Document title	**CLINICAL STUDY PROTOCOL**
Study title	**Applied Public-Private Research enabling OsteoArthritis Clinical Headway study – a 2-year multicentre, European, exploratory study without therapeutic benefit in patients with knee osteoarthritis to describe, validate, and predict phenotypes of knee osteoarthritis by use of clinical, imaging, and biochemical (bio)markers.** **APPROACH study**
Protocol code	**APPROACH-OA-P01**
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Date of the document	**August 25, 2017**
Version of the document	**Final version – version 1.0_NL**

Protocol signature sheet

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List of abbreviations

ACR	:	American College of Rheumatology
AE	:	Adverse Event
e-CRF	:	Electronic Case Report Form
CRO	:	Contract Research Organisation
CT	:	Computed Tomography
DBP	:	Diastolic Blood Pressure
DMOAD	:	Disease Modifying OA Drug
DNA	:	DeoxyriboNucleic acid
EFPIA	:	European Federation of Parmaceutical Industries and Associations
FIHOA	:	Functional Index for Hand OsteoArthritis
GCP	:	Good Clinical Practice
HOOS	:	Hip disability and Osteoarthritis Outcome Score
ICH	:	International Conference on Harmonisation
ICOAP	:	Intermittent and constant OA pain
IMI	:	Innovative Medicines Initiative
I.R.I.S.	:	Institut de Recherches Internationales Servier
IVD	:	Intervertebral Disc
JSN	:	Joint Space Narrowing
JSW	:	Joint Space Width
KIDA	:	Knee Images Digital Analysis
KL	:	Kellgren and Lawrence
KOOS	:	Knee injury and Osteoarthritis Outcome Score
MedDRA	:	Medical Dictionary for Regulatory Activities
MOAKS	:	Magnetic resonance imaging OsteoArthritis Knee Score
MRI	:	Magnetic resonance imaging
mSv	:	milli Sievert
METC	:	Medisch Ethische Toetsings Commissie
MTP	:	MetaTarsoPhalangeal
N	:	Non progressors
NRS	:	Numeric Rating Scale
OA	:	OsteoArthritis
OARSI	:	OsteoArthritis Research Society International
P	:	Pain progressors
PA	:	Posterior Anterior
P+S	:	Pain and Structure progressors
RNA	:	Ribonucleic acid
ROM	:	Range of Motion
S	:	Structure progressors
SAE	:	Serious Adverse Event
SBP	:	Systolic Blood Pressure
SD	:	Standard Deviation
SF-36	:	Short Form (36) Health Survey
SSM	:	Statistical Shape Model
TKR	:	Total Knee Replacement
UMC Utrecht	:	University Medical Centre Utrecht
WBLDCT	:	Whole Body Low Radiation Computed Tomography
WHO-DD	:	World Health Organization, Drug Dictionary
WMO	:	Wet Medisch-wetenschappelijk Onderzoek met mensen - Medical Research Involving Human Subjects Act

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

This section is described in a separate document.
The list of investigators is given in a document attached to the protocol for each country.

2. SUMMARY

Rationale: Despite a large and growing disease burden in osteoarthritis (OA), many pharmaceutical companies have abandoned OA drug development. This is mainly due to the lack of appropriate outcome measures that can robustly identify patients that can benefit from a specific therapy. Different phenotypes of OA may benefit from different types of treatment. Therefore, novel markers to identify selected phenotypes of osteoarthritis may encourage drug development.

Objective: To prospectively describe in detail pre-identified progressing phenotypes of patients with knee OA by use of conventional and novel clinical, imaging, and biochemical (bio)markers, and to validate and refine a predictive model for these (and new) progressing phenotypes based on these markers.

Study design: APPROACH is an exploratory, European, five-centre, 2-year prospective follow-up, cohort study, with extensive measurements. In this study patients are treated according to regular care by their own physician with no study related treatment prescribed. Study related diagnostic and/or monitoring procedures are applied to the patients.

Study population: Patients with tibiofemoral knee osteoarthritis, according to the clinical ACR classification criteria, pre-identified based on demographic (*e.g.* age), clinical (*e.g.* Pain NRS) and tissue structure (*e.g.* radiographic joint space width) parameters.

Main study parameters/endpoints: Joint tissue structure based on radiographs, MRI, and biochemical (bio)markers as well as symptoms (pain, function) and quality of life by questionnaires.

Secondary parameters: A multitude of (novel and conventional) clinical, imaging, and biochemical parameters related to osteoarthritis.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The participants will not have any direct benefit from their participation in this study other than that their OA is maximally diagnosed and followed in detail for up to 2 years (screening, baseline, 6 months, 12 months, 24 months).
Patients will stay in the hospital for 4-5 hours per visit (for screening about 30 min) for physical examination, blood draw, MRI scans, radiographs of knees and hands (only at baseline and 24 months), CT scan of the knee (only at baseline and 24 months), low radiation whole body CT scan (only at baseline and 24 months), HandScan (only at baseline and 24 months), motion analysis, and performance based tests. They will be asked to fill out questionnaires about knee, hand and hip osteoarthritis, and about general health and pain. The patient council in the consortium indicated that the load is acceptable. The patient council will be involved in the execution of the study. The assumed risk is minimal for an individual patient and minimal compared to the contribution to the development of knowledge of their disease. These risks include minimal events due to blood sampling itself (such as hematoma

or localized bleeding), radiation exposure by radiographic imaging techniques (with a minimal increased healthcare risk), and exposure to MRI techniques (without known risks and without use of contrast agents).

3. BACKGROUND INFORMATION

Osteoarthritis (OA), a degenerative joint disease, is a progressive disorder of the joints characterised by gradual loss of cartilage, peri-articular bone changes, and mild synovial inflammation, leading to pain and function limitations.

OA is the most common global arthritic disease and is becoming more prevalent as the population ages and obesity rates rise. OA is already one of the ten most disabling diseases in developed countries. Global estimates are that 9.6% of men and 18.0% of women over 60 have symptomatic OA, 80% of those with OA will have functional limitations and 25% cannot perform their major daily activities of life. Direct and indirect costs of OA for the EU are substantial: in the Scandinavian countries, the Netherlands, and the UK, total costs are estimated to be about 10% of the medical costs, equivalent to 1% of the annual gross national product.

Many pharmaceutical organizations have currently abandoned disease modifying OA drugs (DMOAD) development due to real and perceived hurdles. A number of visible and costly failures have highlighted the challenge. Considering the problem and societal impact, there remains a major unmet need as current treatments are predominantly limited to (often insufficient) symptomatic relief (pain, inflammation, and function) or costly and invasive surgical intervention. Multiple reasons have been identified as underlying causes of past DMOAD failures:

1. Heterogeneity of OA progression rate. The majority of an unselected OA population does not progress substantially radiographically or clinically in a 2 year window as in general the disease is slowly progressing (Felson, 2013); Using the (bio)markers or knowledge should help to prospectively identify patients at risk of clear progression.

2. Limited understanding of OA pathogenesis. Progress in our knowledge of the pathophysiology of OA leads to the division of the disease into several possible different subtypes: such as post-traumatic, metabolic, ageing, inflammatory, bone driven, and genetic. Some of these types are amenable to (specific subtype directed) pharmacologic intervention, and some of which are expected to be less so. Discriminating (bio)markers able to differentiate between these subtypes are lacking.

3. Absence of precision medicine mind-set. Clinical development plans have frequently used a ‘one size fits all’ approach rather than a matching mechanism of action to specific OA patient subtypes.

4. Reliance on relatively insensitive endpoints. Radiograph-based joint space narrowing (the current standard endpoint to demonstrate disease modification) is in its present form insensitive and does not allow visualization of the cartilage tissue, of major relevance in the disease (Bijlsma, 2011).

Therefore the issues in OA drug development are large and complex and in clinical development challenges for identification of selected OA phenotypes could be best addressed by a Public-Private partnership of engaged and knowledgeable and complimentary industrial, academic, and patient experts who can accelerate innovation and provide viable solutions.

The APPROACH project is part of a larger project being conducted under the Innovative Medicine's Initiative (IMI). It is a joint venture bringing together 13 academic institutions across Europe, 6 biotechnology companies, 2 patient advocacies, and 4 pharmaceutical companies with the aim to prospectively describe progressing phenotypes of patients with knee OA. By the use of conventional and novel clinical, imaging, and biochemical (bio)markers and to validate and refine a predictive algorithm for these progressing phenotypes based on these (bio)markers, the APPROACH project intends to bring knowledge about the development of the disease.

For a rough pre-screening of patients, the APPROACH consortium will combine data from a significant number of large existing OA cohorts with knee and hand OA patients from Europe and the U.S. into a unified bioinformatics platform to define differentiating phenotypes of knee OA progression based on existing (bio)markers. This 'datamining' is not part of the present protocol, but will provide the inclusion algorithm comprising demographic (*e.g.* age), clinical (*e.g.* Pain NRS), and tissue structure (*e.g.* radiographic joint space width, MRI measures) parameters used for the present prospective cohort study.

Based on the algorithms for prediction of progression, patients (with a certain chance on) belonging to each of 3 defined progression phenotypes will be selected and asked to participate in the longitudinal APPROACH prospective cohort study. We aim to include a total of 300 patients. The algorithms, based on existing (bio)markers, will only roughly identify patients belonging to one of the knee OA progression phenotypes.

In the prospective follow-up APPROACH study, a large set of conventional (bio)markers supplemented with novel (bio)markers of knee OA, as well as multiple confounding factors of OA in general, will be determined at baseline and 6 months later (to provide data on relatively short term changes in these (bio)markers). Moreover, the progression of the disease in the 3 phenotypes will be monitored by the conventional as well as more state of the art (bio)markers yearly, over 2 years. As such this study will lead to robust prediction models for different phenotypes of knee OA (preferably at the patient level), and will provide robust (bio)markers for following disease progression over time in these phenotypes.

Conventional (bio)markers include clinical characteristics, standard radiographs, commercial biochemical blood/urine markers, and (semi)quantitative MRI imaging. Novel (bio)markers include epigenetic-, transcriptomic-, proteomic-, metabolomic analysis, novel radiographic imaging modalities, qualitative MRI imaging, imaging techniques related to inflammation, and motion analysis techniques. Confounding (bio)markers include amongst others markers of hand and hip OA, joints frequently and concomitantly affected in case of knee OA involvement.

In this study, no new treatment will be provided and no deviations from the standard therapeutic procedures as decided by the treating physician will be introduced. At the end of the study, no follow-up of the participants will be required.

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Declaration of Helsinki and the applicable regulatory requirements.

This project would provide a setting for regulatory guidance and healthcare agency interaction as well as to build stronger collaborations among academic and industrial groups to enable development of effective treatment options.

The APPROACH project has received support from the Innovative Medicines Initiative (IMI) under grant agreement n°115770, resources of which are composed of financial contribution from the European Union and in kind contribution from EFPIA companies.

4. STUDY OBJECTIVES AND PURPOSE

The objectives of the APPROACH study are:

- To validate the prediction model for sustained pain and decrease in (minimal) JSW as developed for the selection/inclusion of patients (primary objective).

- To develop and validate predictive models for OA progression by use of conventional and novel clinical, imaging, and biochemical (bio)markers (secondary objective).

- To discover and predict novel OA phenotypes (*e.g.* such as post-traumatic, metabolic, ageing, inflammatory, bone driven, and genetic) (exploratory objective).

- To prospectively describe in detail the discovered phenotypes of patients with knee OA by use of conventional and novel clinical, imaging, and biochemical (bio)markers (exploratory objective).

5. STUDY DESIGN

5.1. Endpoints and co-variables

(*indicates when (bio)markers are exploratory)

5.1.1. Endpoints for description of the index knee OA progression phenotypes

OA progression of the index knee (one of both knees with the most severe OA, see in paragraph 5.2.1) will be described over 2 years in the different patient phenotypes as defined by changes from baseline to the 1- and 2-year visit at which they are evaluated. The endpoints are grouped by validated and well described evaluation methods and listed below:

1. Structural progression (progression of tissue structure damage/alterations)
   a) Radiographic parameters:
      Knee OA severity assessed by changes in different validated scoring systems (KL grading, OARSI scoring, and KIDA measurements)
   b) Quantitative MRI parameters:
      Quantitative cartilage parameters including thickness, volume, and denuded bone areas of the femoro-tibial joint.
   c) Semi quantitative MRI parameters:
      Semi quantitative scorings of cartilaginous and non-cartilagenous components including bone marrow oedema, meniscal alteration, and synovitis, assessed separately and under a global score (MOAKS).

d) Advanced radiographic parameters:
   - bone shape analyses* on standard radiographs representing OA related bone deformations/adaptations
   - subchondral bone architecture* on standard radiographs representing OA related bone deformations/adaptations
   - bone shape analyses* on high resolution CT representing OA related bone deformations/adaptations at M024
   - subchondral bone architecture* on high resolution CT representing changes trabecular deformations/adaptations

e) Biochemical (bio)markers:
   Protein (bio)markers in blood and urine representing cartilage, bone and synovial matrix turnover as well as inflammation.

2. Pain and function
   a) Questionnaire for knee pain, symptoms, activities of daily living, sport and recreation, function, and knee-related quality of life (KOOS)
   b) Questionnaire for distinction between constant and intermittent knee pain (ICOAP)
   c) General pain and function parameters:
      - Pain numeric rating scale (NRS)
      - Physical examination of knee by a research physician (or research nurse) including range of motion/flexion of the knee

5.1.2. Endpoints for prediction of index knee OA progression phenotypes

Prediction of OA progression (*i.e.* based on the classification sustained pain and decrease in (minimal) JSW as used in inclusion) will be evaluated through machine learning algorithms which will take into account as predictors/features:

- the endpoints of structure, pain, and function (as listed in the paragraph 5.1.1) evaluated on the index knee at baseline, and
  a) Qualitative MRI parameters at baseline:
     - T2 relaxation MRI* representing cartilage collagen distribution
  b) Advanced imaging parameters at baseline:
     - bone shape analyses* on high resolution CT representing OA related bone deformations/adaptations
     - subchondral bone architecture* on high resolution CT representing changes trabecular deformations/adaptations
     - bone shape analysis* on MRI representing bone area and shape
- Changes over 6 months' time (considered a relative short time window) of the parameters of the index knee as mentioned above (5.1.1 and 5.1.2), in case evaluated at 6 months. Relative short term changes of certain parameters are considered better predictors than cross-sectional evaluation of these same parameters.
- Motion analyses (by use of GaitSmart system including knee and hip function)* at baseline and 6 months
- Performance based test (the 30 second chair stand test and the 4 times 10 meter fast paced walk test) at baseline and 6 months

5.1.3. Co-variables

Additionally, co-variables as listed below will also be used in the machine learning modelling:

- Contralateral knee OA
  - Tissue damage by radiographic parameters (KL grading, OARSI scoring, and KIDA measurements)
- Hand OA
  - Inflammation of the hand joints (HandScan)*
  - Tissue damage of the hand joints (hand radiographs; KL, OARSI, Verbruggen-Veys score)
  - Pain and function of the hand joints (FIHOA questionnaire)
- Hip OA
  - Tissue changes of the hip joints by use of low radiation whole body CT*
  - Pain and function of the most painful (or right) hip joint (questionnaires HOOS and ICOAP)
- Facet joint OA and intervertebral disc (IVD) degeneration
  - Tissue changes in the spine (facet, vertebral body and disc by use of low radiation whole body CT)*
- Shoulder OA
  - Tissue changes in the shoulder (acromioclavicur and glenohumeral) joints (by use of low radiation whole body CT)*
- General pain and function parameters
  - Questionnaire for quality of life (SF-36)
  - Pain with concomitant pain medication registration in one month diary*
  - Pain numeric rating scale (NRS) of contralateral knee, both hips, both hands, and spine
  - Pain DETECT questionnaire used to identify the likelihood of a neuropathic pain component in patients
  - Motion analyses (by use of GaitSmart system including knee and hip function)* at 24 months
  - Performance based test (the 30 second chair stand test and the 4*10 meter fast paced walk test) at 24 months
  - Physical examination of contralateral knee, hips (including range of motion/flexion) and hands
- Optional systemic biochemical (bio)markers
  - epigenetic, genomic, transcriptomic, (novel)proteomic, lidipomic and metabolomic markers*
- General clinical data
  - History and type of knee traumatism in case
  - History and type of knee surgery in case
  - Smoking habits
  - Menopause status in case of woman
  - Concomitant treatment
- Advanced parameters
  - bone shape analyses* (on standard radiograph for contralateral knee)
  - subchondral bone analysis* (on standard radiograph for contralateral knee)
  - bone shape analysis of the hip* (on low resolution whole body CT)

5.2. Experimental design

5.2.1. Study plan

This is an exploratory, European, five-centre, 2-year prospective follow-up, cohort study, with extensive measurements, without therapeutic benefit (no study-prescribed modification of standard of care during the two years study period).

Patients with an increased risk of progression of knee osteoarthritis within 2 years, will be included based on two predictive algorithms applied respectively for pre-screening of patients before the screening visit and for their inclusion by checking parameters evaluated at the screening visit.
Three types of progression of the disease will be taken into account:
1. progression based on pain,
2. progression based on tissue structural damage or
3. progression based on pain and tissue structural damage

Structural progression is defined as a reduction of joint space width over time at a threshold of **0.3 mm narrowing per year**.
Pain progression is defined (based on the minimum clinically important difference (MCID); Angst et al. 2001) as:
- *significant pain increase* (change between baseline and follow-up is at least 5 points per year) and *significant pain* at follow-up (at least 40 points),
- *fast pain increase (*change between baseline and follow-up is at least 10 points per year) and *less than significant pain* at follow-up (at least 35 points)
- *stable pain* (no less than 40 points at baseline and follow-up).

For each patient, an index knee will be defined at the screening visit. The index knee will be defined by the expert opinion (physician). In case both knees are affected equally the right knee will be selected as index knee.

The study duration is two years and the following visits will take place:
1. Screening visit/ASSE (-2 months)
2. Inclusion visit/M000
3. Follow-up visits at 6, 12, and 24 months thereafter, that is, M006, M012 and M024.

For selection/inclusion of patients, algorithms for identification of the 3 phenotypes, comprising demographic (*e.g.* age), clinical (*e.g.* Pain NRS) and tissue structure (*e.g.* radiographic joint space width) parameters are used. Patients will be screened based on these algorithms. Because not always recent or appropriate data and images of these patients are available, a screening visit with knee radiograph and knee pain/function assessment is needed to check whether identified patients are indeed eligible for inclusion. Based on the screening data, the final prospective cohort will be enriched by selecting the 70% of patients with the highest predicted probability of belonging to the progression phenotype. As such, 30% of screened patients will not enter the prospective cohort.

Only if eligible for inclusion, patients will be invited for a M000 visit where all additional baseline data and images will be gathered.

According to the feasibility at the clinical centres, to collect blood samples in fasting conditions, the patients will go to the hospitals or home visits will be organized as much as possible.

For each visit, all exams for one visit have to be performed ± one week from the visit. The window between screening and M000 visit will be at maximum of 2 months to allow evaluation of inclusion criteria such as evaluation of the knee radiograph by use of KIDA of the pre-selected patients. For follow-up, a window period of ± one month will apply for M006 visit and of ± two months for M012 and M024 visits.

Patients will be reminded before inclusion, M006, M012 and M024 visits to come to the clinical centres on fasting status if feasible, to bring back the completed questionnaires and the urine samples collected with the containers provided at the previous visit.

5.2.2. Investigation schedule

Table (5.2.2) 1 describes the investigations assessed during the study and Table (5.2.2) 2 describes the associated burden.
For further practical details, methods of measurement are provided in section 7.

Table (5.2.2) 1 - Investigation schedule

	Screening /ASSE	Inclusion/ M000	M006	M012	M024
General					
Informed consent	X				
Informed consent for pharmacogenomics (optional)	X				
In- and exclusion criteria	X				
Defining index knee	X				
Height	X				
Weight	X	X	X	X	X
Waist circumference		X	X	X	X
SBP, DBP, pulse rate		X	X	X	X
Previous treatments		X			
Relevant medical/surgical history related to OA		X			
Adverse events related to protocol procedures		X	X	X	X
Progression of knee OA; structural parameters					
Radiography of index knee (for assessment of KIDA parameters (ASSE) and for assessment of OA severity, bone shape analyses, subchondral bone analysis)	X		X	X	X
MRI of index knee for quantitative analysis (thickness and volume of cartilage, denuded bone area)		X	X	X	X
MRI of index knee for semi-quantitative analysis (MOAKS analysis)		X	X	X	X
Blood and urine for systemic biochemical markers		X	X	X	X
Progression of knee OA; pain and function					
KOOS for index knee	X[a]	X	X	X	X
ICOAP for index knee		X	X	X	X
Pain NRS for index knee	X[b]	X	X	X	X
Physical examination of both knees (ROM,..)	X[c]	X	X	X	X
Prediction of knee OA progression					
Shape analysis on MRI of index knee for quantitative analysis		X	X		
MRI of index knee for qualitative analysis (advanced T2 map)[e]		X	X		
High resolution CT of index knee for advanced structure detection and shape analysis		X			X
Motion analysis		X	X		
Performance based tests		X	X		
Co-variables					
Radiography of contralateral knee (for assessment of OA severity, bone shape analyses, subchondral bone analysis)		X			X
Radiography of both hands		X			X
Handscan to assess inflammation in the hand joints[f]		X			X
FIHOA for function of the hands		X			X
Low dose whole body CT for OA assessment in hips, shoulders and spine and hip bone shape analysis		X			X
HOOS and ICOAP for the most painful or right hip		X			X
SF-36 for quality of life		X	X	X	X
One month diary for pain intensity and pain killers taken		X	X	X	X
Pain NRS for contralateral knee, for both hips separately, lower back and both hands separately	X[b]	X	X	X	X
Pain DETECT		X	X	X	X
Motion analysis					X
Performance based tests					X
Physical examination of the hips, hands		X	X	X	X
Menopausal status/Pregnancy (if women are not menopaused)	X	X	X	X	X
Comorbidities		X	X	X	X
Smoking habits		X	X	X	X
Concomitant treatments		X	X	X	X
Other measurements - Genomic markers[d]					
RNA		X			X
DNA		X			X
Ethnic origin	X				

a: a reduced version of KOOS, with only questions on functions, stiffness and pain, will be used at screening, b: at screening Pain NRS will be evaluated right now and during the last week , c:to check ACR criteria of the index knee d:optional, e:Advanced T2 map MRI is not available for patients included in Oslo, f: Handsdcan analysis will be performed in the participating centers in Utrecht, Leiden and Paris.

Table (5.2.2) 2 - Burden for the patient

Examinations		Time burden	Other burden
Physical examination		15 min	
Questionnaires		30-45 min	
Radiograph	Both knees and hands	15-20 min	Radiation exposure
CT	Low radiation whole body and high resolution index knee	10 min	Radiation exposure
MRI	Quantitative and semi quantitative	30 min	
MRI	T2	10-15 min	Minimal invasive
Blood and urine		10 min	Veni puncture
Hand scan		5 min	
Motion analyses (Gait Smart, 20m walking) and performance based tests (30 sec stand up and 40m walking)		30 min	

Table (5.2.2) 3 provides the volume of blood and urine collected (according SOP 10.1) per participant during the study for the assessment of biochemical and genomic markers. A maximum total volume of 113 mL (if also consent for genomic markers) blood per participant will be collected during the 2 year follow-up of the study. At each visit all blood samples will be taken via a single veni puncture.

Table (5.2.2) 3 - Volume (mL) of blood and urine collected during the study

	Inclusion/M000	M006	M012	M024
Urine for biomarkers	50 mL	50 mL	50 mL	50 mL
Blood for biomarkers				
Serum	21 mL	21 mL	21 mL	21 mL
Plasma	7 mL	-	-	-
Blood for genomic markers (optional)				
DNA	8.5 mL	-	-	8.5 mL
RNA	2.5 mL	-	-	2.5 mL

5.3. Premature discontinuation of the study

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited ethical committees without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited ethical committees. The investigator will take care that all subjects are kept informed.

5.4. In case of TKR or surgery indication

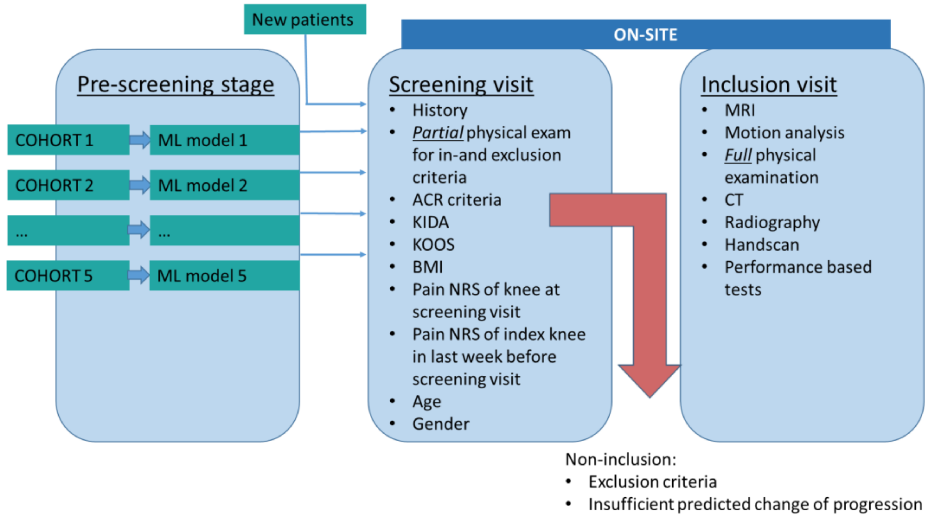
If a patient will have a total knee replacement (TKR) prosthesis surgery of the index knee or contra-lateral knee within the two years of follow-up, images of that specific joint will be irrelevant and not performed. All other acquisitions will be performed as scheduled and patients remain in the study.

6. STUDY POPULATION

6.1. Recruitment of the patients

The recruitment process for the APPROACH cohort will be primarily from existing European osteoarthritis cohorts of the participating centres and expanded with new subjects at these centres. Subjects who are likely to experience disease worsening in the next 2 years (based on the model in case of existing cohorts or based on expert opinion in case of new recruitments) will be identified and invited to a screening visit. A final set of the study participants will be selected by using the data collected at the screening visit (based on a second refinement algorithm).
In contrast to classic approaches, which use conventional inclusion criteria, *machine learning* (ML) models will be used to predict the likelihood of each patient becoming a fast OA progressor. In **pre-screening stage**, a customised ML model will be used for each cohort, that was trained on the historical data. In the **screening stage**,the decision to enroll subjects will be based on predictions of a final ML model, adjusted to work with the specific measurements from the screening visit.
Additional new patients, outside of the existing cohorts, might be recruited and they will follow the same process starting with the screening visit and enrollment is based on the likelihood of becoming a fast progressor.

Figure (6.1) 1 - The overall concept of the recruitment process in the APPROACH project



To demonstrate the feasibility of the recruitment strategy, a simulation of this process was performed on the existing CHECK cohort data. The data at years 0, 2 and 5 were used as baseline for prediction and the real outcomes at years 2, 5 and 8 were used to assess the results of the recruitment process. There were 64% non-progressors (N), 17% pain-related (P), 14% structure-related (S) and 5% both pain and structure-related (P+S) progressors in the original CHECK cohort. The table below shows the distribution of subjects across the progression categories, obtained after enrollment of the 25–150 top ranked subjects.

