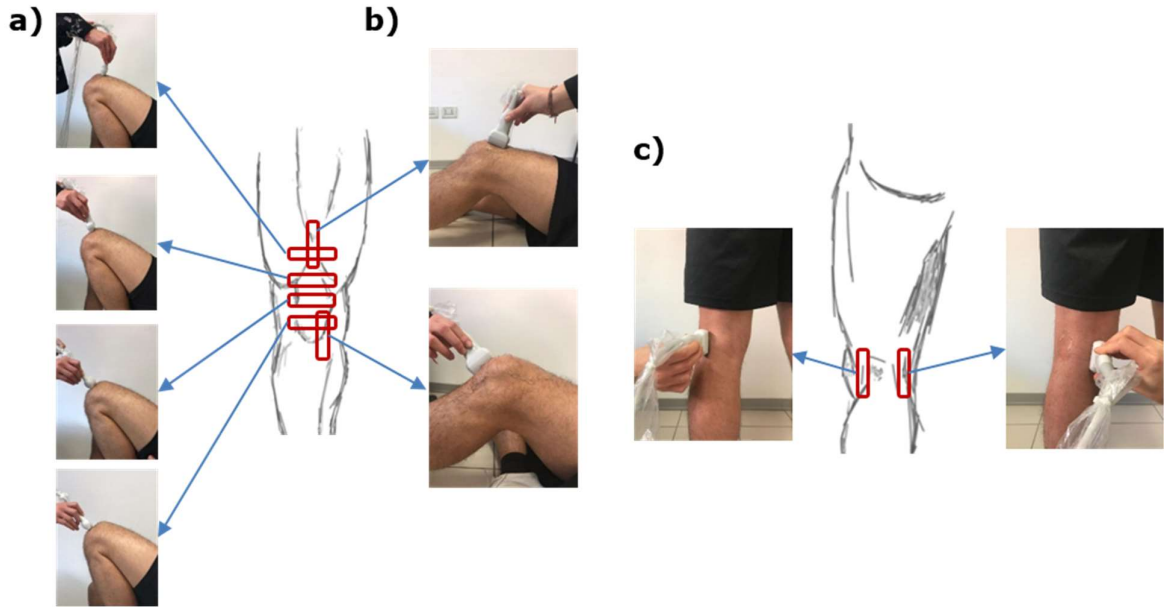

Figure 5: Six images are taken from the anterior part of the knee. a) Four of those images are obtained with the knee bent as much as possible and b) two images are obtained with the knee in a more extended position. c) Two images are taken from the posterior part of the knee joint.

Four diagnostic images should be obtained with the knee tightly bent (angle of 30° between the thigh and the calf), the linear probe in the right-left orientation (axial plane), starting from the patellar pole and moving toward the upper leg, with a range of approximately 6 cm, as shown in Figure 5a and Figure 6.

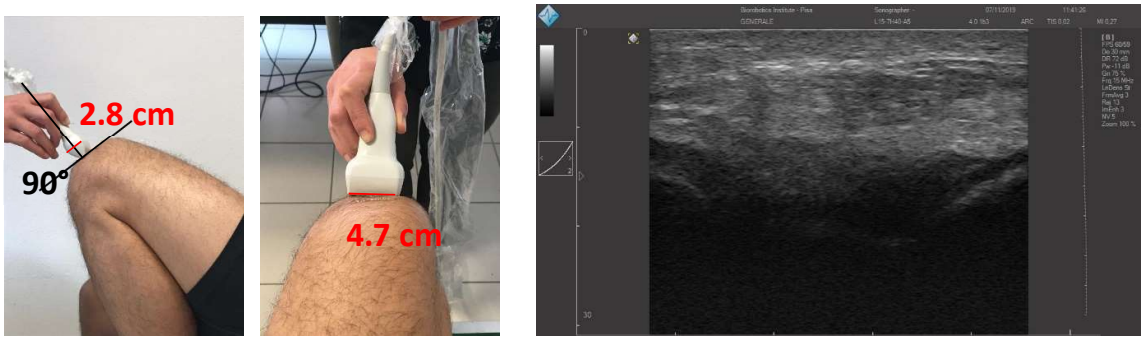

Figure 6: imaging of the patellar pole to look at the cartilage of anterior condyle.

Two images should be obtained in the sagittal plane, with the leg slightly bent (angle of 130° between the thigh and the calf), as shown in Figure 5b and Figure 7. These images are needed to evaluate the synovium and the Hoffa's adipose body, to assess inflammation.

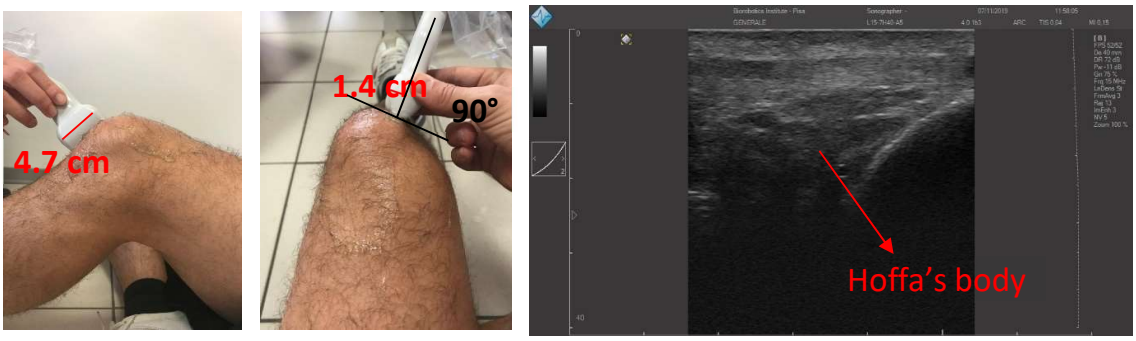

Figure 7: imaging of the inferior patellar pole to look at the Hoffa's adipose body.

Finally, two additional images should be obtained in the sagittal plane with the patient in a standing position, in order to observe the cartilage on the lateral and medial femoral condyle (Figure 5c and Figure 8).

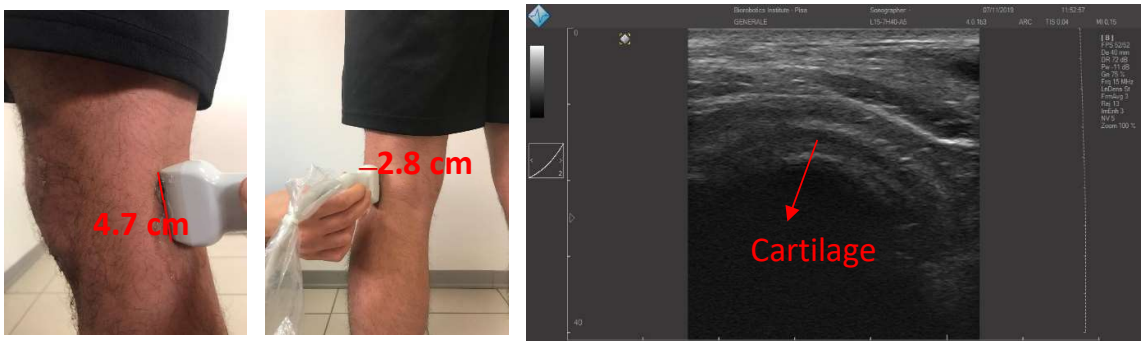

Figure 8: Imaging of the lateral femoral condyle.

A second design of the brace was pursued, to take into account the clinical imaging constraints and to provide an easy way for the patient to perform the US imaging exam without external help (Figure 9, Figure 10, Figure 11, Figure 12 and Figure 13).