Table (6.1) 1 – Distribution of subjects across the progression categories, obtained after enrollment of the 25–150 top ranked subjects

# of subjects	N	P	S	P+S
25	32%	32%	4%	32%
50	34%	40%	2%	24%
75	35%	36%	8%	21%
100	34%	37%	9%	20%
125	34%	38%	10%	18%
150	35%	39%	11%	15%

Although the ML model prediction is not perfect (there were still be about 35% non-progressors enrolled), it enriched the number of progressors in the targeted categories (in comparison to the source distribution). Both the P+S and P categories were relatively larger, at the cost of a smaller S category. The strutural progressors could be further enriched, if needed, by lowering the prediction threshold for the S category (currently at $p = 0.5$ for both P and S). It is essential to the success of the APPROACH project to maximize the number of recruited P+S and S progressors.

6.2. Selection of the patients

At the screening visit after signing informed consent, subjects in existing osteoarthritis cohorts classified as likely to show progression over the next two years based on existing data or new subjects are checked for inclusion and exclusion criteria in order to participate in the APPROACH study as described below.

6.2.1. Inclusion criteria determined at screening visit

1. Informed consent obtained as described in section 12.3 of the protocol.
2. Ambulatory (able to walk unassisted)
3. At least 18 years of age
4. Capable of understanding the study
5. Capable of writing and reading in local language
6. Predominantly tibiofemoral knee osteoarthritis and satisfy the clinical classification criteria of the American College of Rheumatology (ACR): Knee pain and three of the following criteria: over 50 years age, less than 30 minutes of morning stiffness, crepitus on active motion, bony tenderness, bony enlargement, or no palpable warmth.
7. Highest probability to progress based on the algorithm based on the following parameters:
   - KOOS questionnaire
   - BMI (in recording height and weight)
   - Pain NRS of the index knee at the moment of the screening visit
   - Pain NRS of the index knee during the last week before the screening visit
   - Age
   - Gender
   - KIDA parameters of the index knee, based on standardized weight-bearing (KIDA) radiograph, measured < 3 months (patients with a JSW < 2 mm of the index knee will not be included)

6.2.2. Exclusion criteria

6.2.2.1. General exclusion criteria

A potential subject who meets any of the following criteria will be not included in the APPROACH study.

8. Not being able to comply to the protocol
9. Participating in a trial with local therapeutic intervention for index knee OA (pharmaceutical or surgical) or systemic DMOADs or potential DMOADs treatments for OA at the same time or within the past 6 months or anticipated in the forthcoming; participation in non-interventional registries or epidemiological studies is allowed.
10. Surgery of the index knee in the past 6 months (to avoid interferences with imaging)
11. Scheduled or expected surgery of the index knee in the next 2 years (to avoid interferences with imaging)
12. Pregnancy (child bearing woman) because of imaging (radiation and MRI, risks)

6.2.2.2. Medical exclusion criteria

13. Predominantly patellar femoral knee OA (clinical judgment)
14. The following secondary osteoarthritis of the knee: clinically significant deformities of the lower limbs (varus >10°, valgus >10°), septic arthritis, inflammatory joint disease, gout, major chondrocalcinosis (pseudogout), Paget's disease of the bone, ochronosis, acromegaly, haemochromatosis, Wilson's disease, rheumatic symptoms due to malignancies, primary osteochondromatosis, osteonecrosis, osteochondritis dissecans, haemophilia
15. Generalized pain syndrome, for example fibromyalgia
16. Patients with contra indication to MRI or CT
17. Hip replacement or expected hip replacement within 6 months
18. Osteosynthesis material near the knee joint
19. Self-reported severe IVD degeneration or facet OA

6.3. Participant withdrawal

6.3.1. Withdrawal criteria

The reasons for premature discontinuation of the study are:

- **Judgement of the investigator** on potential incapacity of the patient to continue in the study (a cause leading to misinterpretation of the OA progression (significant surgery on the index knee or occurrence of a disease of the index knee OA)).
- **Major deviation to protocol** if it interferes with the study evaluations and/or if it jeopardizes patient's safety (including pregnancy for the foetus).
- **Non-medical reason** *e.g.* consent withdrawal.
- **Lost to follow-up**.

6.3.2. Procedure

If a patient does not attend the planned visit unrelated to consent withdrawal, the investigator will make effort to contact him/her by mail and/or phone to arrange a new visit within the time span allowed.
In case of lost to follow-up, when the investigator has no news of the participant, he/she will make effort to contact him/her by mail and/or phone, to ask if the patient is still willing to stay in the study or wants to withdraw consent.

7. STUDY PROCEDURES

The study parameters will be performed at the designated study visits as indicated in Table (5.2.2) 1. All acquisition procedures are performed according to standard operation procedures (SOPs) as described for each of the procedures separately in appendix 3.

Medical and surgical history
A list of each subject's specific OA related medical and surgical history, including history and type of knee traumatism, history and type of knee surgery, previous treatments, potential cause of secondary OA will be recorded at the inclusion visit.

Previous and concomitant treatments and comorbidities
At inclusion visit, the investigator will ask the patient about previous and concomitant treatments received (including treatments likely to have an action on cartilage or bone metabolism, arthroscopy, intra articular injection…). At each follow-up visit, the patient will be asked for new concomitant treatments since the last visit including surgical treatments. Concomitant treatments related to OA or expected to influence biomarkers of OA will be recorded in the e-CRF.
Comorbidities are recorded according to the Charlson index (Charlson, 1987).

Other information
Smoking habits will be recorded at inclusion and at follow-up visits.
Menopausal status for women will be recorded at the screening visit (menopause is defined by last menstrual bleeding ≥12 months ago, not using oral anticonceptives, etc). If the patient is not in a menopausal status, the investigator will advice her to use effective method of birth control during the whole period of the study. At each visit the investigator will ask her if she is pregnant in order to withdraw her from the study because imaging (radiation risks) can jeopardize patient's safety (for the foetus).
The medical and surgical information related to the index knee at follow-up visits will be reported in specific pages of the e-CRF.

7.1. Physical examination

General physical examination will be performed at each visit by measuring weight, waist circumference, systolic and diastolic blood pressure (SBP and DBP) and pulse rate after 5 minutes rest in the sitting position in a standardised way, according to SOP 11. Each subject's height will be measured at the screening visit only.

The data obtained during the physical examination will be recorded in the patient's hospital medical file as source data and in the e-CRF.

7.1.1. Knee physical examination

For each knee the following knee examinations will be recorded:

- The warmth of the knee (presence yes/no) as well as the presence of an effusion (positive patellar tap) will be assessed.
- Passive ranges of flexion and extension will be measured with a goniometer. Flexion to be reported as <90°; comprises between 90 and 120° or >120°. For the extension, presence of a flexum will be reported as yes or no.
- Presence of varus/valgus
- Pain and grinding in the patellofemoral joint will be evaluated by the grinding test and reported as yes or no.

7.1.2. Hip and hand physical examination

Physical examination of hip and hands will be performed to assess possible OA as co-variables important for *e.g.* biomarker analysis. For both hips the passive ranges of motion will be measured:

- - Flexion will be reported as <90°, between 90 and 120°, or >120°.
- - For the extension, presence of a flexum will be reported as yes or no.
- - Internal and external hip rotations will be reported as <30°, between 30 and 45°, or >45°.

On all hands joints, location and number of Heberden and Bouchard nodes will be evaluated. Number and location of inflamed joints as defined by soft (peri) articular tissue swelling on palpation (sometimes accompanied by redness) will be assessed. Hard tissue enlargement and subluxation of the first thumb metacarpal joint will be reported. Deformity will be assessed in Distal Inter Phalangeal (DIP) joints.

The articular index of Doyle will be used to evaluate the severity of hand osteoarthritis by grading pain (0-3) in 24 joints and joints groups (DIP, PIP, and MCP joints, IP joint of thumb and first carpometacarpal joint) by pressure or passive movement (Doyle, 1981).

Patients will be asked whether pain was present in hand joints during a period of more than 20 days during the last month.

7.2. Imaging with central reading

To evaluate the progression of OA in the index knee, standard radiographs and MRI images of the knee will be performed (see below).

In addition, novel MRI techniques and high resolution CT of the index knee will be performed to evaluate the additional value of these novel techniques in prediction of progression of OA. These different imaging techniques visualize different tissue characteristics in the knee joint, possibly differently involved in the process of osteoarthritis (different phenotypes). In order to correct for concommitant osteoarthritis in hands, hips, shoulders and lower back, radiographs of both hands and a whole body CT will be performed. The low radiation whole body CT provides images of all relevant joints of sufficient quality to assess confounding with similar radiation exposure than performing conventional radiographs of all relevant joints.

The SOPs describing acquisition are in Appendix 3. All reading and analyses of images are performed at central facilities. The responsibilities of the Central reading Centre are described in SOP 4.1 to 6.4 presented in a separate document named "Approach-reading standard operating procedures".

7.2.1. Radiographs

7.2.1.1. Radiography acquisition protocol

Standardised radiographic techniques of the knees and hands will be used as described in SOP 1.1 and 1.2.
The quality of image acquisition will be checked by the central reading facilities:

- for the knee at the screening and inclusion visits for each clinical site, except for subchondral bone analyses, for which the quality of the first three images from each clinical site will be controlled and after the first screening, the quality control could be done on a regular basis every second month, or every 30th examination, (another 3 images), whichever comes first,
- for the hands for the first 10 images from each clinical site. Afterwards this control will be performed on a regular basis.

7.2.1.2. Central reading of radiographic images

The radiographs will be centrally analysed in order to minimize the variability. The designated central readers will perform the central reading on on-going basis (KIDA evaluation) or at the end of the study depending on the methods.

Both knee radiographs, will be evaluated for joint damage using KIDA, the Kellgren and Lawrence grade, and OARSI grade (Marijnissen, 2008; Kellgren, 1957; Altman, 2007). Hand radiographs will be evaluated for osteoarthritic features using the Kellgren and Lawrence grade, OARSI grade and the Verbruggen-Veys score (Kellgren, 1957; Altman, 2007; Verbruggen, 2000).

Bone shape will be analysed by the Active Shape and Appearance Models which provide quantitative, spatial and temporal understanding of all the component tissues within a given joint. Subchondral bone analysis will be performed by fractal methods.

7.2.2. Magnetic Resonance Imaging (MRI) of the knee

As the level of physical activity can influence the results of MRI, the level and time in the previous day of physical activity will be collected in the e-CRF.

7.2.2.1. MRI of the index knee – acquisition protocol

MRI images will be taken from patients' index knee only (as defined at screening). Standardised MRI techniques of the knee will be used as described in detail in SOP 2.1. Standardisation will be checked before inclusion of the first patients in consultancy with the centralised readers. All baseline images for MRI (except semi quatitative) will be checked for quality by the central readers immediately after acquisition. In case of insufficient quality, the patient will be requested to come back to the site for rescanning. In addition, 6 patients per site will be scanned twice with repositioning both at baseline and at M024 visits for

quantitative measurements to calculate the within study variability (test/retest reliability). This control will be performed for post baseline visits regularly.

In addition to the standard MRI techniques to evaluate osteoarthritic features in a quantitative and semi quantitative way (SOP 2.1), also novel exploratory imaging techniques will be performed to evaluate the additional value in prediction of OA progression in specific phenotypes. T2 images (SOP 2.2) give a quantitative measurement for assessing collagen distribution in the cartilage.

7.2.2.2. Central reading of MRI exams

Osteoarthritic features on MRI will be centrally analysed in order to minimize the variability. The designated central readers will perform the central reading on an on-going basis or at the end of the study. The semi-quantitative assessments readings will be performed towards the end of the study when all time points have been acquired and are available.These MRIs will be read in sequential order to allow for direct comparison and within-grade assessment.

The novel imaging marker T2-mapping, quantitative measurement for assessing collagen distribution, will be performed.

The novel exploratory method to analyse tissue shape on MRI, Active Shape and Appearance Models, will also be used on MRI image. It has been demonstrated that bone shape is:
a) highly specific for the presence of OA and a sensitive measure of progression and
b) a more responsive measure of progression than radiographic joint space width and MRI cartilage volume (Bowes, 2015).

7.2.3. High resolution computed Tomography (CT) of the index knee and whole body low dose CT (WBLDCT)

7.2.3.1. CT of index knee and whole body CT- acquisition protocols

High resolution CT of the index knee and whole body low dose CT will be performed according to SOP 3.1. These two examinations will be done without injection of contrast products.
The newest high resolution 3D CT imaging is fast, has extremely low radiation exposure within the range of one normal radiograph, has superior spatial resolution and is widely available.
A WBLDCT will be conducted to assess concomitant hip and/or lumbar and/or shoulder and/or IVD degeneration and/or facet OA. The whole body will be scanned within 10 seconds, with an effective radiation dose comparable to a combination of hip and spine radiographs, which approximately equals the yearly background radiation of 3 mSv.
The quality of image acquisition will be controlled immediately after each patient for the 10 first patients of each centre by the central reading centres. This control will be performed subsequently on a regular basis.

7.2.3.2. Central reading of CT

In order to minimize the variability, the high resolution CT and WBLDCT will be centrally analysed by the designated central reader. The high resolution CT and WBLDCT will be analyzed for the parameters as defined in the APPROACH study protocol. They will not be scored for any other diseases or abnormalities. Patients will be informed about this.

For bone architecture evaluation, advanced structure detection will be performed in 4 different volumes of interest, and includes bone mineral density, anisotropy, inhomogeneity, variogram slope and entropy. For shape analyses, statistical Shape Model (SSM) applications in OA using predefined landmarks on 2D or 3D images, produces a mean shape and modes of shape variation of this joint. Each mode is expressed numerically, where 0 denotes the mean shape, and negative and positive values represent the deviance in number of standard variations from this mean in either direction.
In WBLDCT using a slice thickness of less than 1 millimeter and iterative reconstruction it is possible to reconstruct high quality 3D data providing more detail than standard radiographs. Especially overlapping structures such as the hip and spine profit from the full 3D imaging: CT is needed for facet joint degeneration (Pathria, 1987) and CT assessment is superior compared to plain radiograph for IVD degeneration (Alshamari, 2015). The validated outcome scores based on literature exist for semi-quantitative grades on a 0-3 scale for JSN and osteophytosis, for disc degeneration and hip OA (Lane, 1993 and Turmezei, 2014). For glenohumeral and facet joints, semi-quantitative grades on a 0-3 scale will be used to describe OA based on existing literature (Weishaupt, 1999 and Samilson, 1983). A newly developed semi-quantitative grade will be used to describe acromioclavicular joint OA.

7.3. HandScan

In order to assess concommittant hand involvement, OA related inflammation of the joints of both hands and wrists will be evaluated using the HandScan (Meier, 2012 and Van Onna 2013) in 80 % of the patients (HandScan is available in 3 participating centers). A 2-3 min scan related to the local wrist and finger blood pooling and flow provides a direct measure for inflammation of joints. The HandScan will be used according to the HandScan Manual (see SOP 8).
The quality of data acquired will be controlled immediately after each patient for the 10 first patients of each centre. This control will be performed subsequently regularly. Relevant data will be transferred in the database of the APPROACH study.

7.4. Motion analysis

In order to define gait characteristics, motion analysis will be performed using GaitSmart technique according to the manual (SOP 9.1). For acquisition, 6 sensors are attached to the patient, measuring knee and hip movement. Patients are asked to walk 20 metres at their own self-selected speed. The GaitSmart software reports the data within a couple of minutes. The GaitSmart doesn't interfere with the walking. Data will be transferred to the database of the APPROACH study.

7.5. Performance based test

A 40-m self-paced walk test will be performed. Patients will be asked to walk as quickly but as safely as possible to a mark 10m away, return, and repeat until a total distance of 40m. Subjects are timed for this test and data are expressed as time (minutes) needed for this 40 m walking (SOP 9.2).

A 30 second chair stand-up test will be performed. Patients are asked to stand-up and sit down without use of their hands and arms from a chair. The number of times within 30 seconds a patients is able to stand up from the chair is used as outcome (SOP 9.2).

7.6. Questionnaires

To evaluate the progression of OA in index knee, the KOOS, and the ICOAP questionnaires for knee will be used. The Pain NRS will also be used for both knees separately.

To assess involvement of other joints (as confounding factors), the HOOS and ICOAP will be used for the most painful or right hip, FIHOA for hands, and Pain NRS for both hips separately, both hands separately and lower back.

Pain DETECT and SF-36 are used to evaluate possible other causes of pain, that is depicted in the osteoarthritis specific questionnaires. One month diary to report pain intensity and pain medication taken will also be used.

All questionnaires are self-administered, will take about 30-45 minutes. They will be sent by the sites to the patients by post at least 4 weeks before the visit for M006, M012 and M024 and they should be completed at home and brought to the visit (at screening, the questionnaires will be distributed in the clinical centres and completed there; for inclusion, they will be given at the screening visit, and completed at home and brought to the inclusion visit).

7.6.1. Knee injury and Osteoarthritis Outcome Score (KOOS)

The KOOS (Knee Injury and Osteoarthritis Outcome Score) is self-administered and assesses five outcomes: symptoms, stiffness, pain, activities of daily living, sport and recreation function, and knee-related quality of life (Roos, 1998; see appendix 4) and will be assessed for the index knee (defined at screening). At screening a reduced version of the KOOS will be used with assessment of three outcomes only: activities of daily living, stiffness and pain.

7.6.2. Hip disability and Osteoarthritis Outcome Score (HOOS)

The HOOS is designed to assess patient-relevant outcomes in five separate subscales (pain, symptoms, activity of daily living, sport and recreation function and hip related quality of life; see appendix 4) and will be assessed for the most painful hip (in case of equally affected: for the right hip).
The Spanish version of the HOOS used in the study will be a non-validated version.

7.6.3. Intermittent and constant OA pain questionnaire (ICOAP) for the knee and the hip

The ICOAP will be assessed for the index knee and the most painful hip (or the right hip in case equally affected). The ICOAP is designed to comprehensively evaluate the OA specific pain experience in people with hip or knee OA, including pain intensity, frequency, and impact on mood, sleep, and quality of life, independent of the effect of pain on physical function (Hawker, 2011; see appendix 4).

7.6.4. FIHOA (Functional Index for Hand OsteoArthritis) for both hands

This index assesses the functional impact of hand osteoarthritis in everyday life, over the last 48 hours, on 10 daily activities involving both hands combined (Dreiser, 1995; see appendix 4). The patient is asked to answer each item using a 4-point verbal scale, from "possible without difficulty" (0) to "impossible" (3 points); thus, total scores range from 0 to 30.

7.6.5. Numeric Rating Scale (NRS) for Pain for knees, hips, lower back and hands

The pain NRS for knees, hips, lower back and hands will be assessed at rest. The pain NRS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with rheumatic diseases (Hawker, 2011; see appendix 4). At screening the pain NRS will be assessed right now and during the last week. At other visits, the pain NRS will be assessed during the last week only.

7.6.6. Pain detect

The painDETECT questionnaire is designed to identify the likelihood of a neuropathic pain component in patients with low back pain (Freynhagen, 2006) and is recommended for use by non-specialists (Gauffin, 2013) (see appendix 4).

7.6.7. Short Form (36) Health Survey (SF-36)

The questionnaire for Quality of Life (SF-36 - The Short Form (36) Health Survey) will be assessed to obtain information on vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health (see appendix 4).

7.6.8. One month diary for pain intensity and pain medication taken

A one-month paper diary to be completed at home (max 5 minutes a day) is used to record each day the presence of pain (yes/no) whatever the location and the consumption of pain relief drugs in order to assess whether the outcome of the different questionnaires are influenced by other pain and/ or pain medication (see appendix 4).

7.7. Biological samples

Blood and urine will be sampled according to SOP 10.1 to assess biochemical markers (*e.g.* markers related to cartilage degradation and bone metabolism as well as inflammation and metabolic status). Fasting condition and time of last meal will be recorded for urine sample collection and for blood sample collection. Fasting conditions are defined as no meals, including no sugar, no tea, no coffee for at least 8 hours and current medications are authorised if taken with water only. In addition, the level of physical activity within the last 24 hours and physiotherapy or spa activity within the last 72 hours before the blood collection will be recorded in the e-CRF as these activities can influence biochemical markers, metabolomics and lipidomics.
Patients will provide midstream urine samples, preferably the second morning void. Blood and urine samples will be processed at the clinical centres according to standardised protocol (SOP 10.2). Operations manuals have been produced defining the procedures for, storage/tracking/distribution (SOP 10.3) and logging/storage of biological specimens (SOP 10.4).
Biological samples are stored at the individual clinical sites and shipped on a regular basis to the central laboratories for analyses.
After analysis, the samples analysed will be destroyed at the latest after study end (=end of the consortium agreement).

7.7.1. Biochemical markers

All biochemical biomarkers will be analysed in central laboratories according to the standard operating procedures of the certified laboratories. Parameters associated with joint pathology and metabolism will be measured. The biological pathways of special interest for example are cartilage and bone metabolism (*e.g.* CTX-II), inflammation (*e.g.* C-reactive protein, pro-inflammatory cytokines), oxidative damage and antioxidant status (*e.g.* carotenoids, isoprostanes), and muscular anabolism (*e.g.* pro-collagen-3 N-terminal peptide).
The most state-of-the-art analytic approach will be utilized to examine these pathways when the biological samples are analyzed at study end.

7.7.2. Genomic (bio) markers

Analyses of genomic markers (DNA, protein coding mRNAs, DNA CpG methylation, regulatory RNAs, circulating RNAs) is optional for the patient, by signing a separate informed consent form. This specific consent given to this analysis can be withdrawn separately at any moment without compromising the participation in the overall clinical study investigations.

One of the aims is to investigate associations between genomic markers and the investigated disease, knee osteoarthritis, to assess whether a phenotype of progressors has a different genomic profile from another progressor phenotype at baseline or at study end.

The samples will not be used for any investigations not specified in this protocol.

Blood samples will be taken in PAXgene tubes and stored for a maximum of 6 months according to protocol (SOP 10.2) at each clinical site. These anonymised blood tubes will be shipped to the central laboratories and processed according to the standard operating procedures of the laboratory.

7.7.3. Sample storage

Biological samples for future assessment of biomarkers in ancillary studies are collected at inclusion, 6-, 12-, and 24-month visits and will be stored in the central repository site. The objective of the ancillary studies will be in accordance with the objectives of the APPROACH study.
All remaining biological samples will be stored in the central repository site, Biostorage (Germany), for the duration of the consortium as defined in the consortium agreement. After ending the consortium agreement, samples will be relocated to the original institutes and stored to a maximum of 15 years at these institutes according to local regulations. They could be destroyed earlier on sponsor or patient request.

8. SAFETY REPORTING

8.1. Adverse events and serious adverse events

8.1.1. Adverse events (AEs)

An adverse event is defined as any health-related unfavourable or unintended medical occurrence that happens from the date the participant signs the information and consent form during the study. Only adverse events related to protocol procedures that are not related to standard diagnostic procedures used in clinical practice (viz. motion analyses), either reported spontaneously by the subject or observed by the investigator or his staff will be recorded in the e-CRF by the investigator. Each participant is instructed to report the occurrence of such adverse event at each visit.

8.1.2. Serious adverse events

A serious adverse event is any untoward medical occurrence or effect that:
- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is fetal damages or fetal death; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

Only SAEs related to protocol procedures that are not related to standard diagnostic procedures used in clinical practice (viz. motion analyses), will be recorded in the e-CRF.

The investigator will report only these SAEs to the sponsor without undue delay after obtaining knowledge of the events.

These serious adverse events will be reported to the approving ethics committee according to local regulations and the project's Ethical Advisory Board. Clinically relevant medical findings will be reported by the local investigator to the treating physician.

The sponsor will report these SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for these SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs related to protocol procedures will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.2. Safety considerations for Radiograph, knee high resolution CT and WBLDCT examinations

As part of knees and hands Radiograph, high resolution CT of the index knee and WBLDCT evaluations, subjects are exposed to radiation.

Table (8.2) 1 - Effective dose for the knee and hand radiographs, knee high resolution CT and WBLDCT (in mSv per visit)

	Screening	Inclusion/M000	M006	M012	M024
radiograph index knee	0.0002	-	0.0002	0.0002	0.0002
radiograph other knee		0.0002	-	-	0.0002
QCT index knee		0.25			0.25
Radiograph both hands		0.0002	-	-	0.0002
WBLDCT		3			3
Total effective dose (mSv) per visit	**0.0002**	**3.2504**	**0.0002**	**0.0002**	**3.2506**

The overall radiation exposure during the whole study will be approximately 6.5 mSv. This is much lower than a standard clinical CT of the pelvis (≈ 10 mSv).

8.3. Safety considerations for MRI

MRI imaging uses non-ionizing radiation and is safe when used on subjects who are screened for contraindications. Procedures need to be followed according to guidelines/SOPs of each clinical site.

8.4. Responsibilities of the investigator

For any adverse event related to protocol procedures whatever the seriousness, the investigator must:

- **Note in the participant's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person, …) and any other relevant information which he/she has learned of the event,
- **Report the Serious Adverse event to the sponsor** using the AE form,
  - Evaluate the intensity,
  - **Document** the event with additional useful information,
  - Ensure the follow-up of the event,
- **Fulfil his/her regulatory obligations** to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

8.5. Responsibilities of the sponsor

In accordance with international guidances, the assessment of the seriousness of adverse events is made by the investigator. The sponsor is responsible for ensuring that all serious adverse events related to protocol procedures are reported to Competent Authorities and Ethics Committees. The actual country specific reporting per country is delegated to the principal investigators of the clinical sites.

9. STATISTICS

9.1. Statistical analysis

The statistical analysis will be described in a statistical analysis plan prepared before the database lock.

Validation of prediction model used in the inclusion process (primary objective)

The model based on the existing cohort data, developed to predict radiographic and symptomatic progression from the screening visit data, will be evaluated using the 2-year follow-up outcomes observed in the APPROACH cohort. The predictions made by the model that informed the patient inclusion process, will be compared against the progression measured over the 2 years period. In a previous phase of the project separate prediction models have been developed for the outcome persistent pain (yes/no), structural progression, based on JSW narrowing (yes/no), and both (yes/no) or both not (yes/no) using machine learning techniques. These models use the 15 variables as measured during screening phase of the prospective cohort study. The model predictions will be combined to derive predictions for primary outcome of the study (the 4 categories of progression: pain, structural, structural and pain, , no progression). The ability of the model to discriminate between progressors and non-progressors (discrimination) will be assessed using AUC-ROC analysis (separate for pain and structural progression outcome). Calibration of the combined model will be performed using the prospective cohort data by comparing the predicted outcomes (1 of the 4 categories) with the observed outcome after 2 years. To evaluate whether updating the model is needed and the extensiveness of updating to improve predictions in the new patient sample and balancing this with the risk of overfitting we will consider the methods as described in Vergouwe et al. Stat Med 2016.

Development and validation of a predictive model for OA progression (secondary objective)

The algorithm used to build a predictive machine learning model, will use as input the patient characteristics (including conventional and novel clinical, imaging, and biochemical markers as described in paragraph 5.1.2.) at baseline and/or change over short-term follow-up, and provide a prediction of the outcome at 2 year follow-up (radiographic/symptomatic OA progression or no progression). To train the model, a supervised approach will be used, in which the known outcomes of a subset of the APPROACH cohort population will be used as guidance. The rest of the patients will be used as a test, to verify the model's ability to generalise and perform prediction on cases not seen in training (e.g. using 10-fold cross-validation).
When an extended or new model is developed in the cohort, again the discrimination and calibration will be assessed as described for the primary outcome (internal validation). The prediction model used in the selection process will also be refitted in the prospective cohort and a limited set of additional variables (based on the ability to evaluate (new) predictors with the observed number of events in the cohort) will be added to the model. Their added predictive value will be assessed using up-to-date methods like the net reclassification index (NRI, see i.e.Xanthakis et al. Stat Med 2014) and an optimal model will be selected. External validation of these models (not part of the present project) will then be needed for implementation in practice.

To mitigate the stochastic aspect of the machine learning algorithm, multiple models will be trained and verified at once, and the one with typical behaviour (median performer) will be selected as a point of reference and further used in the phenotype discovery.

Discovery of phenotypes (exploratory objective)

The set of patients with radiographic progression (e.g. based on minimum total JSW loss) and/or symptomatic progression (based on minimum clinically important difference in pain) will be explored to define groups that share common characteristics. First, we will perform a clustering analysis to identify phenotypes based on similarities between the patients (at the level of patient characteristics including conventional and novel imaging or biochemical markers). Next, we will build a predictive machine learning model, able to distinguish between progressive and non-progressive cases, then extract from the model structure the patterns used to describe patients, and finally analyse similarities between these descriptions to identify phenotypes.

A machine learning algorithm best for this purpose, will be selected through experimental evaluation of several supervised learning methods with interpretable representation, such as decision trees, random forest, rule-based evolutionary learning or modern neural networks approaches.

The final set of phenotypes of clinical interest (such as post-traumatic, metabolic, ageing, inflammatory, bone driven, genetic) will be selected in discussion with clinical experts and described in enough detail to be of use in practical OA diagnosis and patient selection.

Description of OA progression in existing and novel phenotypes (exploratory objective)

OA progression of the index knee will be described over a period of 2 years for the identified subgroups. Changes from baseline to the 1- and 2-year will be evaluated graphically and by using descriptive statistics (mean with standard deviation, median with interquartile range or number of patients and proportions). OA progression is based on structural changes and/or changes in pain and function and evaluated by use of conventional and novel clinical, imaging, and biochemical (bio)markers as described in 5.1.1.

Statistical analysis will be defined in a statistical analysis plan before the database lock.

9.2. Determination of sample size

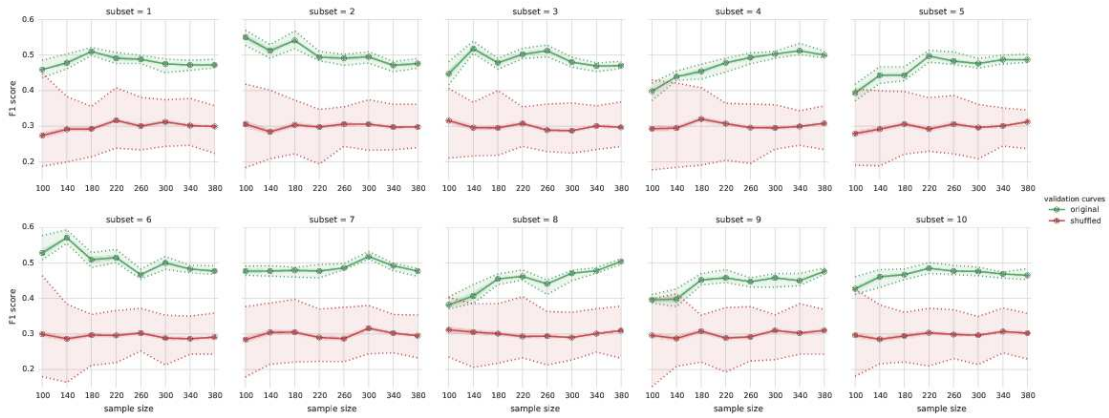
Although the number of subjects in the APPROACH cohort is limited by external factors (e.g. the actual number of fast progressors in the existing cohorts), it is important to ensure that the APPROACH cohort is large enough to be useful for analysis of the primary objective. We would like a guarantee that the cohort is large enough to effectively learn from the data and make better than chance predictions.

To estimate the minimum cohort size required to achieve this, we used a training set of 10 random subsets of subjects from the CHECK cohort. For each subset we maintained the class proportions observed in the projection of the recruitment strategy for including 100 CHECK subjects (34% **N**, 37% **P**,9% **S**, 20% **P+S**). Then we constructed 20 *surrogate training sets* with randomised class labels, where the link between the attribute values and the class a patient belongs to is destroyed. Finally, we compared the prediction quality on both original

and surrogate data. With this experiment setup, we expected to obtain a better result on the original data by chance with the probability of only: p = 1/(20+1) < 5%.

To test the prediction quality, we used a 10-fold cross-validation procedure. For each fold we trained 25 random forest models and we measured their predictive performance with the weighted F_1 score (which considers precision (also called positive predictive value) and recall (also called sensitivity) and is applicable to multi-class problems). The figure below shows the difference in performance on the original and the surrogate data for 10 random subsets of subjects. The difference in performance was statistically significant (at α=0.05 level) when the number of subjects in the training set reached 180. Thus, assuming an anticipated dropout rate of 20%, the minimum sample size for the study is 225. The planned number of 300 patients is therefore anticipated to be sufficient for the study purpose and allows for some variation in the actual distribution of progression categories in the APPROACH cohort.

Figure (9.2) 1 - Permutation test



(The line plot shows the median prediction score, with area plot showing range between minimum and maximum value. Horizontal axis shows the number of samples in the training set.)

10. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The investigator will allow the monitors from the Institut de Recherches Internationales Servier (I.R.I.S.), the sponsor, the persons responsible for audits, the representatives of the IRB/IEC, and of the Competent Authorities to have direct access to source data / documents.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The study monitoring will be performed by I.R.I.S in order to ensure compliance with ICH GCP, local regulations and protocol requirements, and to conduct source data verification and review

12. ETHICAL CONSIDERATIONS

12.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Participant information and consent form" document, the insurance documents, will be submitted to (an) IRB(s)/IEC(s) by the sponsor in the Netherlands. The submission in the participating countries will be performed by the investigator(s) in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

12.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO).

12.3. Recruitment and informed consent

Pre-identified patients potentially fulfilling the inclusion and exclusion criteria including eligibility to one of the defined phenotypes based on the algorithms for identification will be selected from the existing European cohorts and additional institutional databases if needed.

The responsible investigator of the cohort will send (on behalf of the treating physician if needed in case of lack of previous consent) a letter to the patient to inform him/her about the longitudinal APPROACH study and to ask him/her whether he/she would like to receive more information about the study. The patient may reply that he/she is or is not interested by letter, email or phone. If no such reply is obtained within 2 weeks the investigator or his/her delegate of the APPROACH study will call the patient to ask whether he/she received the letter and whether he/she is interested in the study. Patients who are interested in participation will be informed of the screening procedure, objectives, benefits, risks and requirements imposed by the study. The patient will be asked by the investigator or his/her delegate to participate in the longitudinal APPROACH study.

If the patient is willing to participate, the patient will be provided with an information and consent form by post and an appointment for a screening visit is made. The patient may seek further details of the study, and may change his or her mind about participating in the study.

At the beginning of the screening visit, investigator and patient both sign informed consent, and thereafter the screening measurements will be performed. Based on the outcomes patients are excluded or patients are scheduled for an inclusion/M000 visit within 2 months. These patients will be informed that they still may be excluded based on evaluation of their screening's data. Based on final evaluation of inclusion criteria (*a.o.* image analyses for JSW measurement) the decision will be made whether the patient can be included in the longitudinal cohort study. The scheduled inclusion visit will take place or will be cancelled accordingly, with explanation to the patient.

Two original information and consent forms must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.
The participant will be given one signed original information and consent form, the second original will be kept by the investigator.

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Handling

13.1.1. e-CRF

An electronic data capture system is going to be used for this study. An electronic case report form (e-CRF) is designed to record the data required by the protocol and collected by the investigator.
The e-CRF will be produced by I.R.I.S. in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by an e-learning prepared by I.R.I.S.
Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the participant's Medical File.
Upon entry, data will be transmitted via the Internet from the study centre to the IRIS database.
The investigator or the designated person from his/her team agrees to complete the e-CRF, at each participant visit, and all other documents provided by the sponsor.
The e-CRF should be completed within 2 weeks after the visit of participant and before the next scheduled visit. The informed consent approval and date need to be reported at the soonest in the e-CRF after informed consent signature of the patient.
All corrections of data on the e-CRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of the software, including date, reason for modification and identification of the person who has made the change.
In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the sponsor or third parties.

Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.
Data can be frozen during the study after their validation. However the investigator has the possibility to modify data if deemed necessary via a request to the sponsor.
After the last visit of the participant, the investigator or co-investigator must attest the authenticity of the data collected in the e-CRF by entering his/her user name and password.

13.1.2. Central reading

The investigational sites will anonymise and upload images to the central XNAT platform, at the specific visit location (see SOP 7). Post-acquisition anonymized radiographs, MRI exams, high resolution CT, and LWBCT should be sent as soon as possible to the XNAT platform:

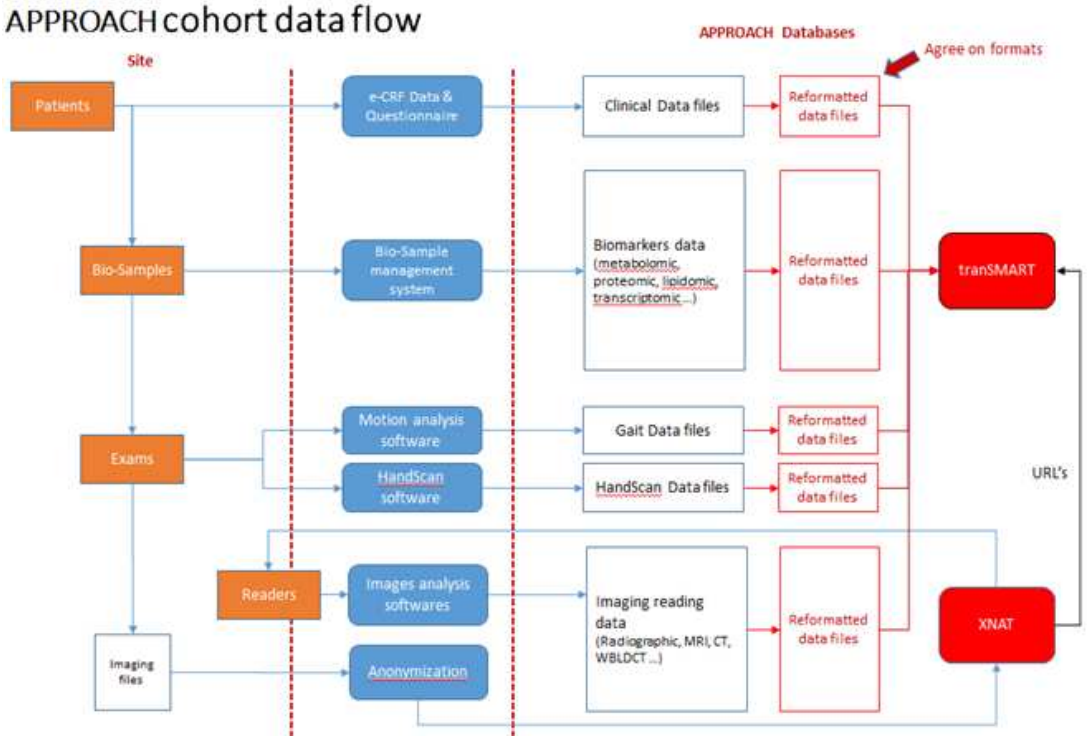
- for the index knee radiographs at screening and the remaining first 10 images of each acquisition technique at each clinical site **within 48 hours** for direct quality check,
- for all remaining images **within one month**.

Data from centralised image reading will be recorded in tranSMART. No data will be transferred to IRIS database.
Data from blood and urine biochemical markers and genomic markers analysis, as well as motion analysis and hand scan, will be recorded in tranSMART. Locally (at central readers location) a copy of these databases will exist prior to the transfer to tranSMART. No data will be transferred to IRIS clinical database.
Data transfers between the central readers and tranSMART will be done according to a specification manual describing the process (see SOP 7).

13.2. Source data

All source clinical data will be kept in the patient medical files in the clinical centres. There are no data to be recorded directly on the e-CRF and to be considered as source data.
Questionnaires filled out by the patients and data reported by the patients (*i.e.* KOOS, HOOS, ICOAP, FIHOA, NRS, Pain detect, SF36, one month diary for pain intensity and pain killers) will be considered as source data. For these parameters, no entry in the e-CRF will be performed except at the screening visit for the reduced version of the KOOS and the two NRS. The other questionnaires will be sent by the site regularly to the data management department of I.R.I.S. (Institut de Recherches Internationales Servier, Suresnes, France) which is responsible for data entry in the clinical database of APPROACH at I.R.I.S.. This data entry will be manual (see paragraph 13.3).
Source data and source documents of the centre should be clearly identified in a specific, detailed and signed document before the beginning of the study. Source data and source documents will be kept as electronic or as written records. The following data will be considered as source documents: patient's medical file, all examinations and reports (laboratory, radiographs, MRI, etc.), patient's questionnaires.

Figure (13.2) 1 - Data processing



13.3. Data management

For data collected on the e-CRF, the Data & Clinical Logistics division of I.R.I.S., is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

For data collected on paper form (Questionnaires as KOOS, SF-36, one month pain diary….) the Data & Clinical Logistics division of I.R.I.S., is responsible for data processing including: independent, blind, double data entry with a third person resolving any discrepancy between first and second entry.

The Medical Data Department of I.R.I.S. or CRO if subcontracted is responsible for data coding including:

- medical / surgical history, adverse events and procedures related to adverse events using MedDRA,
- medications using WHO-DD.

The coding process is described in a specification manual.

When data validation is achieved, a review of the data is performed according to I.R.I.S. standard operating procedure. When the IRIS clinical database has been declared to be complete and accurate, it will be locked and will be then transferred into tranSMART for analysis.

13.4. Archiving

The investigator will keep all information relevant to the study for at least 15 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the investigator will be provided with a copy of each participant's data on a CD-ROM support. These data include the completed e-CRF, all (electronic) CRFcomments, history of all queries, complete signature history and the full audit trail reports.

14. INSURANCE

The sponsor and all participating investigators have a liability insurance which is in accordance with local legal requirements.

For the participating centers in the Netherlands, the sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

For the participating centers in the other European countries, their local insurance which is in accordance with local legal requirements, is applied.

15. OWNERSHIP OF THE RESULTS - DISSEMINATION POLICY

15.1. Ownership of the results

Results of the clinical study shall be jointly owned by all parties according to rules of co-ownership of foreground in accordance to article 12 of the APPROACH Consortium Project Agreement.

15.2. Dissemination policy

Dissemination of information relating to the results arising from the study will be according article 20 of the APPROACH Consortium Project Agreement.

15.3. Administrative clauses concerning the sponsor and the investigator

15.3.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform the Director of the medical institution about the study.

15.3.2. Substantial protocol amendment, amended protocol and modification of informed consent

If the protocol or informed consent forms must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by the investigator or

the coordinator and the sponsor. The substantial protocol amendment must be signed by both parties. Both documents must be kept with the initial protocol.
All substantial amendments and corresponding amended protocols and informed consent forms must be sent by the sponsor and for the participating centers by the investigator(s), in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can only be implemented after a favourable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, with the exception of a measure required to eliminate an immediate risk to the study participants. Each participant affected by the amendment of the informed consent must complete, date and sign two originals of the new version of the informed consent form together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the informed consent form.

When the submission is performed by the investigator or the coordinator, the latter must transmit a copy of IRB/IEC's new written opinion to the sponsor, immediately upon receipt.

Furthermore, the substantial amendment, amended protocol and informed consent are to be submitted to the Competent Authorities in accordance with local regulations.

15.3.3. Final study report

The study report will be drafted by the consortium partners in compliance with the intentions of the goal of the APPROACH project.

All consortium partners must agree on the final version.

15.4. Concerning the investigator

15.4.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to the APPROACH study are strictly confidential as according to the consortium agreement and the trial agreement between sponsor and investigator.

A participant screening log and inclusion list will be completed and kept by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The participant screening log must be completed from the moment the investigator checks that a participant could potentially participate in the study.

15.4.2. Documentation supplied to the sponsor

The investigator undertakes before the study begins:
- to provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s),
- to send (if appropriate), a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible in English) will be collected during the course of the study (at least, members involved in the participants' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

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17. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the OA progression or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and OA progression. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Administrative structure of the study and responsibilities of the investigators

Organisation of the study

Sponsor: UMC Utrecht
Participating centers and principal investigators:

- UMC Utrecht, Netherlands; dr. W.E. van Spil
- Leiden University Medical Center, Netherlands; Prof. dr. G. Kloppenburg
- SERGAS, la Coruna, Spain; dr. F. Blanco
- APHP, Paris, France; Prof. dr. F. Berenbaum
- Diakonhjemmet Hospital AS, Oslo, Norway; dr. I. Haugen

Organisation of the participating centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse…) and any other person involved in the study for this centre (cardiologist, pharmacist,…) must figure in the "Delegation log".

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the centre.

The CVs of all members of the team involved in the study (if possible in English) will be collected during the course of the study (at least, members involved in the participants' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

Documentation of the participating center supplied to the sponsor

The investigator undertakes before the study begins:

- to provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s),
- to provide any other document required by local regulation, and to translate the patient information and consent form and SOPs if needed.
- to send (if appropriate), a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

Appendix 3: Standard Operating Procedures

1. Acquisition radiography
   - 1.1 Knee semi-flexed Posterior Anterior (PA) View
   - 1.2 Hand PA view
2. Acquisition Magnetic Resonance Imaging (MRI)
   - 2.1 quantitative and semi-quantitative MRI of index knee
   - 2.2 T2 MRI of index knee
3. Acquisition computed tomography (CT)
   - 3.1 Quantitative CT of index knee and whole Body Low Dose CT
4. Reading radiographs
   - 4.1 Knee semi-flexed PA view: K&L grade, Altman score, KIDA
   - 4.2 Hand PA view: K&L grade, Altman score, Verbruggen score.
   - 4.3 2D shape analysis of index knee
   - 4.4 subchondral bone trabecular structure of index knee
5. Reading MRI
   - 5.1 semi-quantitative MRI; MOAKS
   - 5.2 quantitative MRI; cartilage volume, thickness,
   - 5.3 T2 MRI
   - 5.5 3 D shape analysis on knee MRI
6. Reading CT
   - 6.1 subchondral bone on knee quantitative CT
   - 6.2 3D shape analysis on knee quantitative CT
   - 6.3 Disc degeneration, OA of Facet joints, hips, Acromioclavicular joints, and glenohumeral joints on whole body low dose CT
7. XNAT/ TranSMART platform
8. HandScan measurements
9. Functional tests
   - 9.1 Motion analysis
   - 9.2 Performance based test
10. Biomarkers
    - 10.1 collection of biosamples: blood and urine
    - 10.2 processing of biosamples: blood and urine
    - 10.3 storage, tracking and distribution of samples at clinical centres
    - 10.4 logging and storage of Approach samples at testing sites
11. Physical examination

Presented in the separated document, Approach Standard Operating procedures

SOP 1.1: Acquisition Knee radiography; knee semi-flexed Posterior Anterior view

V1.0 d.d. 29-01-2016

Aim

To determine the severity of osteoarthritis of the knee, based on joint space narrowing, subchondral sclerosis and osteophytes. This image acquisition will also be used for determination of subchondral bone texture parameters.

Duration of the procedure for the patient

Acquisition of PA radiographs of both knees will take 10-15 minutes.

Preparation and prerequisites

Please follow standard radiation protection practices. Appropriate collimation of the x-ray beam should minimize radiation dose to the patient. Please adhere to institutional policies and procedures for shielding.

- Digital image header should include the patient study identifier not the patient's name or date of birth.
- Explain the examination procedure to the patient
- Do not use any filters
- Place the positioning aid in front of the bucky (see figure below).
- Place the bone density standard against the bucky next to the knee joint (see figure below).

Acquisition

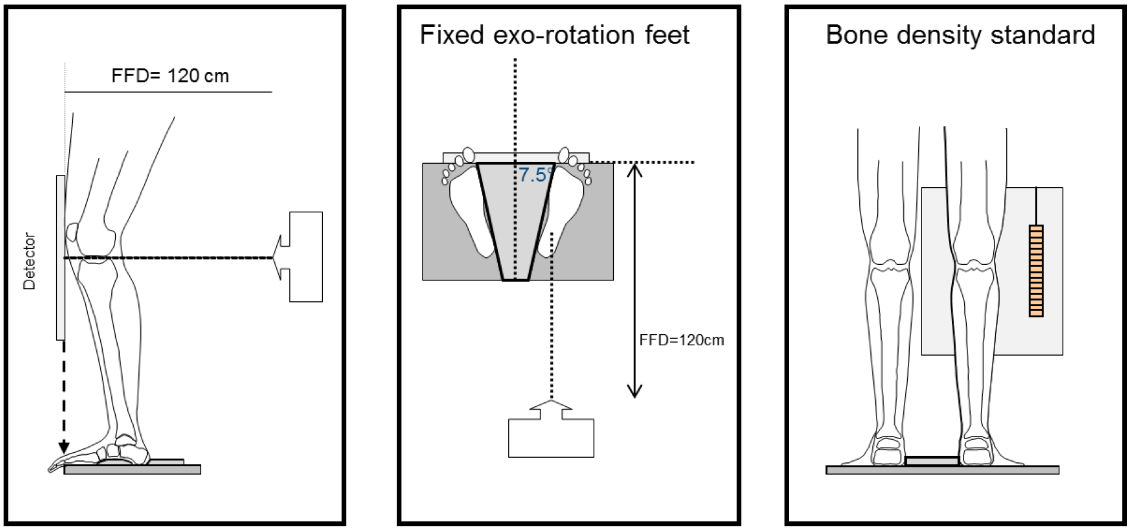
Positioning the patient

Position the patient in a standing upright position, on the positioning aid facing the bucky.
Both feet are fixed in external rotation by pressing the inner aspects of the foot and heel against the V-shaped support on the base of the positioning aid.
Center the knee on the image and center the beam on the knee. Be sure that the bone density standard is visible on the image.
The great toes of both feet are placed over the positioning aid, MTP joint right below the detector
Both knees are flexed until they touch the bucky. This fixes the angulation of the tibias.
Both thighs are also pressed directly against the bucky to fix the angulation of the femurs.
Gently guide the patient forward with your hand in the small of the back to ensure firm contact of both thighs with the bucky.
Body weight is distributed equally between the two legs

Positioning the X-ray beam

- X-ray beam is horizontal, parallel with the floor, perpendicular to the joint (halfway distance between lower side of the patella and the upper side of the tibia (tuberositas tibiae)
- Collimate to the size of the image. Make sure the bone density standard is included in the image.
- Place a R or L marker close to the knee, but where it will not obscure the knee anatomy.
- Expose each knee separately.

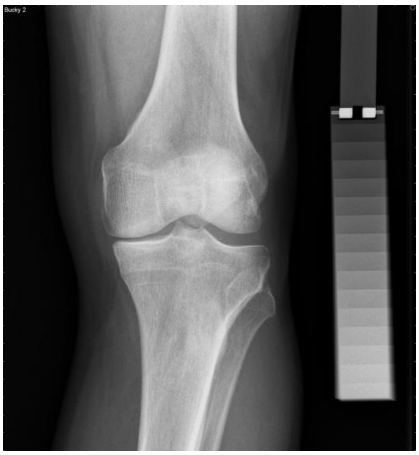
Figure patient and beam positioning



Exposure Technique:

Imaging System	Bucky	recommended
Focus-Detector Distance	120 cm	required
mAs	Dependent on screen system	
kVp Range	55 kVp	recommended
Focal Spot	Small	required
Raster/ grid	NO	
Filter	NO	
Beam angle	Horizontal, parallel to floor	required
Other	Use right/ left marker	required

Example of radiograph



Criteria of good quality knee radiographs

- Each knee is exposed separately.
- Complete coverage of the knee anatomy, this includes the femoral and tibial metaphyses as well as the proximal fibula.
- Optimum exposure to visualize the medial and lateral sides of the knee joint, including bone margins, and soft tissue should be clearly visible without the use of a high intensity light.
- The joint space must be open.
- Medial tibial plateau should be flat (horizontal).
- The knee must appear on the middle of the image.
- The bone density standard has to be completely visible on the image.
- The applicable left/right marker must be on the image.
- The image should not be underexposed or overexposed

SOP 1.2: acquisition Hand radiography; Posterior Anterior view

V1.0 d.d. 29-01-2016

Aim
To determine severity of hand osteoarthritis as confounding factor for knee osteoarthritis parameters in the APPROACH cohort.

Duration of the procedure for the patient
Acquisition of hand radiographs will take 5 minutes.

Preparation and prerequisites

Please follow standard radiation protection practices. Appropriate collimation of the x-ray beam and use of a lead apron to shield the gonads should minimize radiation dose to the patient. Please adhere to institutional policies and procedures for shielding.

- Digital image header should include the patient study identifier not the patient's name or date of birth.
- Explain the examination procedure to the patient
- Do not use any filters

Acquisition

Positioning the patient

- Remove jewelry where possible
- Patient must be seated in front of the imaging table with the entire fore-arm including elbows resting on the X-ray table, with the palm of the hand and wrist relaxed on the detector.
- Fingers extended and slightly separated. Fingers should not be strained far apart.
- Hand and wrist flat and relaxed on the detector (and cassette/receptor) to avoid joint magnification.
- Align 2nd metacarpal in a straight line with the radius (180 degrees).

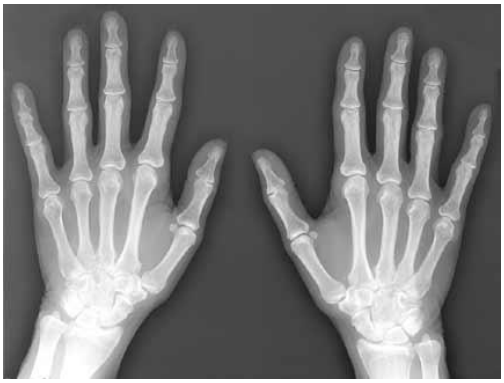
Positioning the X-ray beam

- Beam centering and angulation: centered in the middle of both hands, perpendicular to the plane of the receptor (bucky; Fig. 1).
- Collimate to the size of the image, wrist included.
- Focus detector distance of 100 cm
- Place a R or L marker close to the hand, but where it will not obscure the hand anatomy.
- Expose both hands together.