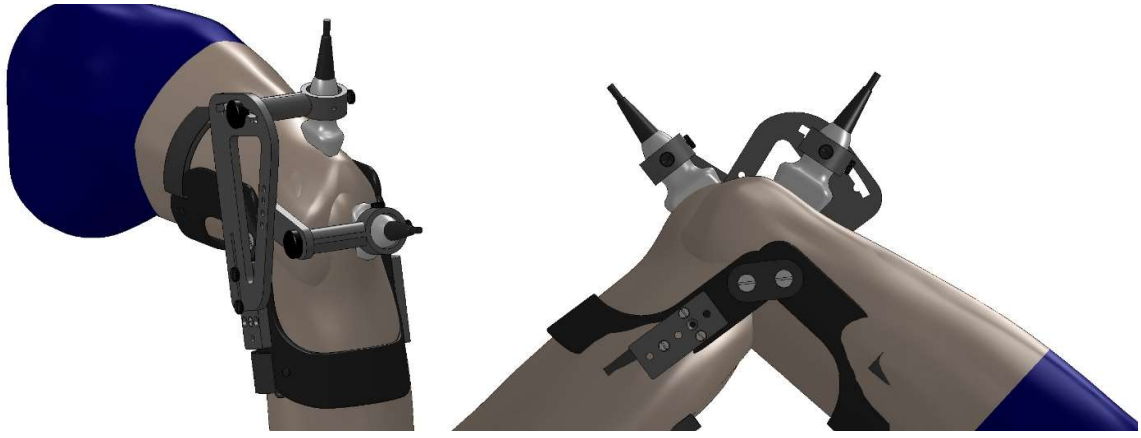

Figure 9: Brace with pre-positioned holders for the US imaging probe.

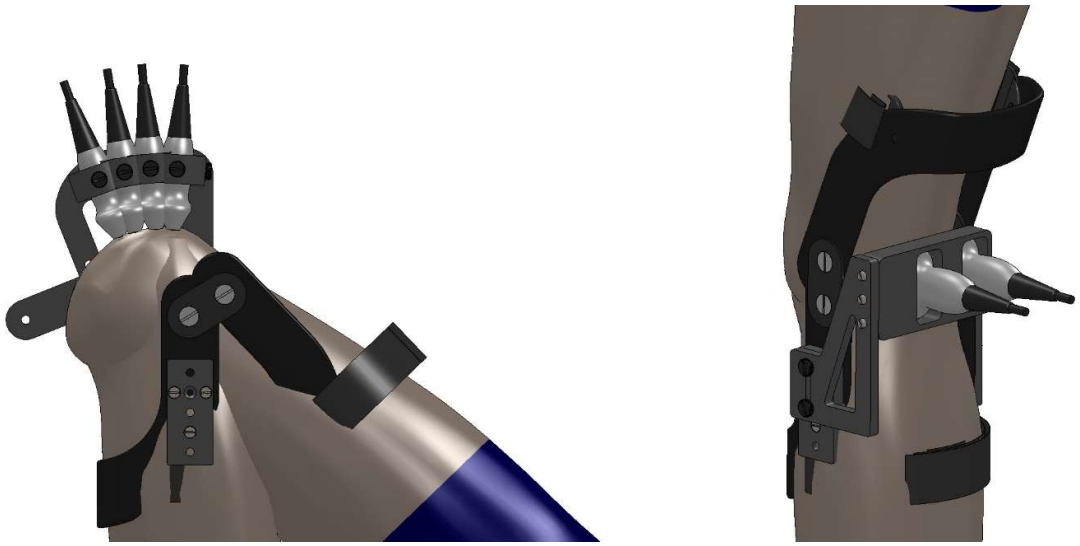

Figure 10: Brace with pre-positioned holders for the US imaging probe.