Exposure Technique:

Imaging System	Bucky/ table	recommended
Focus-detector Distance	100 cm	required
Focal Spot	Small	required
mAs	2,5 mAs	required
kVp Range	46kV	required
Other	Use right/ left marker	required

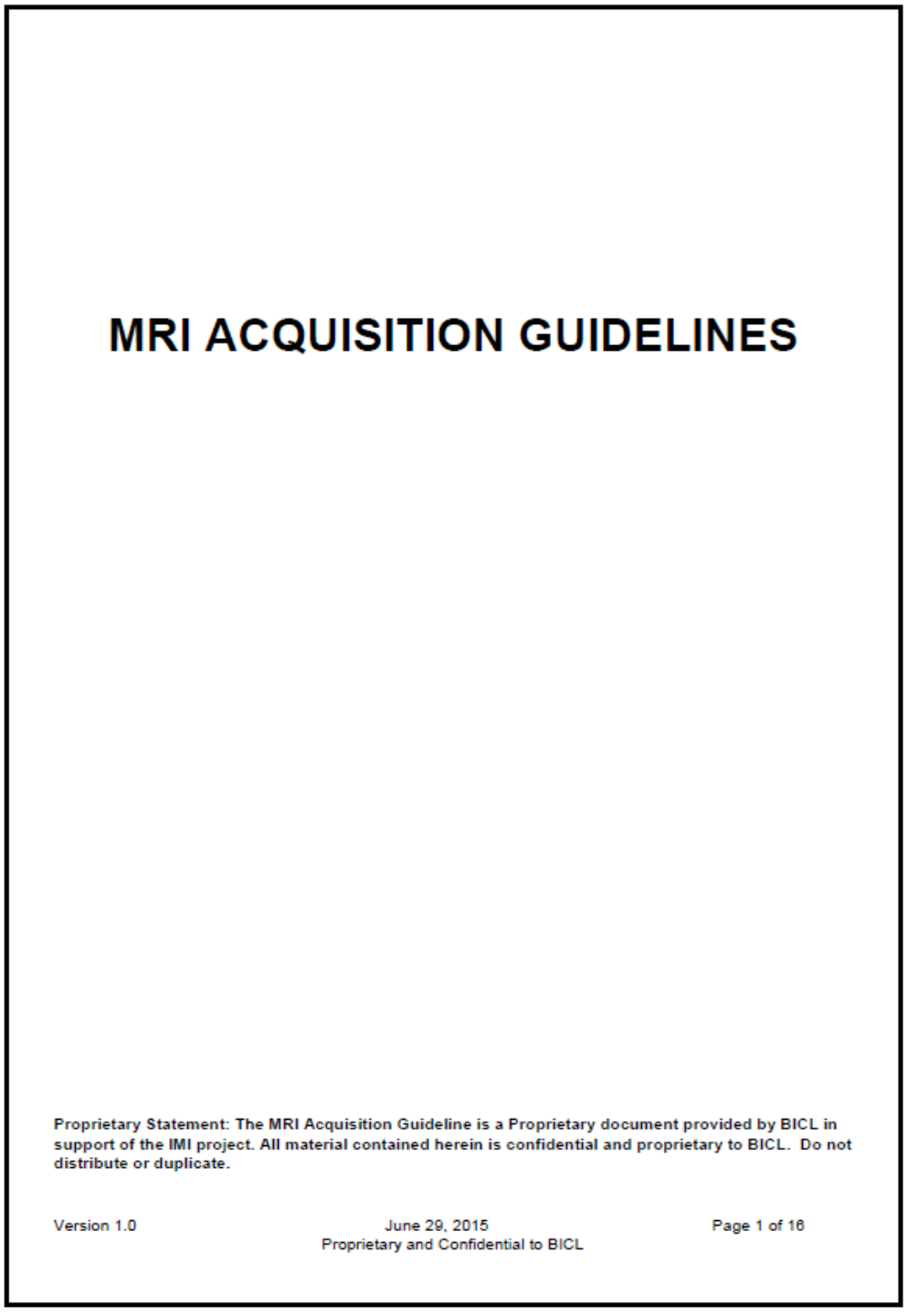
Figure Hand positioning



Criteria of good quality of hand radiographs

- Complete coverage of the hand anatomy, this includes the wrist.
- The joint space of PIP and DIP joints must be open.
- The applicable left/right marker must be on the image.
- The image should not be underexposed or overexposed.

SOP 2.1: acquisition knee quantitative and semi-quantitative MRI



MRI ACQUISITION GUIDELINES

Proprietary Statement: The MRI Acquisition Guideline is a Proprietary document provided by BICL in support of the IMI project. All material contained herein is confidential and proprietary to BICL. Do not distribute or duplicate.

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Introduction

Boston Imaging Core Lab, LLC has developed the following acquisition guidelines for standardization of the study MRI components across radiology centers participating in this clinical research trial.

All MRI for this study should be acquired in **strict adherence to the study protocol and guidelines** provided. If there are any **deviations** from these parameters please provide **explanatory comments on the Image Transmittal Form** (forms supplied by BICL).

- Please ensure the **blinding of all confidential patient/site information** on all images.
- Images sent to BICL shall be **clear of any markings, writings or annotations**.
- **All imaging data will be archived at BICL** as required by regulatory agencies.

SUBMISSION OF IMAGES

Digital Image Transfer
○ All MRI must be in uncompressed DICOM format
○ Images should remain digitally archived at the site until BICL has provided image quality feedback.
○ Submitted MRI should be devoid of any marks or annotations.
○ All confidential patient information must be blinded.

For inquiries regarding these guidelines, please contact:

frank.roemer@bicl.org or ali.guermazi@bicl.org

THANK YOU FOR YOUR PARTICIPATION AND COOPERATION IN THIS CLINICAL STUDY.

GENERAL RECOMMENDATIONS

1. The sites should confirm upfront that NO change in the hardware (scanner, coil, etc.) or software will be necessary during the course of the study.
2. The site should be trained and monitor an adequate MR imaging acquisition protocol (including MRI sequences dedicated to cartilage morphometry).
3. The central readers should receive 2-5 volunteer scans from each site and approve the acquisition protocol dedicated to cartilage morphometry BEFORE the site starts to recruit participants for the trial.
4. The site must make sure that the baseline scans adhere to the specified acquisition protocol as well as that full anatomical coverage, appropriate orientation, and lack of artefacts is provided.
5. Once the baseline scans are acquired, the site must make sure that neither the scanner, not the coil, nor the acquisition parameters (TR, TE, FA, spatial resolution) are ever changed between baseline and follow-up, and that all acquisitions provide full anatomical coverage, appropriate orientation, and lack of artefacts during the study.

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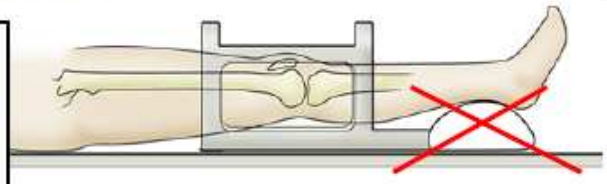
MRI Acquisition Guidelines

PATIENT CONDITIONS

6. Insure there is no contraindication to perform the knee MRI.
7. The patient should be relaxed and should not have performed athletic exercise (i.e. jogging) during the past 3 hours.
8. Ask patient to empty bladder prior to exam, to avoid motion artifacts during image acquisition.
9. Inform the patient that it is critical that she/he does not move the knee at all during image acquisition.

Scanner type	1.5 – 3.0 Tesla
Patient orientation	Supine
Scout view	Axial, sagittal and coronal scout to orient double oblique coronal images
Slice orientation of double oblique coronal images	Axial scout: Orient double oblique coronal acquisition so that the posterior ends of the femoral condyles are WITHIN ONE (coronal) plane Sagittal scout: Orient double oblique coronal acquisition so that the images are acquired parallel to the long axis of femoral shaft
Slice orientation of double oblique sagittal images	Axial scout: Orient sagittal acquisitions perpendicular to the double oblique coronal acquisition Coronal scout: Orient sagittal acquisition perpendicular to the tibial plateaus
Slice orientation of axial images	Sagittal scout: orient axial parallel to the tibial plateaus and scan the region 2 cm below the tibial plateaus to superior tip of the patella
Coil	Knee coil
Knee positioning	- rotate leg for examination, so that the toes and patella face upward. Avoid strong external rotation of the leg (this may be different from standard clinical exam) and make sure the patient is comfortable. - to obtain some degree of flexion of the knee, place back, buttocks and heel of patient directly on the scanner table pads, without elevating them above this level. (see Figure below) - elevate knee by putting cushions below it so that that the center of the knee is placed in the center of the coil. **Avoid scanning the knee in a fully extended or even hyperextended position**, as this affects the region of interest at the femur in coronal acquisitions. - tightly and comfortably pad within the coil on ALL sides using cushions
Scan time	- < 45 min per knee

Please do not use cushions under the heel, this will extend the knee. For some knee flexion, you may use small cushions under the knee. Also use gentle tape if involuntary movement of the patient.



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The table below shows **strongly preferred** parameters. Please use parameters as close to these as possible. Once these values have been selected, they should remain consistent throughout this study for all patients recruited and images in the same clinical site.

Type of MR sequence	Anatomical Orientation	Slice thickness	Acquisition Image matrix	Approximate Image time (min)
Target knee:				
MP Localizer	3 plane	5 mm	256	1 min
1. PD/IW TSE or FSE FS (for BICL SQ analyses)	Double oblique sagittal	3.0 mm	256 x 256	5 min
2. PD/IW TSE or FSE FS (for BICL SQ analyses)	Axial	3.0 mm	256 x 256	3.5 min
3. PD/IW TSE or FSE FS (for BICL SQ analyses)	Double oblique coronal	3.0 mm	256 x 256	3 min
4. T1W SE (for BICL SQ analyses)	Coronal	3.0 mm	256 x 256	4 min
5. T1W 3D SPGR/FLASH/FFE WE or FS (for Chondrometrics morphmetric analyses)	Double oblique sagittal	1.5 mm	512 x 512	10-15 min

PD = Proton Density, IW = Intermediate Weighted, TSE = Turbo Spin Echo, FSE = Fast Spin Echo, SE = Spin Echo, FS = Fat suppressed/saturated, WE = Water Excited, SPGR = SPoiled GRadient echo, FLASH = Fast Low Angle SHot, FFE = Fast Field Echo

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ADDITIONAL MRI PARAMETER DETAILS FOR SIEMENS:

2D IW TSE: (apply to axial, coronal and sagittal intermediate-weighted (IW) MR sequences)

- 3600-5000/30-40 (TR msec/TE msec)
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- Echo train=8
- 1-2 excitation (NEX)
- Slice thickness=3 mm
- Spacing=no gap (0.3 mm gap)
- No phase wrap (NP)
- Frequency-selective fat suppression

2D T1 SE: (apply to coronal MR sequence)

- 360-500/12-15 (TR msec/TE msec)
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- 1-2 excitation (NEX)
- Slice thickness=3 mm
- Spacing=no gap (or 0.3 mm interslice gap)
- No phase wrap (NP)
- No fat suppression

3D T1 FLASH: (apply to sagittal MR sequence)

- 17/7 (TR msec/TE msec)
- Flip angle=around 12° at 3T and 15° at 1.5T
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- 1 excitation (NEX)
- In-plane resolution=0.3125 mm x 0.3125 mm
- Slice thickness=1.5 mm
- Spacing=no gap, no overlap
- No phase wrap (NP)
- Frequency-selective fat suppression or water excitation

Make sure the total scanning time (Localizer – last MRI sequence) is kept within 40 min per knee.

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ADDITIONAL MRI PARAMETER DETAILS FOR GENERAL ELECTRIC:

2D IW FSE: (apply to axial, coronal and sagittal intermediate-weighted (IW) MR sequences)

- 3600-5000/30-40 (TR msec/TE msec)
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- Echo train=8
- 1-2 excitation (NEX)
- Slice thickness=3 mm
- Spacing=no gap (0.3 mm gap)
- No phase wrap (NP)
- frequency-selective fat suppression

2D T1 SE: (apply to coronal MR sequence)

- 360-500/12-15 (TR msec/TE msec)
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- 1-2 excitation (NEX)
- Slice thickness=3 mm
- Spacing=no gap (or 0.3 mm interslice gap)
- No phase wrap (NP)
- No fat suppression

3D T1 SPGR: (apply to sagittal MR sequence)

- 17/7 (TR msec/TE msec)
- Flip angle=around 12° at 3T and 15° at 1.5T
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- 1 excitation (NEX)
- In-plane resolution=0.3125 mm x 0.3125 mm
- Slice thickness=1.5 mm
- Spacing=no gap, no overlap
- No phase wrap (NP)
- Frequency-selective fat suppression or water excitation

Make sure the total scanning time (Localizer – last MRI sequence) is kept within 40 min per knee.

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ADDITIONAL MRI PARAMETER DETAILS FOR PHILIPS:

2D IW TSE: (apply to axial, coronal and sagittal intermediate-weighted (IW) MR sequences)

- 3600-5000/30-40 (TR msec/TE msec)
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- Echo train=8
- 1-2 excitation (NEX)
- Slice thickness=3 mm
- Spacing=no gap (0.3 mm gap)
- No phase wrap (NP)
- frequency-selective fat suppression

2D T1 SE: (apply to coronal MR sequence)

- 360-500/12-15 (TR msec/TE msec)
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- 1-2 excitation (NEX)
- Slice thickness=3 mm
- Spacing=no gap (or 0.3 mm interslice gap)
- No phase wrap (NP)
- No fat suppression

3D T1 FFE: (apply to sagittal MR sequence)

- 17/7 (TR msec/TE msec)
- Flip angle=around 12° at 3T and 15° at 1.5T
- 14-18 cm field of view (FOV), please keep the FOV as close as possible to 14 cm
- 1 excitation (NEX)
- In-plane resolution=0.3125 mm x 0.3125 mm
- Slice thickness=1.5 mm
- Spacing=no gap, no overlap
- No phase wrap (NP)
- Frequency-selective fat suppression or water excitation

Make sure the total scanning time (Localizer – last MRI sequence) is kept within 40 min per knee.

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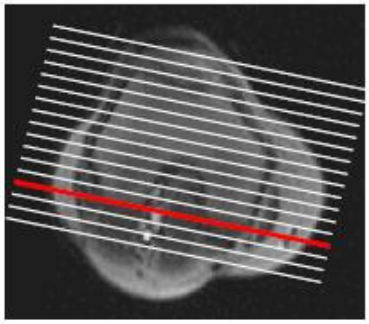
SCOUT VIEW AND SLICE ORIENTATION (double oblique coronals):

The double oblique coronal images should be aligned with the posterior ends of the femoral condyles as shown below making use of the axial localizer image.

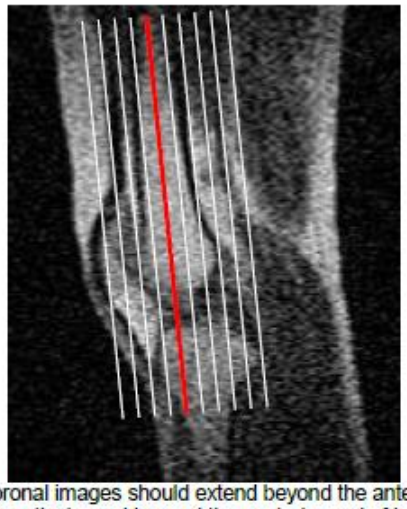
Please make sure the axial scout view shows the most posterior aspect of the femoral condyles.

Also, the double oblique coronal images should extend beyond the posterior end of the femoral condyles posteriorly, to ensure full anatomical coverage.



The double oblique coronal images should be aligned parallel to the shaft (diaphysis) of the femur, making use of the sagittal localizer image.

Please make sure the sagittal scout view shows a relevant aspect of the femoral shaft.



Also, the double oblique coronal images should extend beyond the anterior and posterior rims of the medial and lateral tibia, respectively, and beyond the posterior end of both femoral condyles.

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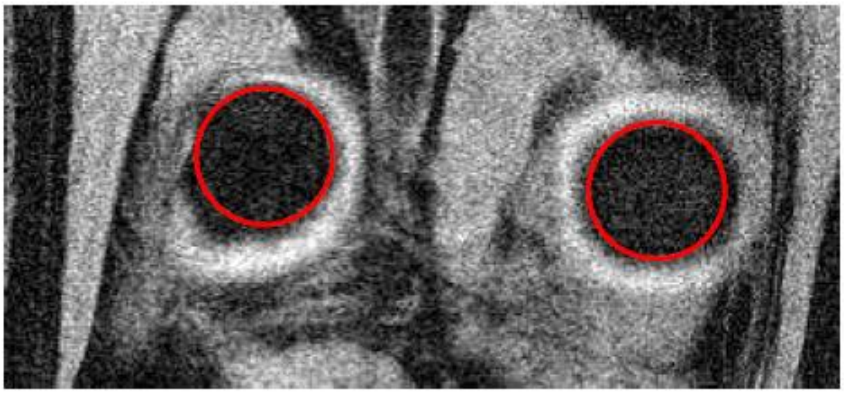
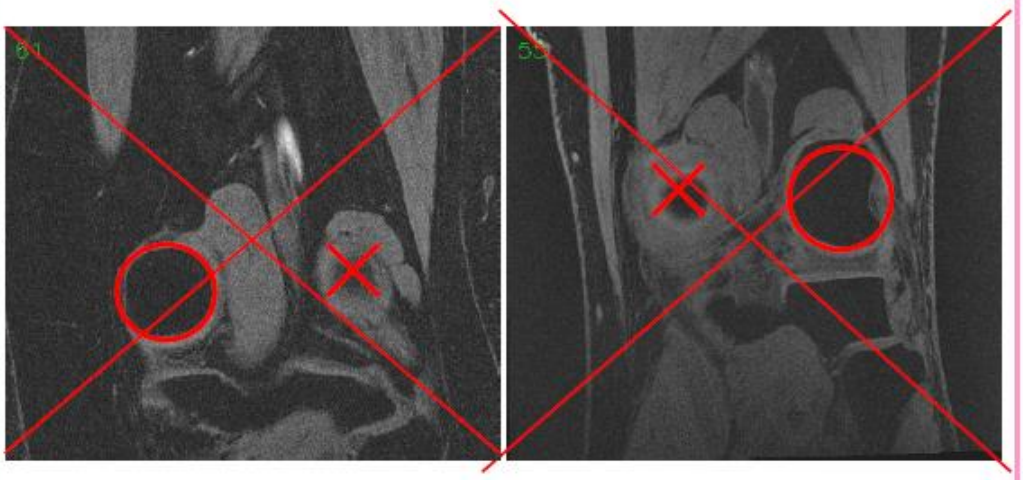
EXAMPLE OF WELL ALIGNED DOUBLE OBLIQUE CORONAL ACQUISITION:

The posterior ends of the medial and lateral femoral condyle are in the same slice and should have approximately the same size in the double oblique coronal images.



Please note that: - a deviation by 1 slice is acceptable;
- a deviation by 2 slices is borderline;
- a deviation of > 2 slices the scan should be repeated

EXAMPLE OF WRONGLY ACQUIRED (MALROTATED) DOUBLE OBLIQUE CORONAL ACQUISITIONS:



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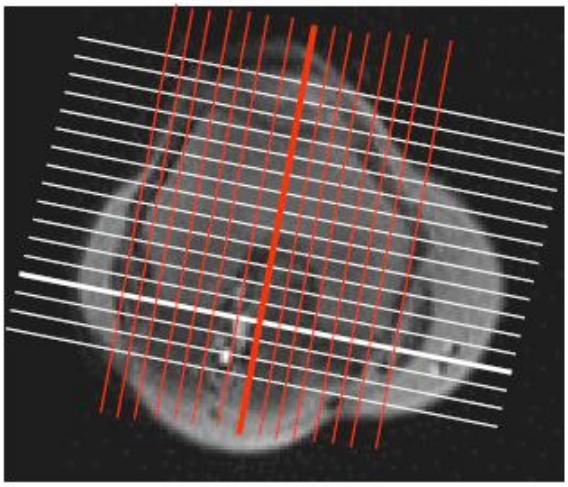
SCOUT VIEW AND SLICE ORIENTATION (double oblique sagittals):

The double oblique sagittal images (red in Figure below) should be aligned perpendicular to the double oblique coronal images, using axial localizer image.

Please make sure the axial scout view shows the most posterior aspect of the femoral condyles.

Also, the double oblique sagittal images should extend beyond the internal and external edges of the femoral condyles to ensure full anatomical coverage.



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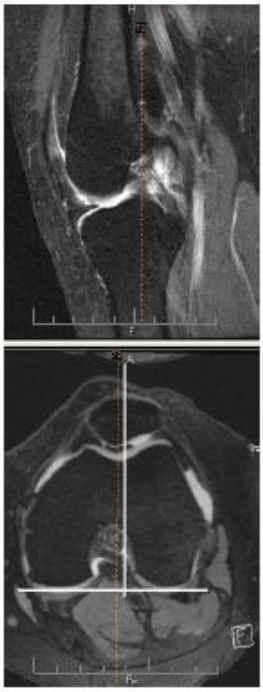
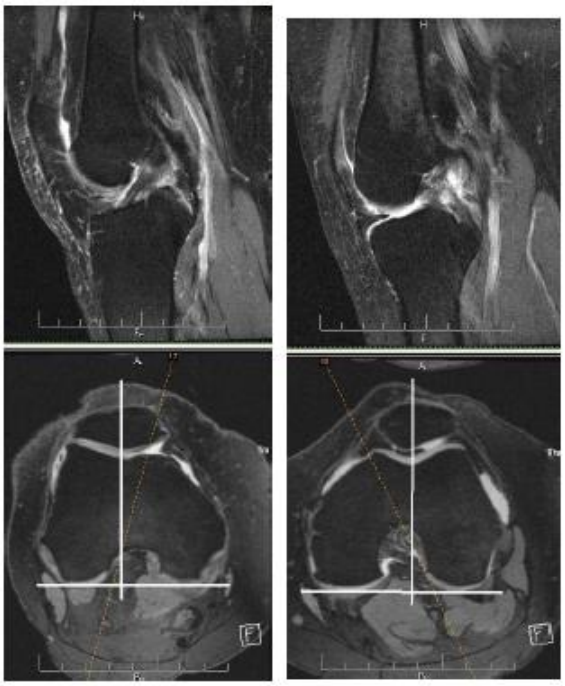
EXAMPLE OF CORRECTLY AND WRONGLY ACQUIRED SAGITTAL ACQUISITIONS:



This is a perfect example of a well-executed sagittal MRI sequence. The sagittal acquisition is perpendicular to the posterior ends of the femoral condyles.



These are 2 bad examples of sagittal MRI sequences. The sagittal acquisition is not perpendicular to the posterior ends of the femoral condyles. As a result, the anterior aspect of the medial femoral condyle and posterior aspect of lateral femoral condyle are represented in one same image.

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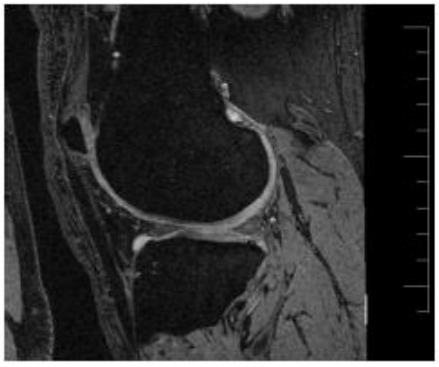
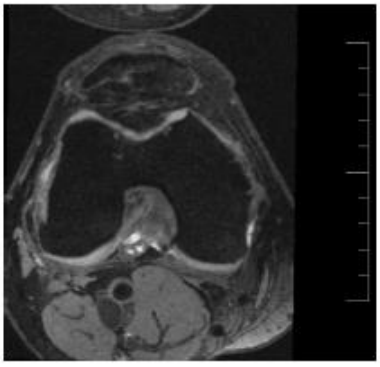
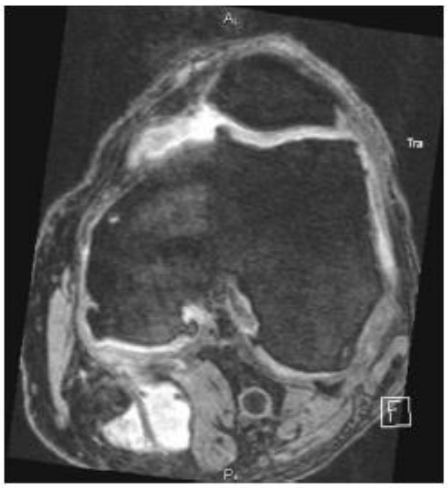
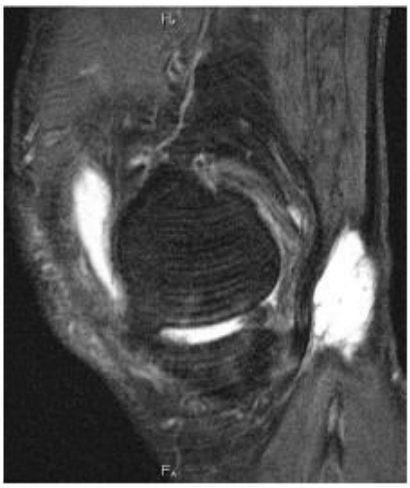
EXAMPLE OF OTHER ARTIFACTS:





These are examples of fold-over artifact in SPGR sagittal and axial planes





These are examples of motion artifact in intermediate-weighted axial and sagittal planes.

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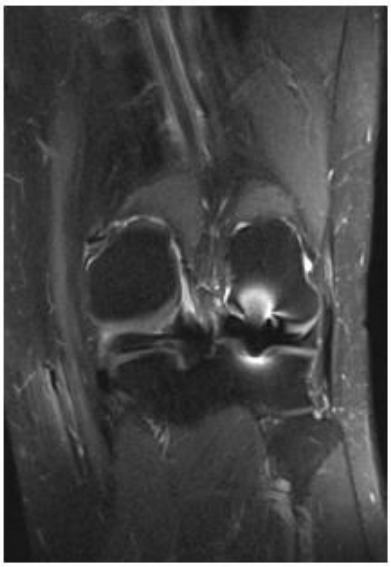


This is an example of metallic artifact on coronal intermediated-weighted coronal MRI

Quality Control of image data after acquisition

1. Please ALWAYS check the data quality before sending the data. The central readers will perform a rigorous quality check on their end when data comes in.
2. Check that the orientation of the scans is satisfactory
3. Check that anatomical coverage is complete (first and last image MUST be OUTSIDE the bone and cartilage plate
4. Check that fat suppression is satisfactory (bone must be dark, bone cartilage interface should be clearly visible without a low signal band appearing below the bone interface)
5. Check that no motion artifacts are present (structures will be blurry or appear at two different locations in the image)
6. Check that no aliasing artifact is present. If aliasing occurs, parts of the anatomical structures will appear at the wrong locations (the very lateral ones on the medial side, or anterior ones in the posterior slices). This problem can be avoided by increasing phase- or slice oversampling. If this occurs, please contact us or the local radiologist to discuss the issue.
7. Check that no "stripes" are present in the images. If this occurs please check with the local radiology facility whether the scanner needs to be serviced.
8. After optimal protocol imaging is obtained, all parameters should remain constant for subsequent patients recruited in the same clinical site.

Storage of image data

1. Please always keep a copy of the original DICOM data at your site.
2. Anonymize all data in a way that no "real" patient name appears in the DICOM header. Images should not have any markings, annotations or confidential patient information.
3. Imaging data (including raw/original data if possible) should remain digitally archived at the site.

Copyright Page

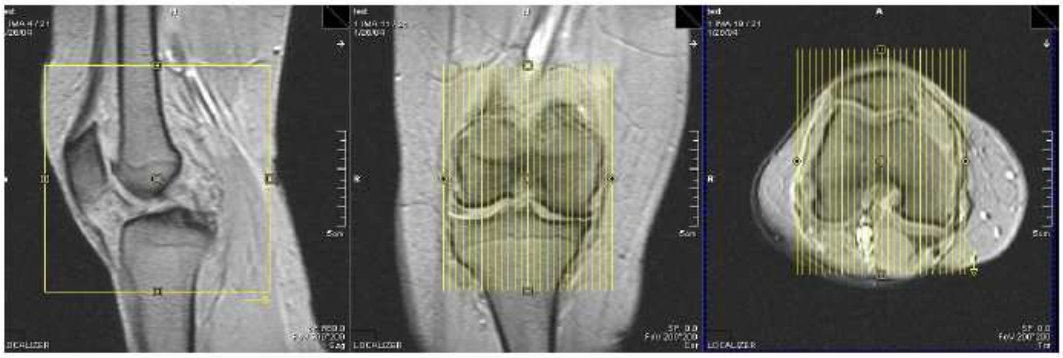
SOP 2.2: acquisition knee T2 MRI

The **Sagittal T2 mapping sequence** is a small FOV exam intended to cover both the patellar and femoral / tibial cartilage only. Using this acquisition, the cartilage morphology and condition, the anterior and posterior meniscal horns, the cruciate ligaments, anterior / posterior femoral and tibial osteophytes, superior / inferior patellar osteophytes, as well as subchondral bone cysts and attrition may be assessed.

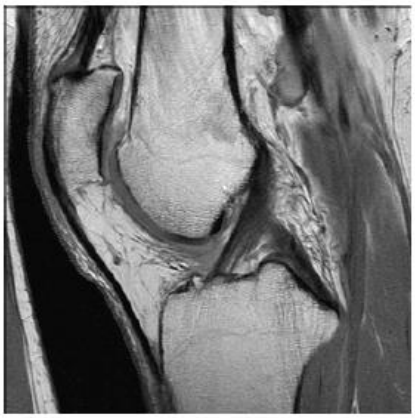
This Sagittal scan is a single oblique acquisition, oriented such that the sagittal slices are perpendicular to a line tangential to the posterior surfaces of the femoral condyles. The easiest manner to create this scan prescription is to copy the center of the slice locations from the 3D DESS image and move (translate) the imaging FOV to minimize the impact of any phase wrap. Check in both the Sagittal and Coronal localizer planes!

If this exam needs to be repeated, the scan prescription instructions follow. First, find the axial localizer slice with the largest cross-section through the condyles and the mid-joint sagittal and coronal localizer. The correct oblique angle is identified by first rotating and translating the imaging FOV such it is aligned with and touches both of the posterior condylar surfaces (appears to be an oblique coronal acquisition). Then, without changing the angulation, perform a right mouse click and select make slices orthogonal (now appears to be sagittal oblique acquisition). Finally, center the imaging FOV (translate only!!) over the knee in the axial plane. Now check the imaging FOV such that it is centered in the coronal and sagittal planes, and adjust if necessary.

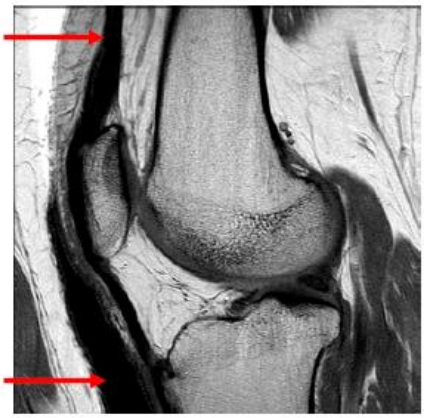
With large knees, phase aliasing artifact will probably occur with this 120mm FOV acquisition. Adjust the imaging locations such that only regions of subcutaneous fat overlap.



Scan prescription for Sagittal T2 map



Acquisition on a small knee



Allowed phase wrap for this acquisition would occur only in the subcutaneous fat regions as shown by the red arrows

Final OAI knee MRI protocol acquisition parameters (Peterfy, Osteoarthritis and Cartilage, 2008)	
Scan	SAG 2D MESE
Plane	Sagittal
FS	No
Matrix (phase)	269
Matrix (frequency)	384
No. of slices	21
FOV (mm)	120
Slice thickness/gap (mm/mm)	3/0.5
Flip angle (°)	n/a
TE/TR (ms/ms)	10,20,30,40,50,60,70/2700
Bandwidth (Hz/pixel)	250
Chemical shift (pixels)	1.8
No. excitations averaged	1
ETL	1
Phase encode axis	A/P
Distance factor (%)	16
Phase oversampling	0
Slice oversampling	0
Phase resolution	70
Phase partial Fourier (8/8=1)	0.875
Readout partial Fourier (8/8=1)	1
Slice partial Fourier (8/8=1)	0.75
X-resolution (mm)	0.313
Y-resolution (mm)	0.313

SOP 3.1: acquisition Knee Quantitative Computed Tomography (QCT) and Whole Body Low Dose Computed Tomography (WBLDCT)

Aim Knee QCT
To study the role of the (subchondral) bone in knee osteoarthritis using parameters including bone mineral density, anisotropy, inhomogeneity, variogram slope and entropy. To facilitate 3D shape analysis of the knee.

Aim WBLDCT
To determine the severity of osteoarthritis in the hip and spine. The interest in the current study is primarily knee OA. The information from WBLCDT will be used to correct for OA in large joints other than the knee, to prevent bias when studying biochemical marker levels in serum and urine. Furthermore, WBLDCT data will facilitate shape analysis of the hip.

Duration of the procedure for the patient
Acquisition and positioning of the patient will take approximately 10 minutes.

Preparation and prerequisites

Standard radiation protection practices can be followed with general institutional policies and procedures for shielding.

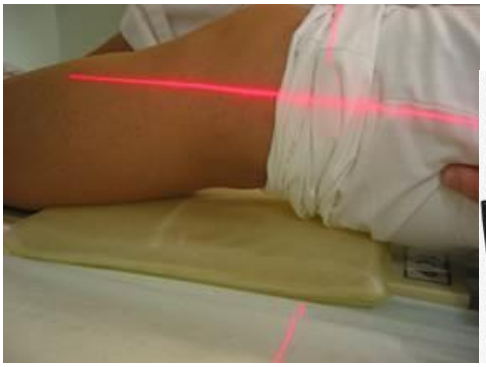
- Digital image header should include the patient study identifier and not the patient's name or date of birth.
- Explain the examination procedure to the patient.
- Confirm presence of BMD calibration phantom, gel bag and internal rotation wedge.

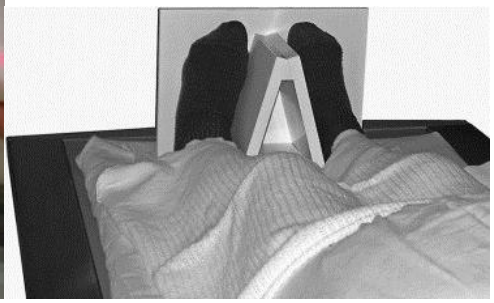
Patient positioning for Knee QCT and for WBLDCT

- Position the patient in a supine position on the CT-table.
- Both hands are placed flat on the CT-table next to the pelvis/legs.
- Both knees are as straight as possible.
- Index knee is on top of the BMD calibration phantom.
- If an air gap between BMD calibration phantom and knee is present use a gel bag to prevent any air gap between BMD calibration phantom and knee.
- Both feet are placed on a wedge ensuring 15 degree endo-rotation of the hip, with ankles in 90 degree flexion.

Scout

- Acquire scout of the whole body in antero-posterior direction.





Knee QCT

Both legs are scanned. Scanning length is 150mm, centered in z-direction on femoro-tibial articular space.

Scan Technique

Imaging System	GE Discovery 750 HD / Toshiba Acquilion one / Philips ICON	
Max dose for 70 kg adult	0.25 mSv	required
mAs	220	required
kV	120	required
Slice collimation	0.625mm or as close as possible	recommended
Pitch	0.8 or as close as possible	recommended
Rotation time	1 second	recommended

Reconstruction Technique Knee QCT

Please note: All reconstructions should of the knee QCT should use filtered back projection

Reconstruction 1 QCT

Center (x, z coordinates) of reconstruction 1 must include all bone of the index knee and the complete calibration phantom

Slice thickness	0.625 mm or as close as possible
Increment	0.3 mm or as close as possible
Kernel	Medium Kernel
FOV	190 mm

Reconstruction 2 QCT

Reconstruction 2 has a smaller FOV than reconstruction 1. It may not include the calibration phantom but must include all femur and tibia bones of the index knee

Slice thickness	0.625 mm or as close as possible
Increment	0.3 mm or as close as possible
Kernel	Medium Kernel
FOV	130 mm

Reconstruction 3 QCT

Reconstruction 3 should be identical to reconstruction 2, but a harder kernel should be used. Center of the reconstruction must be identical to reconstruction 2

Slice thickness	0.625 mm or as close as possible
Increment	0.3 mm or as close as possible
Kernel	High resolution Kernel
FOV	130 mm

Criteria of good quality knee QCT

- Adequate coverage of tibia and femur of the index knee
- Inclusion of the complete calibration phantom in Reconstruction 1
- No significant movement artifacts
- No metal artifacts (exclude all subjects with knee prostheses etc.)
- No air gap between leg and phantom (use gel bags if necessary)
- No streak artifacts caused by air gap or metal parts

WBLDCT

Top of the scan area is marked by the petrous bone. The bottom of the scan area should include the whole feet. Instruct patient to hold inspiration while scan is conducted.

Scan Technique WBLDCT

Imaging System	GE Discovery 750 HD / Toshiba Acquilion one / Philips ICON	
Max dose for 70 kg adult	3.0 mSv	required
mAs	Dependent of dose modulation, reference 15 mAs	
kV Peak	120 kV	recommended
Pitch	0.9	recommended
Rotation time	0.75	recommended
Field of View	Full FOV throughout scan	recommended

The above is based on acquisition using Philips IQON. For other vendors the protocol needs to be fine-tuned with a maximum dose of 3.0 mSv.

Reconstruction Technique WBLDCT

Reconstruction 1 WBLDCT

Should consist of axial slices covering the entire scan.

Plane	Axial	required
Reconstruction method	Iterative	recommended
Slice thickness	1 mm or as close as possible	required
Increment	1 mm or as close as possible	required
Kernel	Medium	recommended
FOV	Full FOV throughout scan	required

Reconstruction 2 WBLDCT – left shoulder

Should be centered on the center of the left humeral head and include humeral head and at least 2 cm of the left clavicula.

Plane	Axial	required
Reconstruction method	Iterative	recommended
Slice thickness	1 mm or as close as possible	required
Increment	1 mm or as close as possible	required
Kernel	Medium	recommended
FOV	10 cm (enlarge if needed to include humeral head and 2 cm of clavicula)	recommended

Reconstruction 3 WBLDCT – right shoulder
Should be centered on the center of the right humeral head and include humeral head and at least 2 cm of the right clavicula.

Plane	Axial	required
Reconstruction method	Iterative	recommended
Slice thickness	1 mm or as close as possible	required
Increment	1 mm or as close as possible	required
Kernel	Medium	recommended
FOV	10 cm (enlarge if needed to include humeral head and 2 cm of clavicula)	recommended

Reconstruction 4 WBLDCT – cervical spine
Should consist of axial slices of the full cervical spine (from petrous bone to spinal level T2).

Plane	Axial	required
Reconstruction method	Iterative	recommended
Slice thickness	1 mm or as close as possible	required
Increment	1 mm or as close as possible	required
Kernel	Medium	recommended
FOV	15 cm (enlarge if needed to include each vertebrae in whole)	recommended

Reconstruction 5 WBLDCT – thoracic spine
Should consist of axial slices of the full thoracic spine (spinal level C7 to spinal level L1).

Plane	Axial	required
Reconstruction method	Iterative	recommended
Slice thickness	1 mm or as close as possible	required
Increment	1 mm or as close as possible	required
Kernel	Medium	recommended
FOV	15 cm (enlarge if needed to include each vertebrae in whole)	recommended

Reconstruction 6 WBLDCT – lumbar spine
Should consist of axial slices of the full lumbar spine (spinal level T12 to os pubis).

Plane	Axial	required
Reconstruction method	Iterative	recommended
Slice thickness	1 mm or as close as possible	required
Increment	1 mm or as close as possible	required
Kernel	Medium	recommended
FOV	15 cm (enlarge if needed to include each vertebrae in whole)	recommended

Reconstruction 7 WBLDCT - hips
Should consist of axial slices of the pelvis and femurs. 25 cm scan length and lower boundary should be 2 cm below the bottom of the lesser trochanters.

Plane	Axial	required
Reconstruction method	Iterative	recommended
Slice thickness	1 mm or as close as possible	required
Increment	1 mm or as close as possible	required
Kernel	Medium	recommended
FOV	Full FOV	recommended

Reconstruction 8 WBLDCT –left hip
Should consist of axial slices of the left femur starting 2 com above femoral head. About 15 cm scan length and lower boundary should be 2 cm below the bottom of the lesser trochanters.

Plane	Axial	required
Reconstruction method	Filtered back projection	recommended
Slice thickness	1 mm or as close as possible	required
Increment	1 mm or as close as possible	required
Kernel	Medium	recommended
FOV	15 cm centered on left hip	recommended

Criteria of good quality WBLDCT

- Complete coverage of at least cervical, thoracic and lumbar spine, shoulders, pelvis, legs and feet.
- Full FOV throughout scan.
- Z-resolution of less than 1 mm
- No significant movement artefacts

SOP 7: APPROACH central data storage and transfer procedure; XNAT/ TranSMART platform

V 1.0 d.d. 08-05-2017

1. Background

The aim of the IMI APPROACH project is a better understanding of disease stratification and acceptance of a guideline to classify osteoarthritis patients. This will provide clear phenotypes directed protocols for disease modifying osteoarthritis drug trials enabling the targeting of subgroups with osteoarthritis that have uniform disease characteristics, thereby increasing the chances of success. Furthermore, one of the APPROACH consortium objectives is:

- Implement and establish a new, integrated and comprehensive database platform of existing data from partners that will be extended with newly collected longitudinal data, incorporating novel high quality biomarkers.

2. Central database platforms

As the central APPROACH database platform for storing and sharing clinical data, image assessment data, laboratory data, HandScan and motion analysis data (Table 1), the open-source tranSMART platform will be used. As the central APPROACH platform for sharing of MRI and X-ray images, the open source XNAT imaging software platform in combination with the CTP de-identification client will be used. Both central database platforms will be used to bring together the different data from the prospective APPROACH study. These systems are not the source systems of the data.

Table 1. Data types and central platforms

Data type	Source system	APPROACH platform
Clinical data	APPROACH eCRF	tranSMART
Image analysis data	Image analysis software	tranSMART
HandScan data	HandScan system	tranSMART
Motion analysis data	Poseidon system	tranSMART
Laboratory data • Biomarker data • Genomic marker data	Reader instrument software	tranSMART
MRI images	PACS* (DICOM)	TraIT XNAT
Radiographs	PACS* (DICOM)	TraIT XNAT
CT-scan images	PACS* (DICOM)	TraIT XNAT

* Picture Archiving and Communication System

In order to store the newly collected longitudinal data of the APPROACH study in the central database platforms, a process and infrastructure for uploading the (source) data files into the database platforms has been set up. This document describes the infrastructure and processes. The central tranSMART instance used for the APPROACH study is hosted at the University of Luxembourg and managed through the IMI eTRIKS project. The central XNAT instance for the APPROACH study is the TraIT XNAT instance and is managed via TraIT resources.

3. Data transfer processes

The data transfer processes, of the data types mentioned in Table 1, from the clinical sites to the central APPROACH tranSMART and XNAT systems are described in Figure 1.

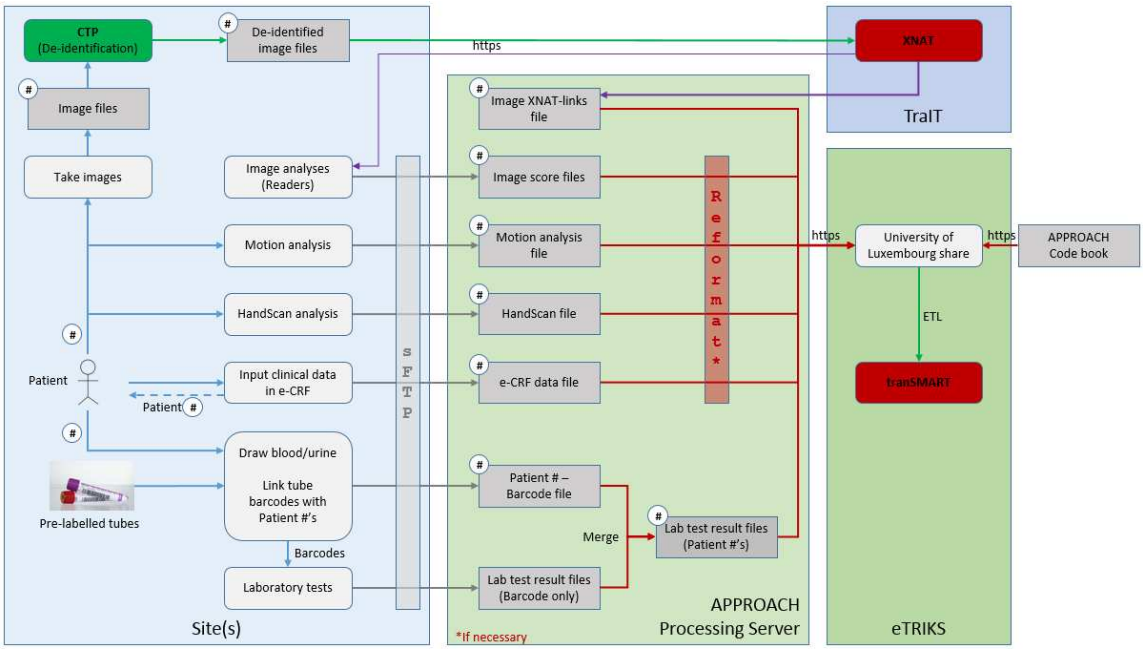


Figure 1. APPROACH study data transfers

tranSMART

Before being processed in the tranSMART ETL (Extraction, Transformation and Loading) step, the sites have to upload the data files to a processing server via sFTP. From there the data files either will be copied directly to the University of Luxembourg share (in case the format is directly suited for ETL into tranSMART) or they will be reformatted into a format suited for tranSMART ETL. The files need to be reformatted if they do not fulfil the requirements as mentioned in section 4 of this SOP. The APPROACH project strives to only receive data files from the sites that are directly suited for copy into the University of Luxembourg share. Only data files without any personal or identifying data are allowed to be uploaded to the processing server. The (clinical) sites are responsible for this. The processing server is hosted by Vancis. A Lygature administrator is responsible for managing access to the processing server and will manage the reformatting of any data files, if applicable. Access will be controlled via a username password combination. Appointed users only will be able to view and upload data files via an sFTP client. Persons that need to process the files will get read, write, and execute rights. The administrator can grant or revoke these permissions. To ensure that only the appropriate persons have access to the processing server, once every quarter an overview listing the current access permissions of every APPROACH project member, will be sent to the APPROACH Work Package leads. Based on their feedback, access will be updated if necessary.
People that have processing rights, will be able to logon to the processing server and perform processing using the applications available on the server. However, the goal is to have a little processing as possible. The processing will be done on a copy of the uploaded data file and the processing steps are recorded in a log file that also will be stored on the processing server. Data files suited for tranSMART ETL will be copied to the University of Luxembourg share. The latter is being used by appointed eTRIKS personnel as the source location for performing the ETL (Extraction, Transformation and Loading) into tranSMART.

Linking of the data from different sources, is done via an *APPROACH patient number* (# in Figure 1 and 2) generated by the e-CRF. This *APPROACH patient number* is unique per patient and does not contain any personal information. This patient number needs to be present on every record of the data files generated.

Screening

A subset of patients invited to the screening visit will be enrolled in the APPROACH cohort. The enrolment will be decided using a machine learning model trained to predict which patients are likely to become fast osteoarthritis progressors. The prediction will be based on the clinical and radiographic data collected at the screening visit (e-CRF data and KIDA scores (1); see also section 6.1 of the clinical study protocol). The data from the screening visits at each clinical site will be uploaded to tranSMART. Periodically all new patient data (batches from all sites) will be analysed by the machine learning model. The data from a screening visit at each clinical site will be uploaded to tranSMART in batches. The processing server will check the data for completeness and pass the patients data to eTRIKS for tranSMART upload when both e-CRF data and KIDA scores are available. e-CRF data will be uploaded by Servier Data Management and the image Readers will upload the KIDA scores files to the processing server. The outcome of this analysis will be a ranking of patients ordered by a progression probability. The **ranking file** will be a CSV file containing the *APPROACH patient number*, rank and a set of descriptors from which the rank was derived from. The ranking data will be uploaded into tranSMART (2) and used to centrally decide the patients' enrolment in the APPROACH cohort (3). The *APPROACH patient numbers* of the patients that should be enrolled will be emailed to the investigators of the corresponding sites (4). The complete data flow in the screening stage is shown in Figure 2.

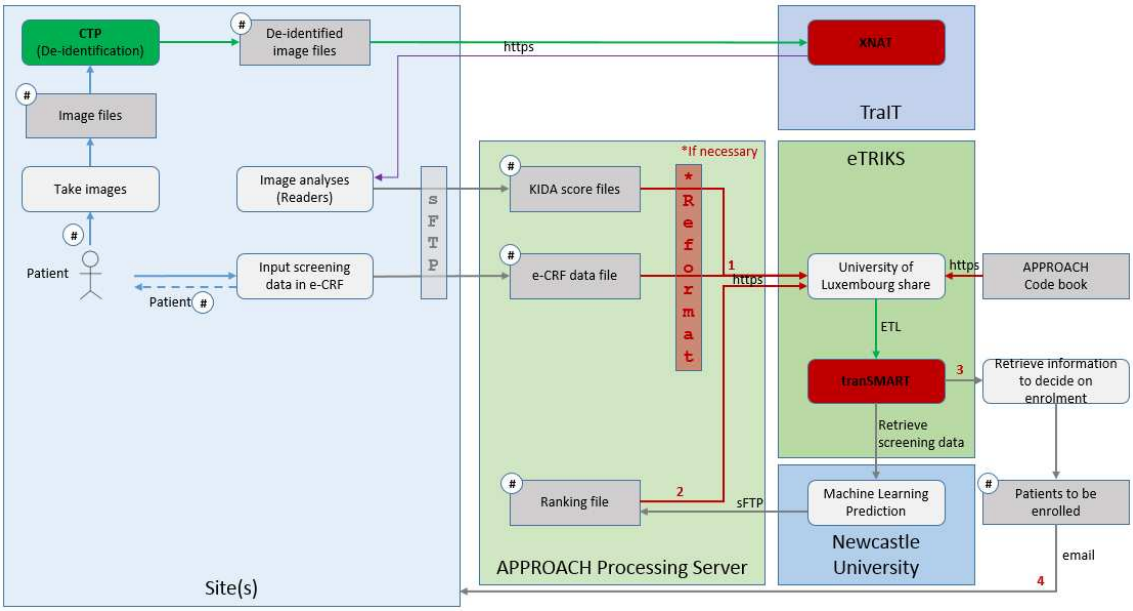


Figure 2. Data flow in the screening stage of the APPROACH study.

XNAT

The TraIT XNAT server, located in the Netherlands, will be used to centrally store the radiograph, CT and MRI images from the APPROACH study in DICOM format. Within the TraIT XNAT instance a protected APPROACH collection has been created, to which only appointed APPROACH people and Trait XNAT administrators will have access. Table 2 describes the XNAT APPROACH user roles.

Table 2. APPROACH collection TraIT XNAT access roles

User Role	Modules and Main Features
Owner	Full Access
Member	Full access except deleting
Collaborator	Only read access

The DICOM images will be uploaded to the central APPROACH XNAT instance using a locally installed CTP client. This CTP client de-identifies the image/DICOM files, by removing any identifying meta data in the DICOM file according to a "collection de-identification profile", which has to be configured and tested per site. Via the CTP client the APPROACH patient number, which is stored in the DICOM file as a comment, will be copied into the DICOM Patient ID field (this is to be configured in the de-identification profile file). Only appointed local site personnel is allowed to start the de-identification and upload into XNAT using CTP.
Through the so-called XNAT Gateway many viewer applications can interface with XNAT. For more information on these capabilities see http://xnat.bigr.nl/index.php/Xnat:Viewing. Viewing and downloading is only possible via username/password logon.

4. Data files for tranSMART upload

Data files for upload into tranSMART should be delimited text files (*e.g.* CSV). The first line of the file should contain the parameter names and should be consistent across the APPROACH study. The other lines contain the data separated by a delimiter (preferably a "|", but in any case it should be consistent). Furthermore, the data files should not contain the characters mentioned in the Table 3 and the data field length should not exceed 255 characters. All data files, except the laboratory result files, should contain the *APPROACH patient number* (as generated by the e-CRF) for each data record. The laboratory results files should contain the tube barcode on each data line. In a processing step these barcodes are amended with the *APPROACH patient numbers*. Furthermore, a data file is not allowed to contain any identifying data (*e.g.* name, social security number, full address, date of birth, etc.).

Table 3. Forbidden data file characters

Forbidden character	Proposed to replace by
Ø	OE
Å	AA
°	degr
µ	u
‘	*<depends>*
<superscript>	*<normal font>*
<subscript>	*<normal font>*

5. APPROACH codebook file

For the APPROACH study one codebook, describing all parameters determined in the APPROACH study, will be created. For the APPROACH tranSMART upload the codebook file should be a CSV file containing the columns listed in Table 4. All columns should be present, even if they are empty.

Table 4. APPROACH codebook parameter meta data

Column name	Description
Category 1	APPROACH main parameter category
Category 2	APPROACH parameter sub-category (optional)
Category 3	APPROACH parameter sub-sub-category (optional)
Parameter	Parameter name including time point/visit information
BaseParameter	Parameter name, time point independent
Visit number	Visit indicator (*e.g.* Screening, Inclusion, Month 6, Month 12, Month 24)
Short Description	Short description of the (Base)parameter
Values	The possible values the parameter is allowed to have, separated by ";"

6. File life cycle

A sustainability plan will be created as part of the APPROACH project deliverables, which describes how the APPROACH tranSMART and XNAT instances and data will be sustained.
The files uploaded to the remote desktop will remain on that share until 1 month after the APPROACH project has finished. After that the files will be deleted from the remote processing environment. The same holds true for the University of Luxembourg share.

7. tranSMART ETL

From the University of Luxembourg share, https://owncloud.lcsb.uni.lu/, eTRIKS representatives at the University of Luxembourg will take the files for ETL (Extraction, Transformation and Loading) into the APPROACH tranSMART instance, following the eTRIKS procedures for uploading into tranSMART (tranSMART ETL Guide.pdf). A high-level description of this is given in Figure 3. The column mapping and tooltips files will initially be created, based on the parameters file and re-used for consecutive data file uploads.

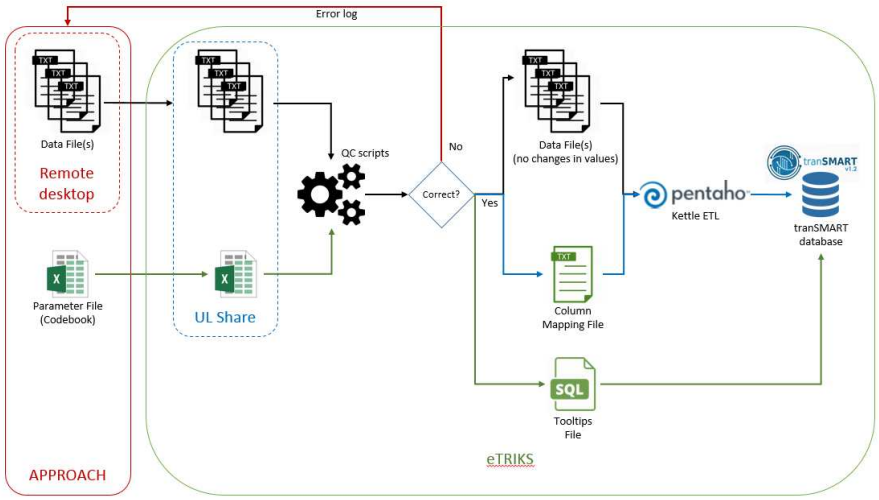


Figure 3. The APPROACH tranSMART ETL process

SOP 8: HandScan measurements

V1.0 d.d. 29-JAN-2016

Aim
To asses inflammation of hand and wrist joints at Inclusion and M024.

Duration of the procedure for the patient
A complete measurement run takes less than 3 minutes

Preparation and prerequisites
- The operator has to be certified by Hemics for using the HandScan
- Always operate according to the instructions in the Hemics HandScan User Manual.
- Remain present in the investigating room with the patient during the complete measurement procedure.
- During a measurement the device's lid has to be closed.