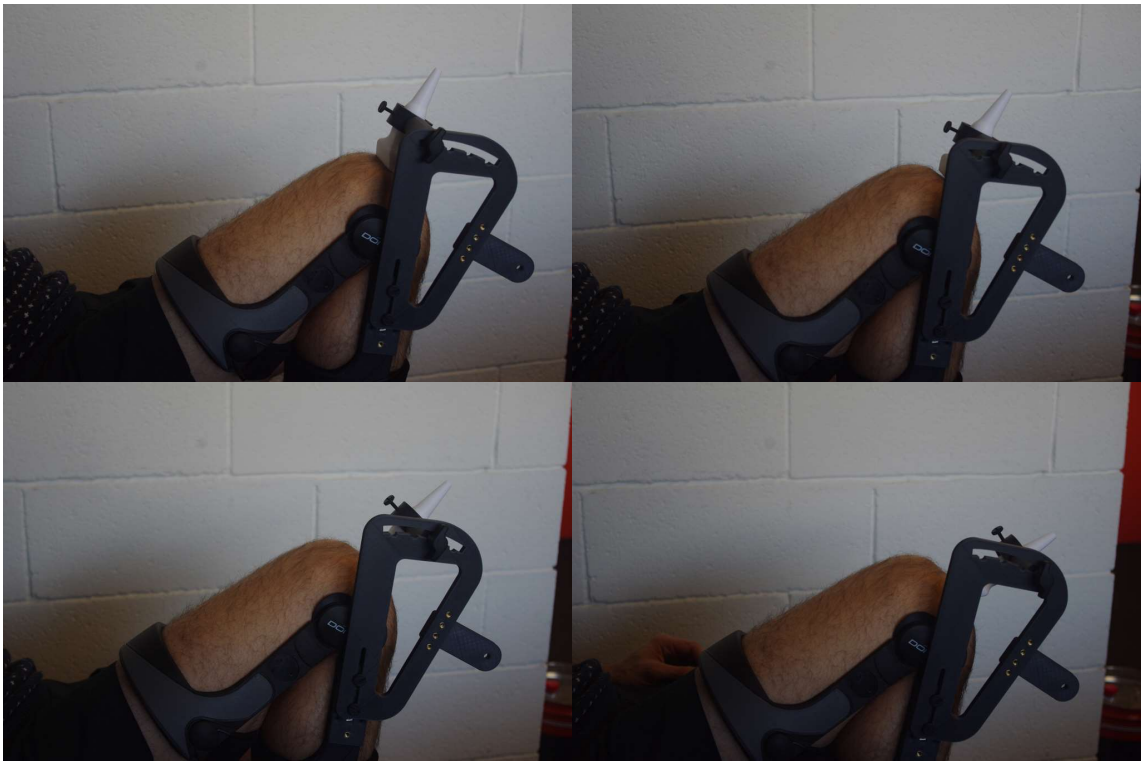

Figure 11: Actual brace with a probe holders that can be shifted into the four positions for imaging the patellar pole.

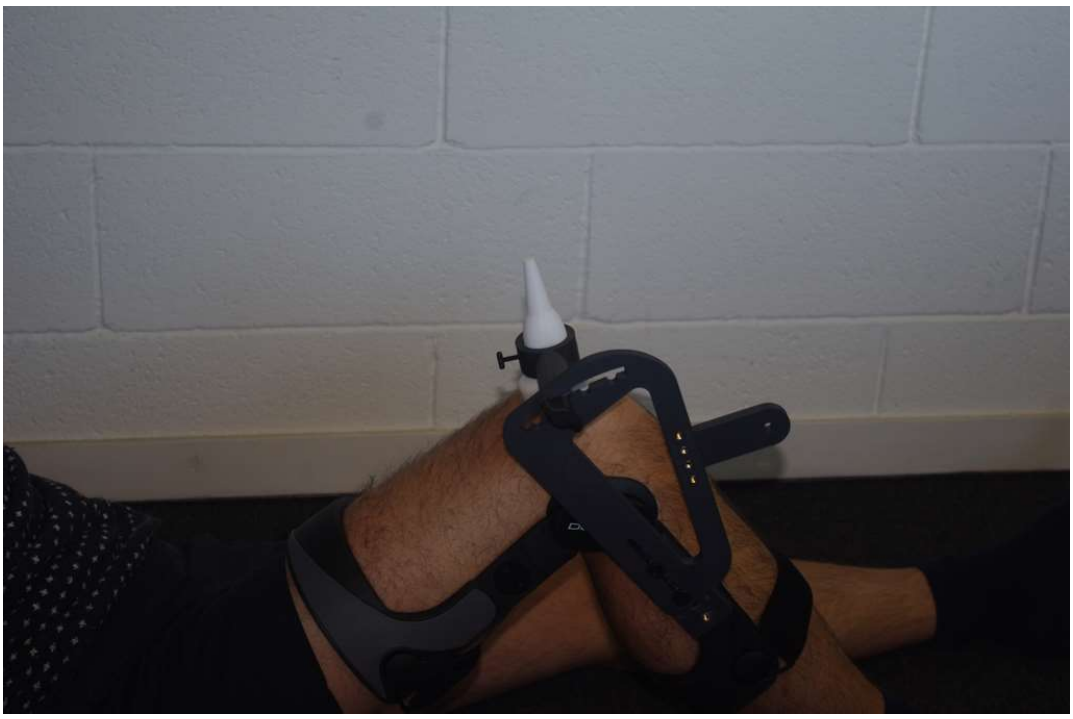

Figure 12: Actual brace with a probe positioned for imaging the patellar pole in the sagittal plane.