Acquisition
Log on to the user interface of the HandScan (username and password needed).
Before evaluation create a new patient identification or select the existing patient.

Patients
- Be sure that the patient does not wear any jewelry (including watches) on arms, wrists, and fingers, that can be easily removed. NOTE: Do not remove jewelry if force is needed, to prevent artificial changes in blood flow.
- Support the patient in the right comfortable and upright position
- Verify that the patient doesn't move during the measurement process.

Measurement protocol
- Ask the patient to put his/her hands in the appropriate positions inside the cuffs and on the hand rests. The hands should be positioned such that the thumbs and index finger touch the hand positioning wedge (see image below). Verify that the fingers are comfortably and equally spread within the illumination area.
- Click the button **New Measurement** and subsequently **Start Measurement**.
- Monitor the patient and the measurement progress.
- The measurement process stops automatically when it is completed. The "lasers active" indicator disappears.
- The device’s lid can now be opened. Instruct the patient to remove his/her hands from the scanner.
- NOTE: The hand rests must be cleaned after each measurement.

Analysis
- After a measurement the scanner automatically starts with phase 1 of the data analysis which may take about ten seconds.
- After you have completed a measurement, the software calculates the sizes and positions of the reference and joint ROIs automatically, and projects these on a reflection image in the **ROI Positioning** screen
- In case ROIs are not at the right place they have to be moved manually according to figure 3.
- Joints need to be excluded in case of e.g. a prosthesis, or jewelry is present on the reference position or joint ROI, using the exclusion button.
- From the **ROI Positioning** screen, click the **Start Analyze** button.

- The data analysis takes about 30 seconds to complete, after which the software automatically proceeds to the screen **View/Print Results**.
- Click the button **Approve Scan** to actually approve that a scan was performed technically correct.

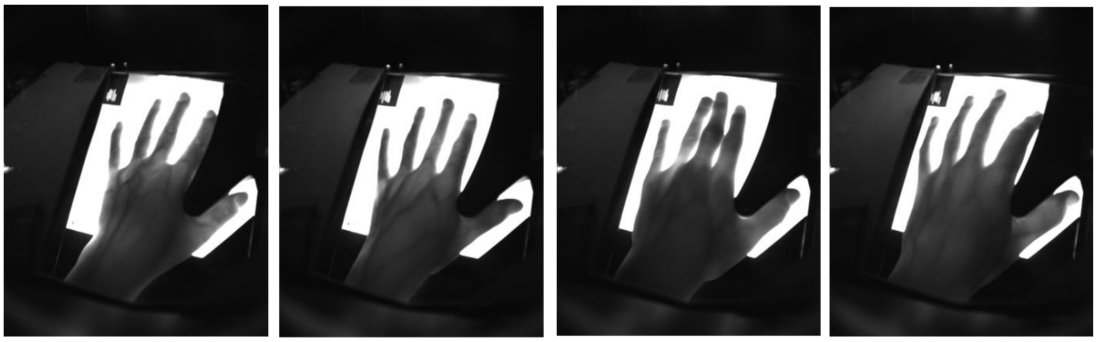
Quality check

- All relevant joint and reference positions have been illuminated (not very dark) and not over-illuminated (not completely white)
- ROIs are at the proper position
- No jewelry, prosthesis or other artifact at joint or reference ROI

Outcome parameters for database

Patient identification number	x-xxx		
Date of image	DD-MM-YYYY		
	unit	*min. value*	*max. value*
inflammation left CMC1	continuous value	0	3
inflammation left PIPs (5)	continuous value	0	3
inflammation left DIPs (5)	continuous value	0	3
inflammation left MCPs (5)	continuous value	0	3
inflammation left thumb IP	continuous value	0	3
inflammation left wrist	continuous value	0	3
inflammation right CMC1	continuous value	0	3
inflammation right PIPs (5)	continuous value	0	3
inflammation right DIPs (5)	continuous value	0	3
inflammation right MCPs (5)	continuous value	0	3
inflammation right thumb IP	continuous value	0	3
inflammation right wrist	continuous value	0	3

Figure 1 HandScan



Proper placement:
Thumb and index finger placed against positioning wedge
Fingers comfortably spread

Index finger not placed against positioning wedge

Index finger not placed against positioning wedge
Fingers 2-4 not spread

Hand not flat on glass surface

Figure 2 Hand positioning

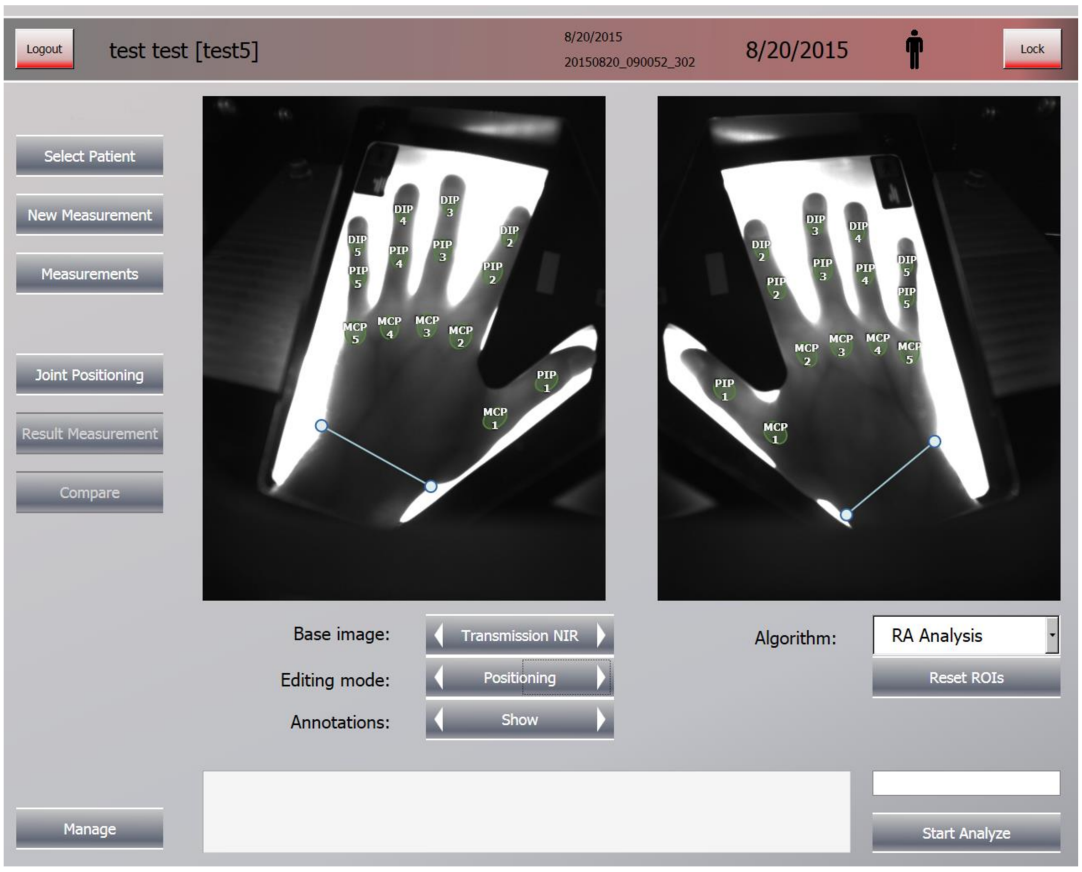


Figure 3 User interface for adjusting region of interest positions

SOP 9.1: Motion analysis

V1.0 d.d. 29-01-2016

Aim

To determine motion characteristics of knee and hip joints at inclusion, M006 and M024

Duration of the procedure for the patient

A complete measurement takes between 15 and 20 minutes.

Preparation and prerequisites

- The operator has to be trained by ETB personnel (European Technology for business LTD, UK)
- A 20 m quiet (discrete) straight corridor has to be available
- Always operate according to the instructions in the GaitSmart User Manual.
- Patients need to wear flat or low heeled shoes with proper support and use the same footwear at baseline and 6 months evaluation if possible.
- Pain medication questionnaires have to be filled out.

Acquisition

- GaitSmart™ comprises six sensor modules with accompanying Velcro straps. The sensors are inertial measurement units and contain three orthogonal gyroscopes and three orthogonal accelerometers that measure angular velocity and acceleration.
- The six sensors must first be synchronized using the dedicated software (Poseidon) and then disconnected from the computer.

Patients

- Each sensor is switched on and then mounted in to the appropriate pocket within Velcro straps (according to the manual).
- The Velcro straps must be applied on the lateral sides of the hip, just above the iliac crest, the thigh, just below the greater trochanter and the belly of the gastrocnemius muscle of the calf (according to the images in the manual).

Measurement protocol

- Patients must stand still for ten seconds in order to calibrate the sensors.
- Subsequently each patient must walk up and down a 20 meter corridor at their self-selected speed.
- Once the evaluation is completed the sensors must be removed from the straps, switched off and attached back to the laptop via the USB connectors.

Analysis

- Poseidon software will then be used to analyse the data.
- The observer must choose a minimum of 5 strides where the stride duration was continuous to within 5% of the mean and from this the most representative stride of the gait pattern will be calculated automatically, i.e. the stride with the lowest error compared to the other strides. This must then be indicated within the programme and a report prepared.

- The gait parameters are provided for this stride and shown graphically and in tabular form. Gait parameters included pelvis, hip, thigh, knee and calf range of motion in the sagittal plane; thigh and calf medial-lateral movement; knee stance flexion; joint and segment symmetry and stride duration.
- All data provided in the report is also saved in a csv file that will be stored by ETB. For the overall project database, a restricted dataset will be saved. This set has been shown to be the main predictors of the severity of knee OA. Knee ROM in swing and stance and hip ROM is stored for both the affected and non-affected side.

Outcome parameters for database:

Patient identification number x-xxx
Date of image DD-MM-YYYY

	unit	*min. value*	*max. value*
ROM swing left knee	degrees	0	80
ROM swing right knee	degrees	0	80
ROM left hip	degrees	0	80
ROM right hip	degrees	0	80
ROM stance left knee	degrees	0	80
ROM stance right knee	degrees	0	80

Figure 1: GaitSmart application

SOP 9.2: Performance based test

40m (4x10m) Fast Paced Walk Test

Recommendations on performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. OARSI website

Abbreviation: 40m FPWT

Purpose / Domains:
A test of short distance walking activity.
A test of walking speed over short distances and changing direction during walking.

Description:
A fast-paced walking test that is timed over 4 x 10m (33 ft) for a total 40 m (132 ft) (1).

Guidelines for use:
As a direct measure of the ability to walk quickly over short distances, which is an activity that is important but often limited in people with hip and/or knee OA.

Equipment:
- Timer/stop watch.
- 10 m (33 ft) marked walkway with space to turn safely around at each end.
- 2 cones place approximately 2 metres beyond each end of the 10m walkway.
- Calculator to convert time to speed.

Preparation:
Environment
- Mark out a 10 m (33 ft) walkway with bright coloured tape at each end.
- Place a cone approximately 2 metres before the start mark and 2 meters beyond the finish mark of the 10m walkway for turning.
- Ensure there is enough space to turn safely around at each end (i.e. 2-3m each end).

Participant
Comfortable walking footwear (e.g. tennis shoes/cross trainers) should be worn.

Tester
- If safety is of concern, the tester should follow slightly behind and off to one side to the participant but not as to pace or impede them.
- If there is no concern for safety, the tester should follow well to the side so as they can view crossing at the 10m walkway at both ends.

Practice
A practice trial of 1-2 turns is recommended before testing to check understanding.

Procedure:
- Participants are asked to walk as quickly but as safely as possible, without running, along a 10 m (33 ft) walkway and then turn around a cone, return then repeat again for a total distance of 40 m (132 ft) (3 turns).
- Regular walking aid is allowed and recorded.

Verbal instructions

"For this test, do the best you can by going as fast as you can, without running, but don't push yourself to a point of overexertion or beyond what you think is safe for you.

1. Start with both feet on the start line.
2. On start, walk as quickly but as safely as possible, without running.
3. Walk up to the end cone, turn around and walk back to the starting cone behind you, turn again and back to the end cone, then turn once more and return back to the start cone again so that you walk the 10m walkway 4 times in total.
4. Get ready and START".

Scoring

- Timing starts on the signal to start at the start line and terminates once the participant crosses back over the start line after completing the 40 m (4x10 m).
- When the participant crosses the 10m mark, timing is paused whilst the participant turns around the cone and then is resumed once they cross the 10m mark again. The same is repeated for the following turns and is stopped once the participant crosses the start line for the final time.
- Time of one trial is recorded to the nearest 100th of a second.
- Time of one test trial is recorded and expressed as speed m/s by dividing distance (40m) by time (s).
- Regular walking aid is allowed and use should be recorded.

Minimal reporting standards:

Assistive devices such as usual walking aids - walking stick etc.

N.B. The individual should use the assistive device (if any) they would normally use to perform the activity at the time of testing, irrespective of how they performed it previously. However, if an assistive device/rail is used, then it should be recorded for that occasion.

References:

1. Wright AA, Cook CE, Baxter GD, Dockerty JD, Abbott JH. A Comparison of 3 Methodological Approaches to Defining Major Clinically Important Improvement of 4 Performance Measures in Patients With Hip Osteoarthritis. J Orthop Sports Phys Ther. 2011;41:319-27.

40m (4 x 10m) Fast Paced Walk Test Score Sheet:

Date	Assistive walking aid (list)	**Time** (seconds: 00.00)	**Speed** (40/time in seconds) (0.00 m/sec)	Adaptations
1. / /				☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused
2. / /				☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused
3. / /				☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused
4. / /				☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused
5. / /				☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused

30-second Chair Stand Test

Recommendations on performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. OARSI website

Abbreviation: 30s-CST

Purpose / Domains:
A test of sit-to-stand activity.
Also a test of lower body strength and dynamic balance.

Description:
The maximum number of chair stand repetitions possible in a 30 second period (1-3).

Equipment:
- Timer/stop watch.
- Straight back chair with a 44cm (17 inch) seat height, preferably without arms.
- Same chair should be used for re-testing within sites.

Preparation
Environment
Ensure the chair cannot slide backwards by placing the back of the chair against a wall.

Participant
- Comfortable walking footwear (e.g. tennis shoes/cross trainers) should be worn.
- The participant sits in the chair in a position that allows them to place their feet flat on the floor, shoulder width apart, with knees flexed slightly more than 90 degrees so that their heels are somewhat closer to the chair than the back of their knees.
- The arms are crossed at the wrists and held close to the chest (across chest).

Tester
The tester stands close to the side of the chair for safety and so as they can observe the technique, ensure that the participant comes to a full stand and full sit position during the test.

Practice
A practice trial of one or two slow paced repetitions is recommended before testing to check technique and understanding.

Procedure
- From the sitting position, the participant stands up completely up so hips and knees are fully extended, then completely back down, so that the bottom fully touches the seat. This is repeated for 30 seconds.
- Same chair should be used for re-testing within site.
- If the person cannot stand even once then allow the hands to be placed on their legs or use their regular mobility aid. This is then scored as an adapted test score.

Verbal instructions
"For this test, do the best you can by going as fast as you can but don't push yourself to a point of overexertion or beyond what you think is safe for you.
1. Place your hands on the opposite shoulder so that your arms are crossed at the wrists and held close across your chest. Keep your arms in this position for the test.
2. Keep your feet flat on the floor and at shoulder width apart.

3. On the signal to begin, stand up to a full stand position and then sit back down again so as your bottom fully touches the seat.
4. Keep going for 30 seconds and until I say stop.
5. Get ready and START".

Scoring

- On the signal to begin, start the stop watch. Count the total number of chair stands (up and down equals one stand) completed in 30 seconds. If a full stand has been completed at 30 seconds (i.e. standing fully erect or on the way down to the sitting position), then this final stand is counted in the total.
- The participant can stop and rest if they become tired. The time keeps going.
- If a person cannot stand even once then the score for the test is zero.
- Next, allow the hands to be placed on their legs or use their regular mobility aid. If the person can stand with adaptions, then record the number of stands as an adapted test score (see score sheet). Indicate the adaptations made to the test.

Minimal reporting standards

- Chair height.
- Adaptations – such as using hands on legs or using a walking aid.

N.B. The individual should use the assistive device (if any) they would normally use to perform the activity at the time of testing, irrespective of how they performed it previously. However, if an assistive device/rail is used, then it should be recorded for that occasion.

REFERENCES

1. Gill S, McBurney H. Reliability of performance-based measures in people awaiting joint replacement surgery of the hip or knee. Physiother Res Int. 2008;13(3):141-52.
2. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. 1999;70(2):113-9.
3. Kreibich DN, Vaz M, Bourne RB, Rorabeck CH, Kim P, Hardie R, et al. What is the best way of assessing outcome after total knee replacement? Clin Orthop Relat Res. 1996(331):221-5.

30-second Chair Stand Test Score Sheet:

Time point Date	Chair seat height (cm)	Score (Repetitions in 30 seconds)	Adaptations	Adapted score
1. / /	cm		☐ Uses hands on legs ☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused	
2. / /	cm		☐ Uses hands on legs ☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused	
3. / /	cm		☐ Uses hands on legs ☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused	
4. / /	cm		☐ Uses hands on legs ☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused	
5. / /	cm		☐ Uses hands on legs ☐ Uses walking aid ☐ Not tested – Unable ☐ Not tested - refused	

--> If the score is adapted (i.e., if the patient uses an adapted strategy, such as using hands on legs or using a walking aid), the score will be zero.

SOP 10.1: collection of biosamples: blood and urine

V1.0 d.d. 23-08-2016

Aim

To evaluate prediction of progression of osteoarthritis of the knee and to determine the change in biomarkers with the severity of osteoarthritis of the knee.

Duration of the procedure for the patient

Blood sampling and urine collection will take 10-15 minutes.

Preparation and prerequisites (see flowcharts at end of SOP 10.2 for collection and processing relationship for each visit)

Blood should be collected using standard venipuncture techniques present at each clinical center. Care should be taken to attempt to draw all blood samples (i.e. different collection tubes) via a single venipuncture. Preferred order of collection of blood tubes are listed below. Each serum sample will be collected as close as possible to the planned time detailed in the protocol. For urine collection patients are asked to provide a midstream urine sample into a collection container.

The date, exact time, that each sample is collected, and fasted or non-fasted status will be recorded in the source documents.

Blood collection

Details per subject per visit:

Materials needed for blood collection (per subject, at inclusion visit M000):

- 3 x ≥7mL serum separator blood collection tubes
- 1 x ≥7.0mL EDTA blood collection tube
- 1 x 8.5mL PAXgene Blood DNA tube (at room temperature (18-25°C) prior to use)
- 1 x 2.5mL PAXgene Blood RNA tube (at room temperature (18-25°C) prior to use)

Inclusion visit M000	Collection Tube Type	# of Collection Tubes	Approximate Volume/Tube (mL)	Total Volume (mL)	Draw Order
Serum	Serum Separator	3	7	21	1
Plasma	EDTA	1	7	7	2
DNA	PAXgene Blood DNA	1	8.5	8.5	3
RNA	PAXgene Blood RNA	1	2.5	2.5	4
Total/Visit		**6**		**39**	

Materials needed for blood collection (per subject, Visits M006 and M012):

- 3 x ≥7mL capacity serum separator blood collection tubes

Visits M006 & M012	Collection Tube Type	# of Collection Tubes	Approximate Volume/Tube (mL)	Total Volume (mL)	Draw Order
Serum	Serum Separator	3	7	21	1
Total/Visit		**3**		**21**	

Materials needed for blood collection (per subject, Visit M024):

- 3 x ≥7mL serum separator blood collection tubes
- 1 x 8.5mL PAXgene Blood DNA tube (at room temperature (18-25°C) prior to use)
- 1 x 2.5mL PAXgene Blood RNA tube (at room temperature (18-25°C) prior to use)

Visit M024	Collection Tube Type	# of Collection Tubes	Approximate Volume/Tube (mL)	Total Volume (mL)	Draw Order
Serum	Serum Separator	3	7	21	1
DNA	PAXgene Blood DNA	1	8.5	8.5	2
RNA	PAXgene Blood RNA	1	2.5	2.5	3
Total/Visit		**5**		**32**	

Procedure

1. Apply barcode label to blood collection tube
    a. **Note: See SOP 10.3 for cross-referencing Patient number with APPROACH WP2 Clinical Centre Excel spreadsheet and eCRF**
2. Collect blood according to the table, using standard venipuncture technique
    a. for serum into serum separator tubes, gently invert (do not shake) the tube 5 times, and keep the tubes upright at room temperature.
    b. for plasma into EDTA blood collection tubes, gently invert (do not shake) the tube 8-10 times, and keep it on ice.
    c. for DNA into PAX gene DNA blood collection tubes, gently invert the tube 8-10 times, and keep it at room temperature.
    d. for RNA into PAX gene RNA blood collection tubes, gently invert the tube 8-10 times, and keep it at room temperature.
3. **Within 4 hours after collection** prepare the blood for serum storage according to SOP 10.2.
4. **Within 4 hours after collection** prepare the EDTA blood collection tubes for plasma storage according to SOP 10.2.
5. **Within 4 hours after collection** prepare the PAX gene DNA and PAX gene RNA blood collection tubes for storage according to SOP 10.2.

Urine collection

Materials needed for urine collection (per subject, Visits M000-M024):

- 1 x 50 mL primary urine collection container

Procedure

1. For each visit, ask the patient to collect a midstream urine sample (~50mL) into a primary urine collection container and store on ice.

Within 4 hours after collection prepare the urine sample for storage according to SOP 10.2.

SOP 10.2: processing of biosamples: blood and urine

V1.0 d.d. 23-08-2016

Serum sample processing (see flowcharts at end of SOP 10.2 for collection and processing relationship for each visit)

Materials for Serum only (Per Subject, per time point):

- 1 x 15.0mL sterile conical tube for pooling
- 13 x 1.0mL sterile screw cap cryotubes
- 1 x 5.0mL sterile screw cap cryotube

Materials for Serum only cryostorage (total/study)

- 240 (10x10) cryoboxes for 1.0mL cryotubes labelled specifically for distribution to testing/storage sites
- 20 (10x10) cryoboxes for 5.0mL cryotubes labelled specifically for distribution to storage site

Procedure

1. **Within 4 hours after collection,** centrifuge serum separator tubes at 2500 x g for 15 minutes, approximately 4°C in a refrigerated centrifuge equipped with a swing-bucket rotor.

2. Remove the blood collection tube cap carefully to avoid disturbing the pellet or causing splashing of the blood. **The serum samples should not contain red blood cells/clot (**due to either a pipetting error (aspiration of the blood clot) or perturbation of the blood clot). Care should be taken to avoid haemolysis of the sample.

3. Transfer serum from the three serum separator tubes at each visit using a sterile pipette and combine in a single 15 mL sterile conical tube to form a pooled sample for aliquotting. **Care should be taken to avoid taking any red blood cells over into the serum.**

4. Gently invert 15 mL tube containing pooled serum 5-10 times to generate a uniform sample.

5. A pipette with appropriate filter tip should be used to transfer thirteen 0.5mL and one 5.0mL aliquots of serum into supplied labelled cryotubes.

   Aliquots should be filled in the order 01-14 with volumes as indicated below example for Visit M000.

Aliquot Number	Volume (mL)
01-13	0.5
14	Remainder, ~5.0

6. Barcode labels are applied to sample aliquot tubes in a vertical orientation (shown below) to ensure compatibility with the barcode reader.

OR

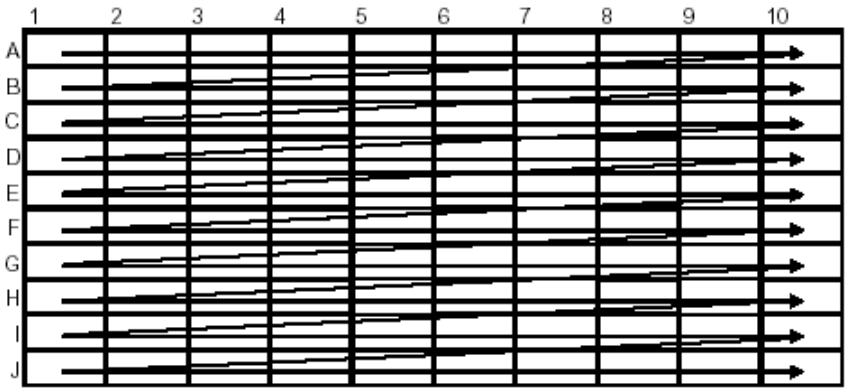
7. Freeze and store the cryotubes immediately at -70°C to -80°C freezer.

Cryotube Storage and sample log for distribution:
A separate SOP and tranining will be provided to clinical centres for sample entry for storage/distribution using barcode readers and sample inventory software.

Sample Testing/Storage Site Information

Distribution Site	Analysis	Sample Type(s)	Sampling Visits	Aliquots (per visit)	Aliquot Volume (mL)	Subjects	Total Visits (per subject)	Total Tubes	# of (10x10) cryoboxes	Aliquot #s (from barcode label)
Nordic Bioscience	Biomarker	Serum	M000-M024	5	0.5	500	4	10000	100	SR .5-.9
Artialis	Biomarker	Serum	M000-M024	3	0.5	500	4	6000	60	SR .10-.12
Lund	Biomarker	Serum	M000-M024	3	0.5	500	4	6000	60	SR .13-.15
Surrey	Metabolomics	Plasma	M000	2	0.5	500	1	1000	10	PL .2-.3
Sergas	Proteomics	Plasma	M000	2	0.5	500	1	1000	10	PL .4-.5
LUMC	Lipidomics	Plasma	M000	2	0.5	500	1	1000	10	PL .6-.7
AbbVie	Transcriptomics Genomics Epigenetics	DNA and RNA	M000 and M024	1 DNA 1 RNA	8.5 DNA 2.5 RNA	500	2	1000 DNA 1000 RNA	10 DNA 10 RNA	DN .1 RN .1
BST	Short Term Storage	Serum	M000-M024	2	0.5	500	4	4000	40	SR .16-.17
BST	Long Term Storage	Serum and Urine	M000-M024	1 Serum 1 Urine	5.0 Serum 10.0 Urine	500	4	2000 Serum 2000 Urine	20 Serum 20 Urine	SR .18 UR .3

The cryotubes should be placed into labelled cryoboxes (10x10). The cryobox will be filled from the left hand corner (A1) with aliquots being filled left to right top to bottom.



The cryobox is placed immediately into -70ºC to -80 ºC freezer for storage. New aliquots may be placed into a partially filled box. This should be done such that the thawing effect on the samples already frozen is minimised. Samples should never reach a temperature of ≥ -20 ºC.

Plasma Sample Processing

Materials for Plasma only (Per Subject, per time point):

- 1 x 15.0mL sterile conical tube for pooling
- 4 x 1.0mL sterile screw cap cryotubes with colored (red) cap indicator insert
- 2 x 1.0mL sterile glass vials prefilled with 0.5mL methanol for Lipidomic samples

Materials for Plasma only cryostorage (total/study)

- 20 (10x10) cryoboxes labelled specifically for distribution to Proteomic and Metabolomic testing sites
- 10 (10x10) cryoboxes labelled specifically for distribution to Lipidomic testing/storage site (LUMC)

Procedure

8. **Within 4 hours after collection,** centrifuge EDTA plasma collection tubes at approximately 2500 x g for 15 minutes, at approximately 4°C in a refrigerated centrifuge equipped with a swing-bucket rotor.

9. Remove the collection tube cap carefully to avoid disturbing the pellet or causing splashing of the blood. **The plasma samples should not contain red blood cells (**due to either a pipetting error (aspiration of the blood clot) or perturbation of the blood clot). Care should be taken to avoid haemolysis of the sample.

10. Using a pipette with appropriate filter tip, plasma is carefully transferred to a 15mL centrifuge tube, recapped and inverted 5-10 times to create a uniform sample.

11. A pipette with appropriate filter tip should be used to transfer four 0.5mL aliquots of plasma into supplied cryotubes and two 0.5mL aliquots into the glass vials containing methanol.

12. Barcode labels are applied to sample aliquot tubes in a vertical orientation (shown below) to ensure compatibility with the barcode reader.

OR

13. Freeze and store the cryotubes immediately at -70°C to -80°C using the same cryobox filling recommendations shown for serum.

Blood DNA Sample Processing

Materials for DNA PAXgene only cryostorage (total/study)

- 10 (10x10) cryoboxes labelled specifically for distribution to Genomic/Epigenetic testing site (AbbVie)

Procedure

1. **Within 4 hours after collection** store the PAXgene Blood DNA Tube upright at -20°C from 0.5-72 hours prior to transfer into long term storage at -70°C to -80°C using the same recommendations as for cryotubes for serum.

Guidelines for Freezing PAXgene Blood DNA Tubes Containing Blood Samples. To freeze PAXgene Blood DNA Tubes, stand them upright in a metal or plastic wire rack. **Do not freeze tubes upright in a Styrofoam™ tray as this may cause the tubes to crack.**

Blood RNA Sample Processing

Materials for RNA PAXgene only cryostorage (total/study)

- 10 (10x10) cryoboxes labelled specifically for distribution to Transcriptomic testing site (AbbVie)

Procedure

1. **Within 4 hours after collection** store the PAXgene Blood RNA Tube upright at room temperature (18-25°C) for 2-72 hours prior to transfer to -70°C to -80°C freezer for long term storage using the same recommendations as for cryotubes for serum.

Urine Sample Processing

Materials for Urine (Per Subject, per time point):

- 1 x 15 mL sterile conical centrifuge tube
- 1 x 10 mL sterile barcode labelled cryotube

Materials for Urine only cryostorage (total/study)

- 20 (10x10) cryoboxes labelled specifically for distribution to storage site (BST)

Procedure

1. Within four hours of collection, samples (~15mL) are transferred to a sterile conical centrifuge tube and placed on ice until centrifugation.

2. Tubes are spun at 1,500 × g for 10 minutes at approximately 4°C in a refrigerated centrifuge equipped with a swing-bucket rotor to pellet any cells.

3. 10mL of centrifuged urine sample is transferred to a sterile cryotube using sterile pipette.

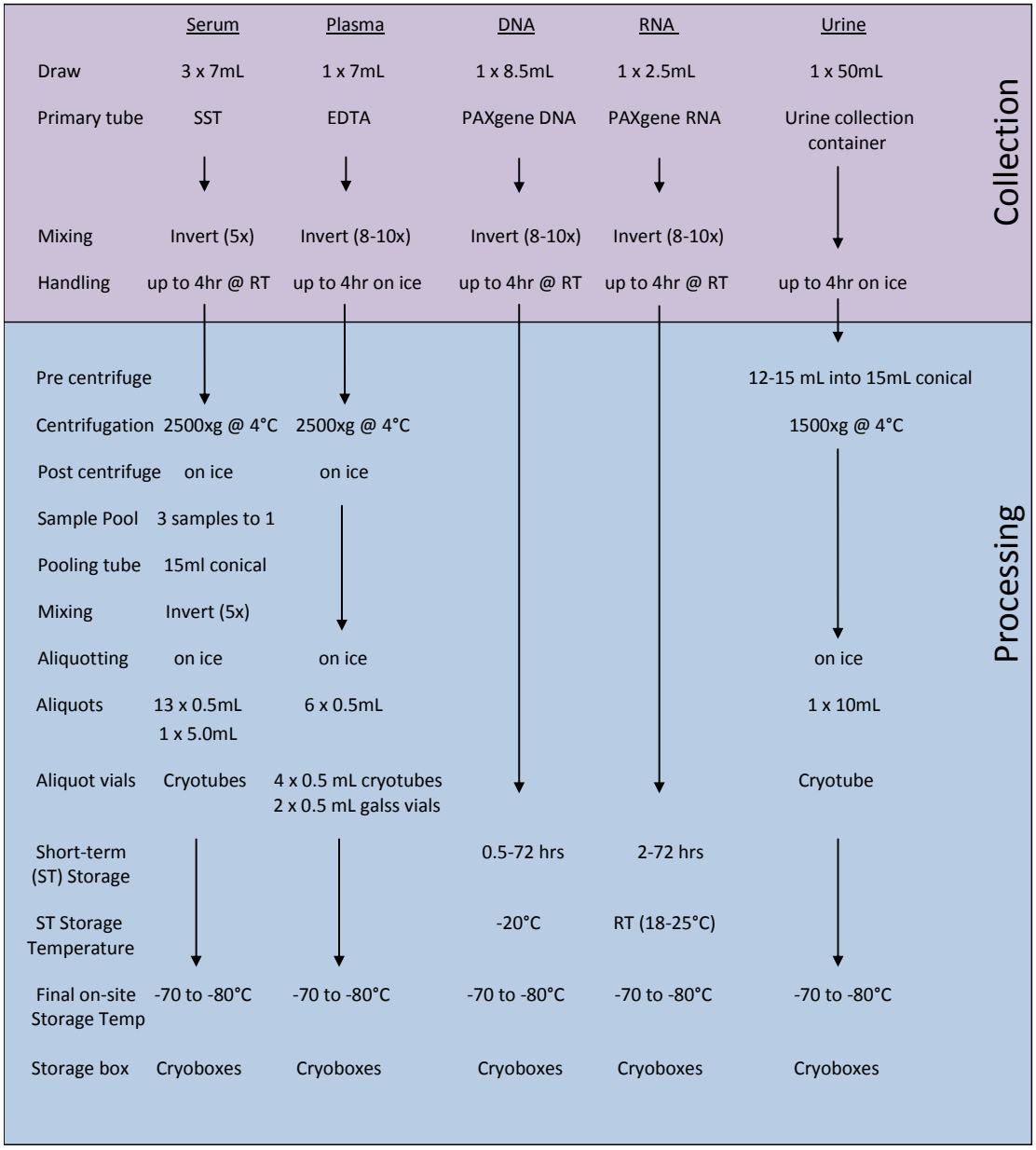
4. Barcode labels are applied to sample aliquot tubes in a vertical orientation (shown below) to ensure compatibility with the barcode reader.

OR

5. All processed samples are transferred to a -70°C to -80°C freezer within two hours of collection using the same recommendations than for cryotubes for serum.

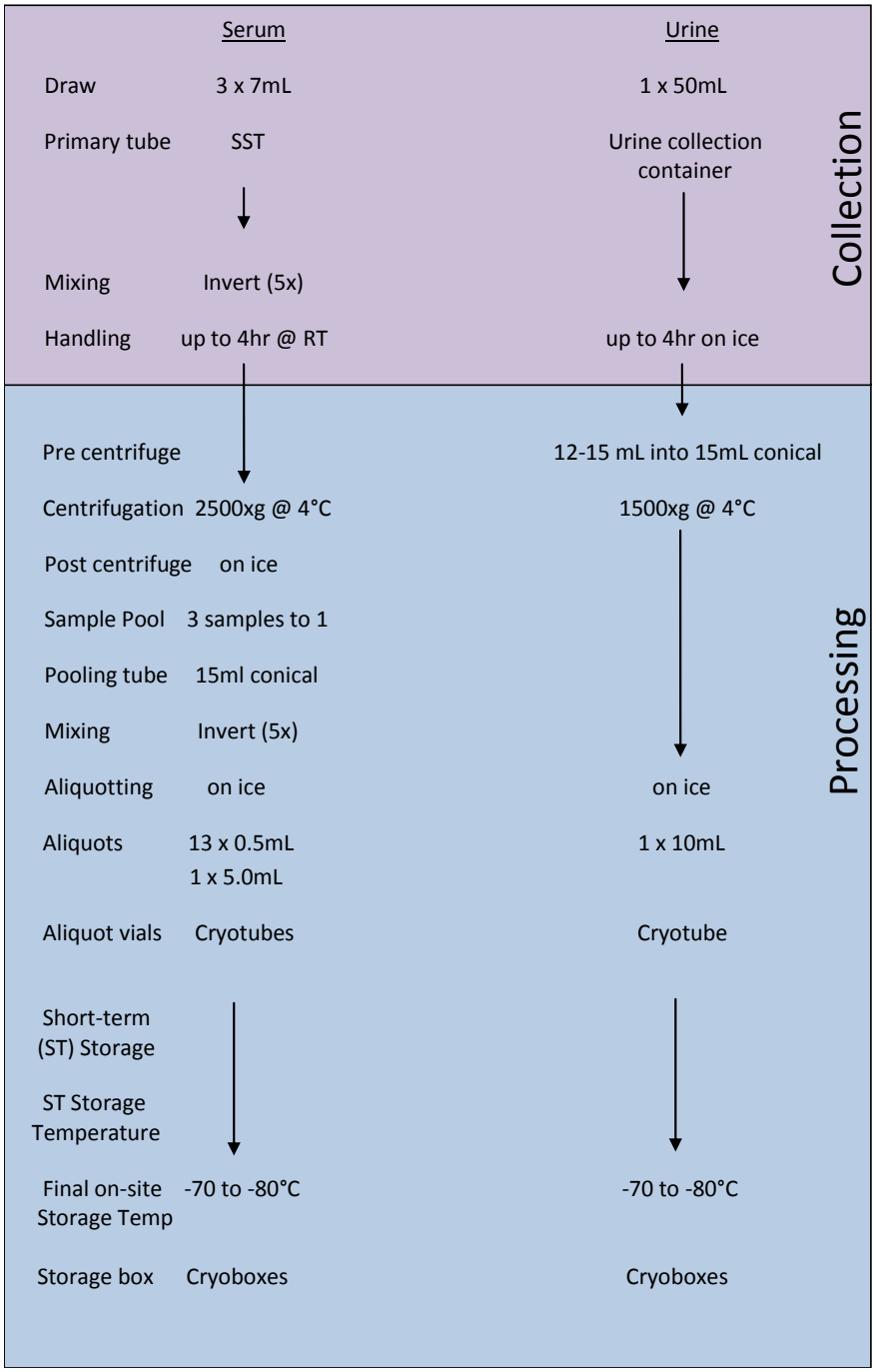
APPROACH Sample Collection and Processing Flow Charts

APPROACH Visit 1



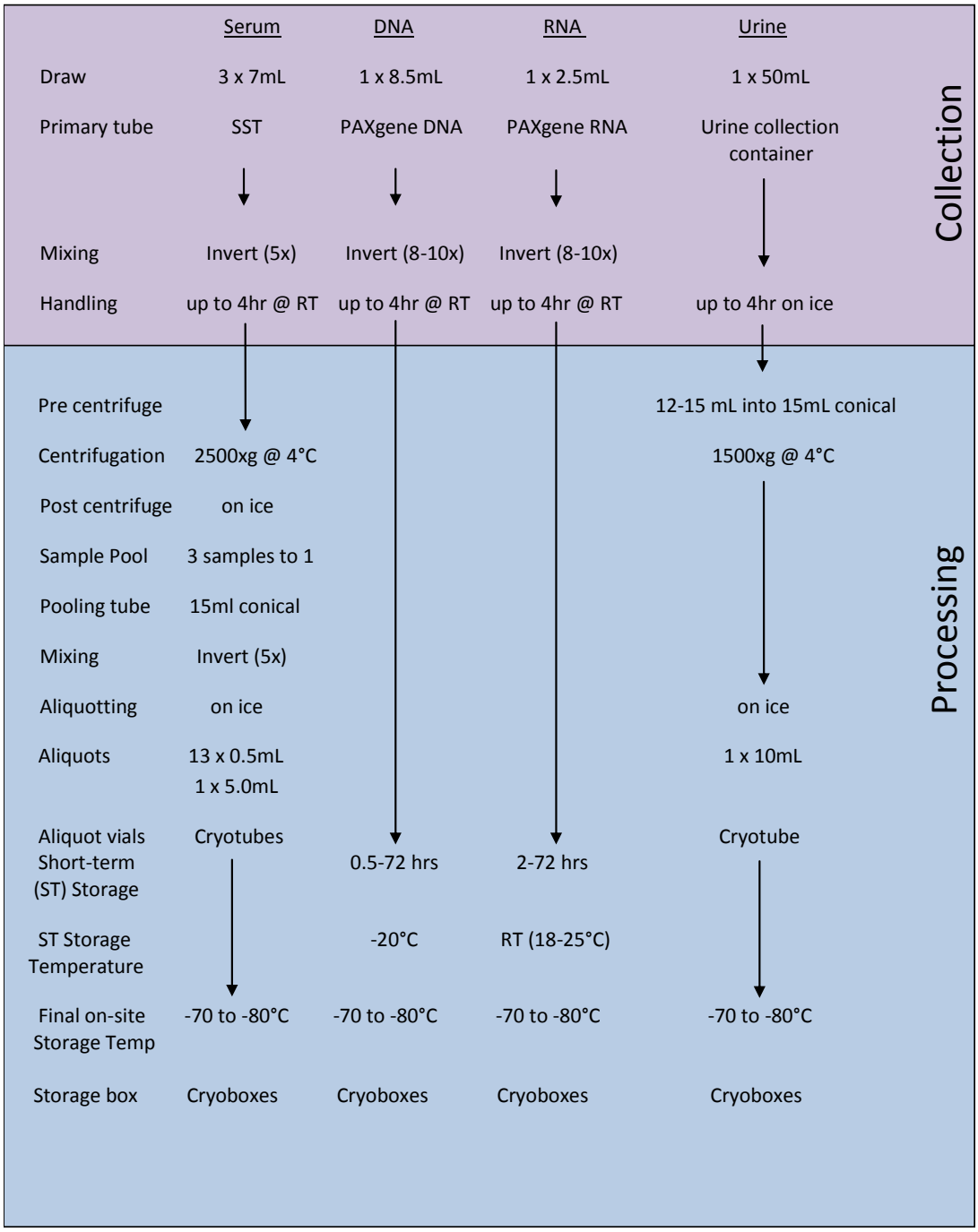
APPROACH Sample Collection and Processing Flow Charts

APPROACH Visits 2 & 3



APPROACH Sample Collection and Processing Flow Charts

APPROACH Visit 4



SOP 10.3: Storage, Tracking and Distribution of Samples at Clinical Centres

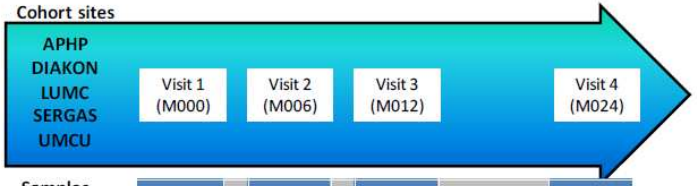
Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

SOP 10.3: Storage, Tracking and Distribution of Samples at Clinical Centres

V1.0 d.d. 23-08-2016

Graphical study design



Samples	Visit 1	Visit 2	Visit 3	Visit 4
Serum	X	X	X	X
Urine	X	X	X	X
Plasma	X			
RNA	X	-	-	X
DNA	X	-	-	X

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Page 1

Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

Study flow chart for sampling

Phase		Study Period			
Visit at clinical site		1	2	3	4
Month		M0	M6	M12	M24
Sample collection for biomarker assay(s)	Collection Tube	Total Sample draw			
Serum:	SST	X 21ml	X 21ml	X 21ml	X 21ml
Urine :	Urine	X 10ml	X 10ml	X 10ml	X 10ml
DNA :	PAXgene blood DNA	X 8.5mL			X 8.5mL
RNA :	PAXgene blood RNA	X 2.5mL			X 2.5mL
Plasma :	EDTA	X 7mL			

Aliquots per visit

Serum (V1-4) 12 x 0.5mL + 1 x 5.0mL = 11.0 mL Total Serum Vol
Urine (V1-4) 1 x 10 mL = 10.0 mL Total Urine Vol
Plasma (V1) 6 x 1.0mL = 6.0 mL Total Plasma Vol
RNA (V1&4) 1 x 2.5 mL = 2.5 mL Total Blood Draw Req'd into PAXgene blood RNA tubes
DNA (V1&4) 1 x 8.5 mL = 8.5 mL Total Blood Draw Req'd into PAXgene blood DNA tubes

Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

Sample collection logging and cross referencing to eCRF

Site-specific sample collection kits will be supplied to each clinical centre (quantity based on expected enrollment/site)

Contents:

Consumables:

- Preprinted barcode labels (1 bag/patient labeled with unique patient number)
  - Each bag contains 4 smaller bags containing necessary barcode labels for each visit
- Prelabeled cryostorage boxes with aliquot storage and distribution details
- Collection, processing and storage tubes provided in bulk

Hardware:

- Barcode reader

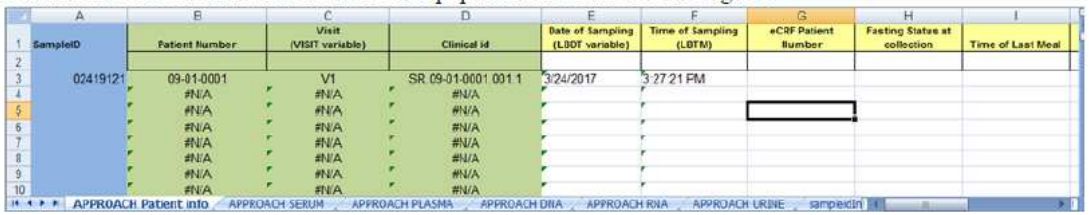
Sample Tracking Spreadsheet:

- APPROACH WP2 Clinical Centre Excel spreadsheet (Appendix 2)

Procedure

Designation of WP2 unique patient number – Visit 1 (M000) Only

1. Patient number is designated by selecting an unused barcode label bag at enrolment visit (bag is then patient-specific and will contain barcode labels for all subsequent visits).
   a. To simplify retrieval at subsequent visits Personal Patient info (Name, etc) may be attached to or written on bag at this point. Bags will be discarded at local site at completion of study.
2. Open APPROACH WP2 Clinical Centre Excel spreadsheet 'Patient Info' Tab (below) and click on next open cell in 'SampleID' colun (A) and scan barcode label on the internal bag labeled 'inclusion/M000' using the barcode reader – Corresponding barcode number wil be added into the cell and other fields are autopopulated in columns B through F.



	A	B	C	D	E	F	G	H	I
1	SampleID	Patient Number	Visit (VISIT variable)	Clinical id	Date of Sampling (LBDT variable)	Time of Sampling (LBTM)	eCRF Patient Number	Fasting Status at collection	Time of Last Meal
2									
3	02419121	09-01-0001	V1	SR 09-01-0001 001 1	3/24/2017	3:27:21 PM			
4		#N/A	#N/A	#N/A					
5		#N/A	#N/A	#N/A					
6		#N/A	#N/A	#N/A					
7		#N/A	#N/A	#N/A					
8		#N/A	#N/A	#N/A					
9		#N/A	#N/A	#N/A					
10		#N/A	#N/A	#N/A					

APPROACH Patient info | APPROACH SERUM | APPROACH PLASMA | APPROACH DNA | APPROACH RNA | APPROACH URINE | sampleidn

3. Log eCRF unique Patient Number from the eCRF into column G for cross referencing
4. 'Save' updated APPROACH WP2 Clinical Centre Excel spreadsheet into APPROACH database

Patient-specific visit details – All visits

5. At each visit locate patient-specific barcode label bag containing smaller visit-specific bags.
6. Open the APPROACH WP2 Clinical Centre Excel spreadsheet to the 'Patient Info' tab (taking care to confirm that appropriate cell is highlighted prior to scanning barcode)
7. Scan the barcode label (as above) on the internal bag with the barcode labels for that visit.
8. Manually log details into 'Fasting Status at collection' and 'Time of Last Meal' columns (G and H)

Applying labels to sample aliquot tubes (referenced here as example from SOP 10.2 for consistency)

1. Barcode labels are applied to sample aliquot tubes in a vertical orientation (shown below) to ensure compatibility with the barcode reader.

OR

Sample Logging

1. Navigate to APPROACH WP2 Clinical Centre Excel spreadsheet tab specific for sample type (e.g. Serum, Plasma, Urine, DNA and RNA)
2. Click on uppermost open cell in 'SampleID' column (A) – Take care to confirm that appropriate cell is highlighted

3. Labeled sample aliquot tubes are scanned one by one from lowest to highest (for example; numbers ending in .5-.18 for serum) using the barcode scanner
    a. Cells in columns B-G will automatically populate and selected cell in column A will move down one row awaiting the next input
4. Manually enter sample specific information in columns with yellow headers
5. Complete this for each sample type and aliquot on the appropriate tab of the spreadsheet
6. 'Save' updated APPROACH WP2 Clinical Centre Excel spreadsheet into APPROACH database

Sample Storage for Shipping

1. Place sample aliquots in appropriate cryostorage box for storage/distribution (supplied prelabeled as demonstrated below).
    a. SR = Serum, PL = Plasma, UR = Urine, DN = DNA and RN = RNA
    b. Final number on barcode label (.1-.18, depending on sample type, circled in example below) designates aliquot number and destination storage box

Sample Testing/Storage Site Information

Distribution Site	Analysis	Sample Type(s)	Sampling Visits	Aliquots (per visit)	Aliquot Volume (mL)	Subjects	Total Visits (per subject)	Total Tubes	# of (10x10) cryoboxes	Aliquot #s (from barcode label)
Nordic Bioscience	Biomarker	Serum	M000-M024	5	0.5	300	4	10000	100	SR .5-.9
Artialis	Biomarker	Serum	M000-M024	3	0.5	300	4	6000	60	SR .10-.12
Lund	Biomarker	Serum	M000-M024	3	0.5	300	4	6000	60	SR .13-.15
Surrey	Metabolomics	Plasma	M000	2	0.5	300	1	1000	10	PL .2-.3
Sergas	Proteomics	Plasma	M000	2	0.5	300	1	1000	10	PL .4-.5
LUMC	Lipidomics	Plasma	M000	2	0.5	300	1	1000	10	PL .6-.7
AbbVie	Transcriptomics Genomics Epigenetics	DNA and RNA	M000 and M024	1 DNA 1 RNA	8.5 DNA 2.5 RNA	300	2	1000 DNA 1000 RNA	10 DNA 10 RNA	DN .1 RN .1
BST	Short Term Storage	Serum	M000-M024	2	0.5	300	4	4000	40	SR .16-.17
BST	Long Term Storage	Serum and Urine	M000-M024	1 Serum 1 Urine	5.0 Serum 10.0 Urine	300	4	2000 Serum 2000 Urine	20 Serum 20 Urine	SR .18 UR .3

2. The cryotubes should be placed into the appropriate Distribution site labelled cryoboxes (see label examples below) based on the appropriate aliquot # (see Aliquot #s column above).

Cryobox Labels for aliquot distribution:

Serum Aliquots

APPROACH SERUM Aliquots (0.5mL)
Include SR tubes ending in: .5, .6, .7, .8 and .9

Shipment to: Nordic Bioscience

APPROACH SERUM Aliquots (0.5mL)
Include SR tubes ending in: .10, .11 and .12

Shipment to: Artialis

APPROACH SERUM Aliquots (0.5mL)
Include SR tubes ending in: .13, .14 and .15

Shipment to: Lund

APPROACH SERUM Aliquots (0.5mL)
Include SR tubes ending in:.16 and.17

Shipment to: BST

APPROACH SERUM Aliquots (5mL)
Include SR tubes ending in: .18

Shipment to: BST

Urine Aliquots

APPROACH URINE Aliquots (10mL)
Include DN tubes ending in .3

Shipment to: BST

Plasma Aliquots

APPROACH PLASMA Aliquots (0.5mL)
Include PL tubes ending in .2 and .3

Shipment to: LUMC

APPROACH PLASMA Aliquots (0.5mL)
Include PL tubes ending in: .4 and .5

Shipment to: Surrey

APPROACH PLASMA Aliquots (0.5mL)
Include PL tubes ending in: .6 and .7

Shipment to: Sergas

DNA Samples

APPROACH DNA Samples
Include DN tubes ending in .1

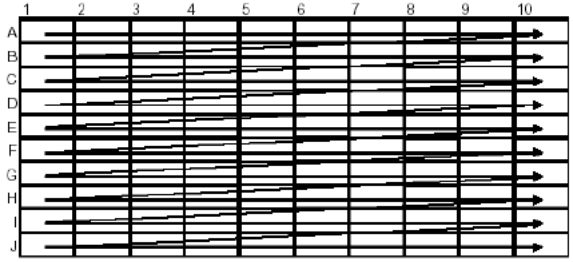
Shipment to: AbbVie

RNA Samples

APPROACH RNA Samples
Include RN tubes ending in .1

Shipment to: AbbVie

3. The cryobox should be filled from the left hand corner (A1) with aliquots being filled left to right top to bottom.



4. The cryobox is placed immediately into -70° C to -80° C freezer for storage until distribution.
    a. New aliquots may be placed into a partially filled box.
    b. This should be done such that the thawing effect on the samples already frozen is minimised.
    c. Samples should never reach a temperature of ≥ -20 ºC.

5. Samples are stored locally for distribution to testing facilities every 6 months, or as warranted by local freezer capacity at clinical centres.

Shipment Procedures

Every 6 months, or as warranted, stored samples may be shipped in bulk to the testing facilities by contacting local BioCair representative listed below for each Clinical Centre:

UMCU – Utrecht, The Netherlands

APHP – Paris, France
LUMC – Leiden, The Netherlands

DIAKON – Oslo, Norway

SERGAS – Coruna, Spain

Shipment Assembly

1. Sample filled cryostorage boxes are individually secured to ensure maintained closure during shipping (rubber band)
2. Cryostorage boxes specific for each testing site are stacked upright into a plastic bag and closure is secured with a zip-tie.