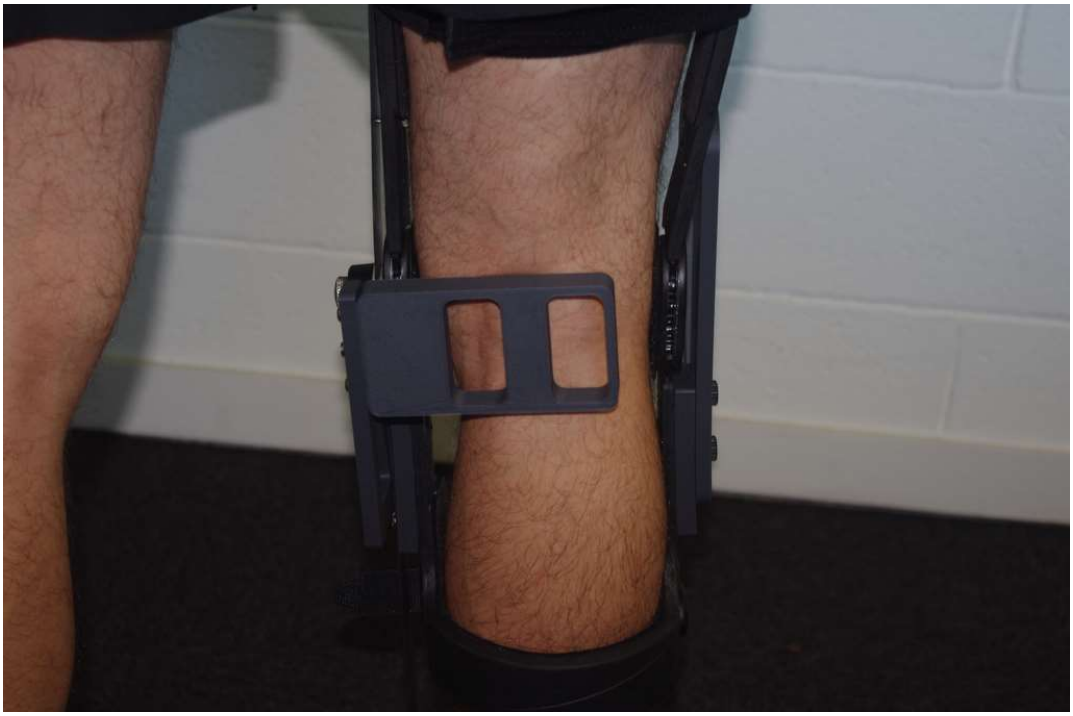

Figure 13: Probe guide for imaging of the lateral femoral condyles.

2.5 Sensors to monitor patient motion and joint inflammation

Besides direct measurement of the cartilage healing process through US imaging, some measurements provide indirect means of assessing the state of the knee joint.
The simplest of those measurement is simply the maximum angle achievable when extending the leg as much as possible. Indeed, the extension of the leg is impaired by the disease and thus a better ability to extend the leg is a sign of recovery. A goniometer is therefore attached to the brace to monitor both the maximum extension of the leg and to guide the leg flexion for the best US imaging configuration. On the first prototype, the goniometer is a simple model which is not connected (Figure 14, Figure 15 and Figure 16). **Error! Reference source not found.**However, the second version of the prototype will be provided with a connected goniometer so that the monitoring can be done automatically via the monitoring app.

Figure 14: Measurement of the angle between thigh and calf with a digital non-connected goniometer and with a connected goniometer.

Another useful measurement that is commonly used as a proxy to assess the improvement of the knee joint is the activity monitoring using a wristband accelerometer. This allows a precise measure of the number of steps taken, which correlates with the overall well-being of the patient and with the pain in the knee.

Integration of the wristband measurements is being performed independently from the brace design.

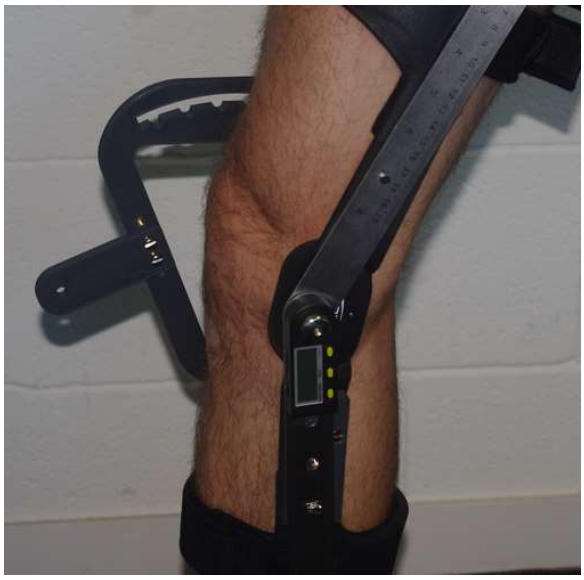

Figure 15: Measurement of the angle between thigh and calf with a digital non-connected goniometer attached to the brace.

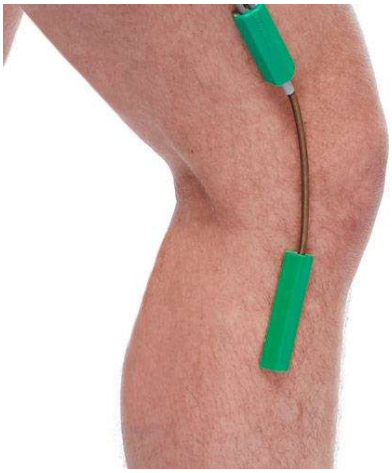

Figure 16: Flexible system to measure angle between the thigh and the calf with wireless data collection (http://www.biometricsltd.com/goniometer.htm).

Another useful measurement that is commonly used as a proxy to assess the improvement of the knee joint is the activity monitoring using a wristband accelerometer. This allows a precise measure of the number of steps taken, which correlates with the overall well-being of the patient and with the pain in the knee.

Integration of the wristband measurements is being performed independently from the brace design.

Another potential sign of inflammation is the temperature measured on the knee skin. The brace allows the positioning of a skin temperature sensor on the joint. An elegant solution for temperature measurement is provided by bluespark technologies (http://bluesparktechnologies.com/) with their temptraq™ product (Figure 15). It consists of a patch that can be applied anywhere on the patient and which communicates the measured

temperature via Bluetooth to a connected device. The main drawback of the product is the relatively short measurement span (72 h), which is not very well adapted to the long treatment times of osteoarthritis.

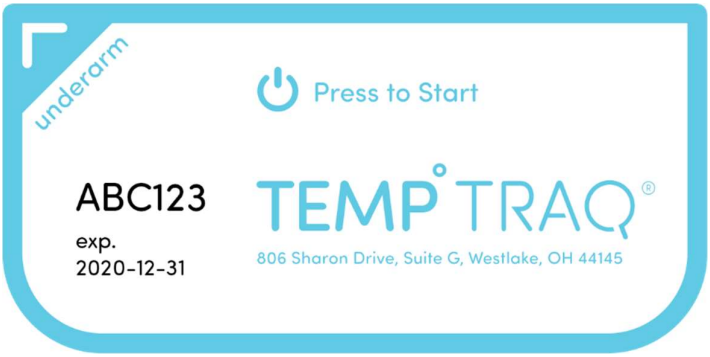

Figure 15: Very easy to install, skin temperature measurements with Bluetooth connectivity.

Another solution is to use a ready-made device such as the one made by shimmer (http://www.shimmersensing.com/) with their skin surface temperature probe, or alternatively to design a custom skin temperature sensor based on the TI reference design (https://www.ti.com/lit/ug/tiduay7/tiduay7.pdf), as shown in Figure 16. This last solution would enable a precise control on the measurement periodicity and the upload of data to the app via a Bluetooth connection. The most appropriate sensor to be integrated will be selected in the next months.

Figure 16: Programmable temperature measurements unit with Bluetooth connectivity from TI (reference design).

3 Conclusions

A first prototype of the stimulation and monitoring brace has been designed and built. Given the complexity of the clinical US imaging exam and the fact that the acoustic window for treatment is the same as the one for imaging, it seems preferable to divide the brace in two configurations:

- A monitoring configuration with removable accessories to perform in a reliable way the US imaging exam required to assess the healing process in the cartilage;
- A stimulation configuration with a support for the two LIPUS transducers.

The patient should also be provided, in the future, with a customized chair to enable proper positioning of the knee for both the US imaging exam and for the LIPUS stimulation.

The TELEMED US probe does not need to be used on the patient all the time, but needs to be connected during the imaging session, which is limited in time. The same applies to the LIPUS transducers. The generator can therefore be attached to the customized chair and connected for the treatment, only when required. The customized chair will also host the US imaging system.

The LIPUS transducers are simply positioned in contact with the patient skin. The acoustic coupling is made through a degassed gel filled membrane sealed on top of the transducer.

The brace also accommodates two different sensors:

- A digital goniometer to monitor joint maximum extension;
- A wireless temperature sensor to measure skin temperature in order to assess inflammation.