Addresses for testing sites:

- Nordic Bioscience A/S
  Herlev Hovedgade 205-207
  2730 Herlev
  Denmark
  Attn:
  Tel: +45 4452 5252
  Fax: +45 4452 5251

- Artialis
  11, Avenue de l'Hôpital
  Tour GIGA +3
  4000 Liège (Sart-Tilman)
  Belgium
  Attn:
  Tel. +32 4 242 77 27
  Fax +32 4 242 77 28

- Lund University
  Department of Rheumatology
  Kioskgatan 3, SUS
  222 42 Lund, Sweden
  Attn: Patrik Önnerfjord

Tel: +46 46 2223129
Fax:

- LUMC
  Department of Rheumatology, Leiden University Medical Center
  C1-38, Leiden, The Netherlands
  Attn: Andreea Ioan-Facsinay
  Tel: +31 71 526 6868
  Fax: +31 71 526 6752

- Surrey
  16DK03, Duke of Kent Building, University of Surrey
  Guildford, Surrey, GU2 7XH,
  United Kingdom
  Attn: Ali Mobasheri
  Tel: +44 (0) 1483 682536
  Fax:

- Sergas
  Proteomics Platform INIBIC-CHUAC
  Hospital Teresa Herrera (Annex Building - 2nd floor)
  Xubias de Arriba, 84
  15006 A Coruña
  Spain
  Attn:
  Tel:
  Fax:

- AbbVie

- BioStorage Technologies (BST)
  BioStorage Technologies European Operation
  Im Leuschnerpark 1B
  64347 Griesheim
  Germany
  Attn:
  Tel: +49 6922 221 2291
  Fax: +49 6155 898 1090

Clinical trial protocol
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Study APPROACH

Indvidual Shipment Form

From: Centre test Adresse test 92100

To:

Date of shipment	Day	Month	Year	Time
	///	///	////	

Sample Type	Number of Cryoboxes	Number of Sample Tubes	Reception: OK/NOT OK	If NOT OK, Issue	Monitoring Date	Comments
Serum	6	600				

Acknowledgement at reception: Date / / Time :

Name:

Signature:

At Reception please fax this form to

Contacts

For Collection and Labeling kits:

For Distribution/Shipping:

Appendix 1: Barcode label information

Patient ID

- Study protocol: APPROACH-OA-P01
- Patient ID : OA-P01-AA-BB-CCCC
  Example for site 1 (UMCU, first patient): OA-P01-02-01-0001
  - ✓ Disease code : OA
  - ✓ Protocol: P01
  - ✓ APPROACH Participant Number: 02 (UMCU)
  - ✓ Site number : 01
  - ✓ Patient Number :from 0001

Clinical Centre Details

Study protocol (APROACH-OA-P01)	**Participant number (AA)**	**Site number (BB)**	**Patient ID (OA-P01-AA-BB-CCCC)**
University Medical Center Utrecht (UMCU)	**02**	Starting from 01	For site 1 for UMCU, patient ID starting from OA-P01-02-01- 0001

Site number/Patient ID	**PI**	**Address of Rheumatology department**	**Town**

01 / OA-P01-02-**01**-0001	Prof. Dr. Floris Lafeber		Utrecht

Study protocol (APROACH-OA-P01)	**Participant number (AA)**	**Site number (BB)**	**Patient ID (OA-P01-AA-BB-CCCC)**
Leids University Medical Center (LUMC)	**14**	Starting from 01	For site 1 for LUMC, patient ID starting from OA-P01-14-01- 0001

Site number/Patient ID	**PI**	**Address of Rheumatology department**	**Town**
01 / OA-P01-14-**01**-0001	Prof. Dr. Margreet Kloppenburg	Leids University Medical Center (LUMC) Albinusdreef 2, 2333 ZA Leiden	Leiden

Study protocol (APROACH-OA-P01)	**Participant number (AA)**	**Site number (BB)**	**Patient ID (OA-P01-AA-BB-CCCC)**
AP-HP Saint-Antoine hospital (APHP)	**18**	Starting from 01	For site 1 for APHP, patient ID starting from OA-P01-18-01- 0001

Site number/Patient ID	**PI**	**Address of Rheumatology department**	**Town**
01 / OA-P01-18-**01**-0001	Prof. Dr. Francis Berenbaum		Paris

Study protocol (APROACH-OA-P01)	**Participant number**	**Site number (BB)**	**Patient ID (OA-P01-AA-BB-CCCC)**

	(AA)		
Servizo Galego de Saúde (SERGAS)	**17**	Starting from 01	For site 1 for SERGAS, patient ID starting from OA-P01-17-01- 0001

Site number/Patient ID	**PI**	**Address of Rheumatology department**	**Town**
01 / OA-P01-17-**01**-0001	Dr. Francisco Blanco		Coruna

Study protocol (APROACH-OA-P01)	**Participant number (AA)**	**Site number (BB)**	**Patient ID (OA-P01-AA-BB-CCCC)**
Diakonhjemmet Hospital AS (DIAKON)	**19**	Starting from 01	For site 1 for DIAKON, patient ID starting from OA-P01-19-01- 0001

Site number/Patient ID	**PI**	**Address of Rheumatology department**	**Town**
01 / OA-P01-19-**01**-0001	Dr. Ida Haugen		Oslo

Tubes and labelling

Test	Visits	Blood volume to collect	Collection tubes	Mix by inversion	Clotting	centrifugation	Pooling	Transfer to sample aliquot	Storage and shipment	Labels to be used : see example

Test	Visits	Blood volume to collect	Collection tubes	Mix by inversion	Clotting	centrifugation	Pooling	Transfer to sample aliquot	Storage and shipment	Labels to be used : see example
Serum	V1, V2, V3 and V4	**21 mL**	**3 × 8 mL** Serum separator Tubes	4-6 times	30 min at room temperature	1500 to 2000 rpm for 15 min	**1× 15mL pooling tube** Pool serum from collection tubes into pooling tube and mix by inversion (5x) for aliquotting	**16× 2mL** cryotubes containing at least 0.5mL of serum **1× 5mL** cryotube containing at least 5mL of serum	Transfer sample tubes to appropriate labeled cryoboxes for storage at -70°C to -80°C. Shipping of cryoboxes to testing centres to occur every 6 months	**Blood Collection Tubes:** APROACH 02419121 SR.09 – 01 – 0001.001.1 V1 **Pooling Tube:** APROACH 02419124 SR.09 – 01 – 0001.001.4 V1 **Storage Tubes: for analysis** **Serum (0.5mL)** APROACH 02419125 SR.09 – 01 – 0001.001.5 V1 **Serum (5.0mL)** APROACH 02419138 SR.09 – 01 – 0001.001.18 V1

Test	Visits	Urine volume to collect	Collection tubes	Transfer to centrifuge tube	Centrifugation	Transfer to sample aliquot	Labels to be used : (see example°)
Urine	V1, V2, V3 and V4	<50mL	1 X 50mL sterile primary urine collection container	12-15 mL of urine into 15mL centrifuge tube	1500 to 2000 rpm for 15 min	**1 X 10mL** cryotube containing at least 10mL of urine	Urine Collection Tube  Urine Centrifuge Tube  Storage tube 

Test	Visits	Blood volume to collect	Collection tubes	Mix by inversion	Handling	Centrifugation	Transfer to sample aliquot	Storage and shipment	Labels to be used : (see example))
RNA	V1 and V4	**2.5 mL**	**1 X 2.5 mL** PAXgene blood RNA tube	8-10 times	Tubes stored in upright position at room temperature for 2-72 hrs prior to transfer to minus			Transfer sample tubes to appropriate labeled cryoboxes for storage at -70°C to -80°C. Shipping of cryoboxes to testing centres to occur every 6 months	Tube containing RNA 
DNA	V1 and V4	**5 mL**	**1 X 8.5 mL** PAXgene blood DNA tube	8-10 times	Tubes need to be in upright position at minus 20°C for 16-72 hrs			Transfer sample tubes to appropriate labeled cryoboxes for storage at -70°C to -80°C. Shipping of cryoboxes to testing centres to occur every 6 months	Tube containing DNA 
Plasma	V1	**7 mL**	**1 X 8.0 mL** EDTA blood collection tube	8-10 times	0.5-1hour on ice	1500 to 2000 rpm for 15 min	**4 X 2 mL** cryostorage tubes containing at least 0.5 mL of plasma **2 x 2mL** glass cryostorage tubes prefilled with 0.5 mL Methanol containing at least 0.5 mL of plasma	Transfer sample tubes to appropriate labeled cryoboxes for storage at -70°C to -80°C. Shipping of cryoboxes to testing centres to occur every 6 months	Plasma Collection Tube  Storage tube 

Clinical trial protocol
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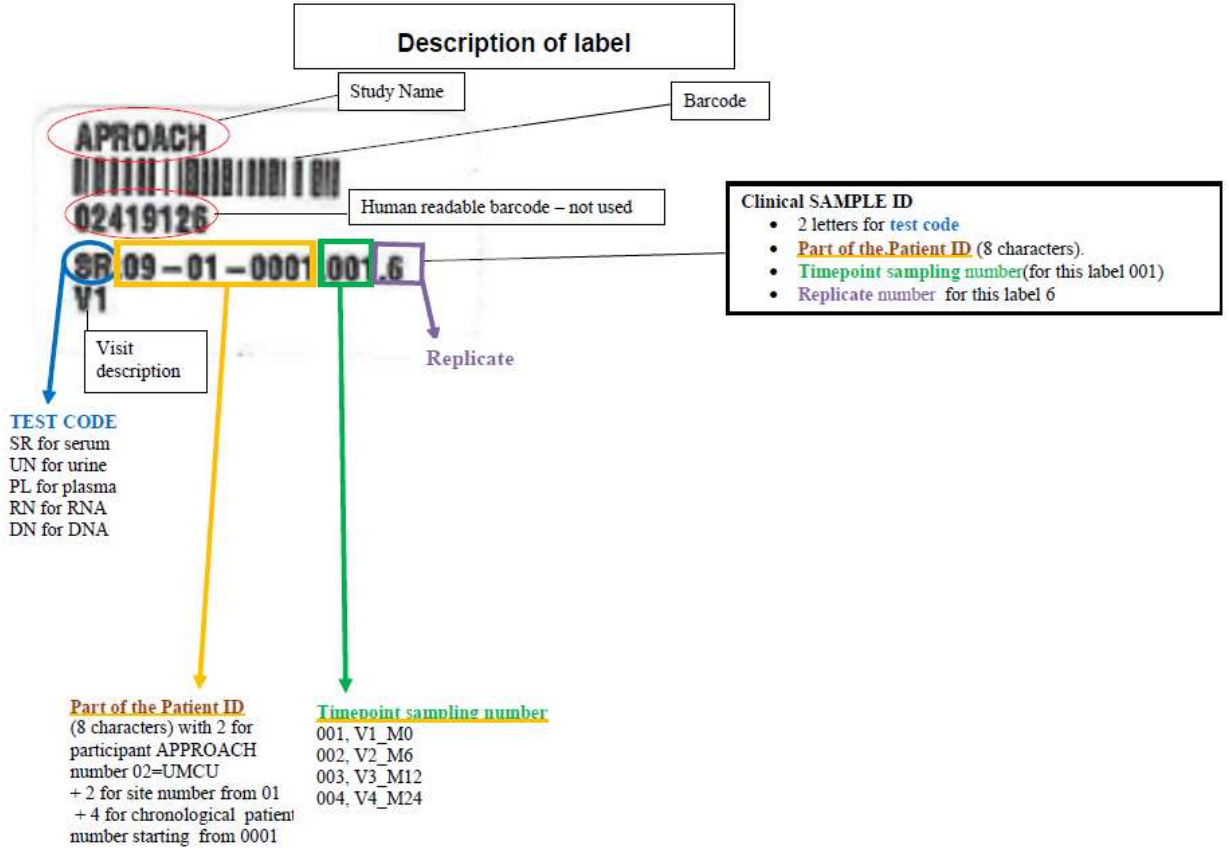

Property of APPROACH-OA - strictly confidential

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Usage of Labels per visit as follows

(see example for site 09-01)

VISIT V1-M0 (1/5)

SERUM : For *collection* tubes: 1-3

SERUM: For Pooling tube 4

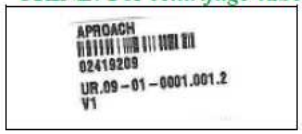
SERUM: For *storage* tubes from 5 to 18

APROACH 02419125 SR.09 – 01 – 0001.001.5 V1	APROACH 02419126 SR.09 – 01 – 0001.001.6 V1	APROACH 02419127 SR.09 – 01 – 0001.001.7 V1	APROACH 02419128 SR.09 – 01 – 0001.001.8 V1
APROACH 02419129 SR.09 – 01 – 0001.001.9 V1	APROACH 02419130 SR.09 – 01 – 0001.001.10 V1	APROACH 02419131 SR.09 – 01 – 0001.001.11 V1	APROACH 02419132 SR.09 – 01 – 0001.001.12 V1
APROACH 02419133 SR.09 – 01 – 0001.001.13 V1	APROACH 02419134 SR.09 – 01 – 0001.001.14 V1	APROACH 02419135 SR.09 – 01 – 0001.001.15 V1	APROACH 02419136 SR.09 – 01 – 0001.001.16 V1
APROACH 02419137 SR.09 – 01 – 0001.001.17 V1	APROACH 02419138 SR.09 – 01 – 0001.001.18 V1		

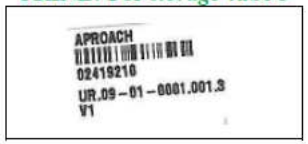
VISIT V1-M0 (2/5)

URINE : For *collection* tube 1

URINE: For *centrifuge* tube 2

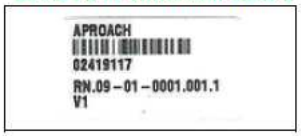


URINE: For *storage* tube 3



VISIT V1-M0 (3/5)

RNA : For *collection* tube 1



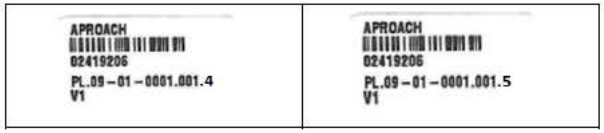
VISIT V1-M0 (4/5)

DNA for *collection* tube 1

VISIT V1-M0 (5/5)

PLASMA for *collection* tube 1

PLASMA for *storage* tubes 2 to 5 for Proteomic and Metabolomic samples



PLASMA for *storage* tubes 6 and 7 for Lipidomic samples

VISIT V2-M6 (1/2)

SERUM : For *collection* tubes: 1-3

SERUM: For Pooling tube 4

SERUM: For *storage* tubes from 5 to 18

APROACH 02419146 SR.09 – 01 – 0001.002.5 V2	APROACH 02419147 SR.09 – 01 – 0001.002.6 V2	APROACH 02419148 SR.09 – 01 – 0001.002.7 V2	APROACH 02419149 SR.09 – 01 – 0001.002.8 V2
APROACH 02419150 SR.09 – 01 – 0001.002.9 V2	APROACH 02419151 SR.09 – 01 – 0001.002.10 V2	APROACH 02419152 SR.09 – 01 – 0001.002.11 V2	APROACH 02419153 SR.09 – 01 – 0001.002.12 V2
APROACH 02419154 SR.09 – 01 – 0001.002.13 V2	APROACH 02419155 SR.09 – 01 – 0001.002.14 V2	APROACH 02419156 SR.09 – 01 – 0001.002.15 V2	APROACH 02419157 SR.09 – 01 – 0001.002.16 V2
APROACH 02419158 SR.09 – 01 – 0001.002.17 V2	APROACH 02419159 SR.09 – 01 – 0001.002.18 V2		

VISIT V2-M6 (2/2)

URINE : For *collection* tube 1

URINE: For *centrifuge* tube 2

URINE: For *storage* tube 3

VISIT V3-M12 (1/2)

SERUM : For *collection* tubes: 1-3

SERUM: For Pooling tube 4

SERUM: For *storage* tubes from 5 to 18

APROACH 02419167 SR.09-01-0001.003.5 V3	APROACH 02419168 SR.09-01-0001.003.6 V3	APROACH 02419169 SR.09-01-0001.003.7 V3	APROACH 02419170 SR.09-01-0001.003.8 V3
APROACH 02419171 SR.09-01-0001.003.9 V3	APROACH 02419172 SR.09-01-0001.003.10 V3	APROACH 02419173 SR.09-01-0001.003.11 V3	APROACH 02419174 SR.09-01-0001.003.12 V3
APROACH 02419175 SR.09-01-0001.003.13 V3	APROACH 02419176 SR.09-01-0001.003.14 V3	APROACH 02419177 SR.09-01-0001.003.15 V3	APROACH 02419178 SR.09-01-0001.003.16 V3
APROACH 02419179 SR.09-01-0001.003.17 V3	APROACH 02419180 SR.09-01-0001.003.18 V3		

Clinical trial protocol
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Version number: 1.0

VISIT V3-M12 (2/2)

URINE : For *collection* tube 1

URINE: For *centrifuge* tube 2

URINE: For *storage* tube 3

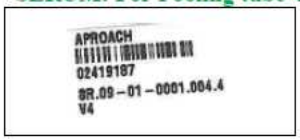
Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

VISIT V4-M24 (1/4)

SERUM : For *collection* tubes: 1-3

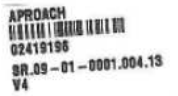
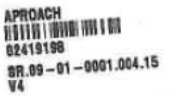
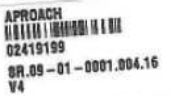
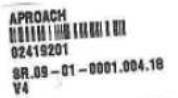
SERUM: For Pooling tube 4



Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

SERUM: For *storage* tubes from 5 to 21

Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

VISIT V4-M24 (2/4)

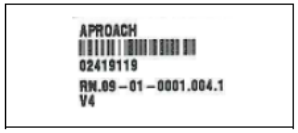
URINE : For *collection* tube 1

URINE: For *centrifuge* tube 2

URINE: For *storage* tube 3

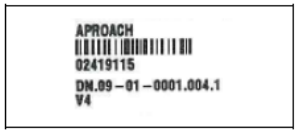
VISIT V4-M24 (3/4)

RNA : For *collection* tube 1



VISIT V4-M24 (4/4)

DNA for *collection* tube 1



Appendix 2: APPROACH WP2 Clinical Centre Excel Spreadsheet

APPROACH WP2
Clinical Centre Spreac

SOP 10.4: Logging and Storage of APPROACH Samples at Testing Sites

Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

SOP 10.4: Logging and Storage of APPROACH Samples at Testing Sites

V1.0 d.d. 23-08-2016

Sample Logging Kits

Sample logging kits will be supplied to each testing site

Contents:

Hardware:

- Barcode reader

Sample Tracking Spreadsheet:

- APPROACH WP2 Testing Site Excel spreadsheet (Specific for each Testing Site – Master Spreadsheet attached in Appendix 1)

Sample Receipt and Storage

Procedure

1. Upon receipt of sample shipments from clinical centres, complete Reception portions of shipment form that is included in the shipment (Example in Appendix 2) and Fax completed form to:
2. Cryoboxes (example labels shown in Appendix 3) are to be stored in -70°C to -80°C freezer until testing is performed.

Sample Logging and Results

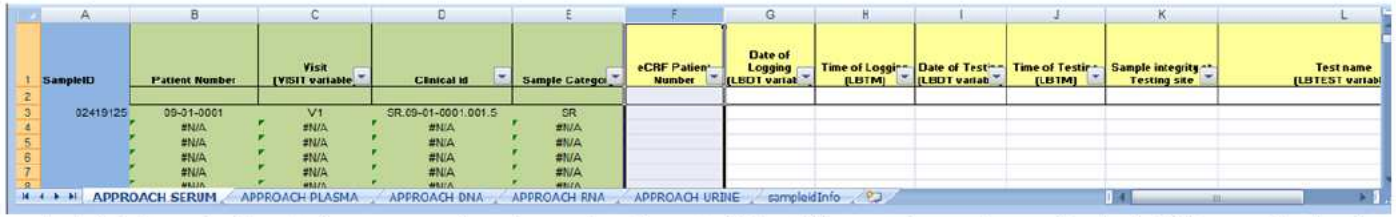
1. Upon receipt (or at initiation of testing), sample tubes should be scanned into APPROACH WP2 Testing Site Excel spreadsheet.
    a. **Note: It is acceptable to use local standard testing site practices, if present, to log, handle and track samples.**
    b. **However, APPROACH specific data should ultimately be consolidated into the supplied APPROACH WP2 Testing Site Excel spreadsheet described below.**
2. Navigate to APPROACH WP2 Testing Site Excel spreadsheet tab specific for sample type being tested (e.g. Serum, Plasma, Urine, DNA or RNA)
3. Click on uppermost open cell in 'SampleID' column (A) – Take care to confirm that appropriate cell is highlighted

Property of APPROACH-OA - strictly confidential

Page 1

Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0



4. Labeled sample aliquot tubes are scanned one by one from lowest to highest (for example; numbers ending in .5-.18 for serum) using the barcode scanner
    a. Cells in columns B-E will automatically populate and selected cell in column A will move down one row awaiting the next input
5. Manually enter sample specific information and testing assay results in columns with yellow headers.
6. Complete this for each sample type and aliquot on the appropriate tab of the spreadsheet
7. 'Save' updated APPROACH WP2 Clinical Centre Excel spreadsheet into APPROACH database

Appendix 1: APPROACH WP2 Testing Site Excel Master Spreadsheet

APPROACH WP2
Testing Site Spreadsh

Property of APPROACH-OA - strictly confidential

Page 2

Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

Appendix 2: Shipment Form

Study APPROACH
Indvidual Shipment Form

From: Centre test Adresse test 92100

To:

Date of shipment	Day	Month	Year	Time
	/_/_/	/_/_/	/_/_/_/_/	

Sample Type	Number of Cryoboxes	Number of Sample Tubes	Reception: OK/NOT OK	If NOT OK, Issue	Monitoring Date	Comments
Serum	6	600				

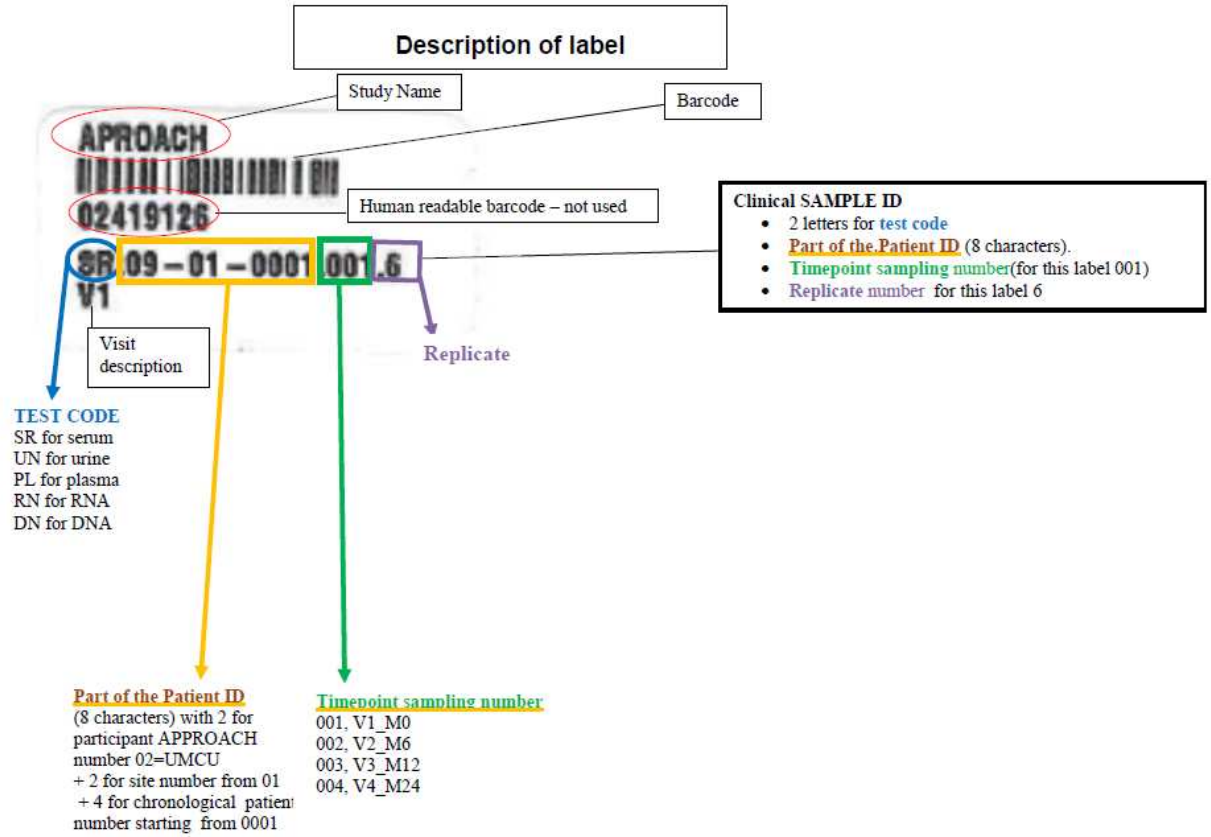
Acknowledgement at reception: Date / / Time :

Name:

Signature:

At Reception please fax this form to

Appendix 3: Sample Barcode and Cryostorage Box Labeling



Clinical trial protocol
Study number : APPROACH-OA-P01

6 January 2017
Version number: 1.0

Sample Testing/Storage Site Information

Distribution Site	Analysis	Sample Type(s)	Sampling Visits	Aliquots (per visit)	Aliquot Volume (mL)	Subjects	Total Visits (per subject)	Total Tubes	# of (10x10) cryoboxes	Aliquot #s (from barcode label)
Nordic Bioscience	Biomarker	Serum	M000-M024	5	0.5	300	4	10000	100	SR .5-.9
Artialis	Biomarker	Serum	M000-M024	3	0.5	300	4	6000	60	SR .10-.12
Lund	Biomarker	Serum	M000-M024	3	0.5	300	4	6000	60	SR .13-.15
Surrey	Metabolomics	Plasma	M000	2	0.5	300	1	1000	10	PL .2-.3
Sergas	Proteomics	Plasma	M000	2	0.5	300	1	1000	10	PL .4-.5
LUMC	Lipidomics	Plasma	M000	2	0.5	300	1	1000	10	PL .6-.7
AbbVie	Transcriptomics Genomics Epigenetics	DNA and RNA	M000 and M024	1 DNA 1 RNA	8.5 DNA 2.5 RNA	300	2	1000 DNA 1000 RNA	10 DNA 10 RNA	DN .1 RN .1
BST	Short Term Storage	Serum	M000-M024	2	0.5	300	4	4000	40	SR .16-.17
BST	Long Term Storage	Serum and Urine	M000-M024	1 Serum 1 Urine	5.0 Serum 10.0 Urine	300	4	2000 Serum 2000 Urine	20 Serum 20 Urine	SR .18 UR .3

Cryobox Labels for aliquot distribution:

Serum Aliquots

APPROACH SERUM Aliquots (0.5mL)
Include SR tubes ending in: .5, .6, .7, .8 and .9

Shipment to: Nordic Bioscience

APPROACH SERUM Aliquots (0.5mL)
Include SR tubes ending in: .10, .11 and .12

Shipment to: Artialis

APPROACH SERUM Aliquots (0.5mL)
Include SR tubes ending in: .13, .14 and .15

Shipment to: Lund

APPROACH SERUM Aliquots (0.5mL)
Include SR tubes ending in:.16 and.17

Shipment to: BST

APPROACH SERUM Aliquots (5mL)
Include SR tubes ending in: .18

Shipment to: BST

Urine Aliquots

APPROACH URINE Aliquots (10mL)
Include DN tubes ending in .3

Shipment to: BST

Plasma Aliquots

APPROACH PLASMA Aliquots (0.5mL)
Include PL tubes ending in .2 and .3

Shipment to: LUMC

APPROACH PLASMA Aliquots (0.5mL)
Include PL tubes ending in: .4 and .5

Shipment to: Surrey

APPROACH PLASMA Aliquots (0.5mL)
Include PL tubes ending in: .6 and .7

Shipment to: Sergas

DNA Samples

APPROACH DNA Samples
Include DN tubes ending in .1

Shipment to: AbbVie

RNA Samples

APPROACH RNA Samples
Include RN tubes ending in .1

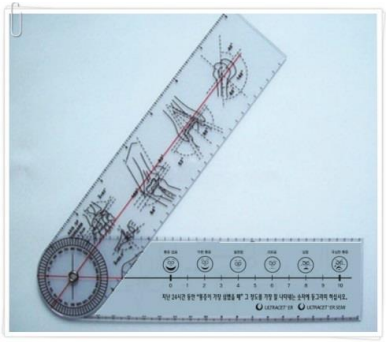
Shipment to: AbbVie

SOP 11: Physical examination

V1.0 d.d. 29-MAR-2017

Aim
To determine physical condition.
To determine knee, hip, and hand joint function (stiffness and inflammation)

Duration of procedure
Approximately 30 minutes



Preparation/prerequisites

- Automated blood pressure monitor
- Room with examination table
- Wall ruler
- Body weight scale
- Measuring tape
- Goniometer

Time points evaluated
Height, weight and index knee: Screening, M006, M012, and M024
Vital signs, hips, hands, contralateral knee: Inclusion, M006, M012, and M024

Acquisition

- **Blood Pressure (SBP/DBP in mmHg)**
  Patient needs to sit down for 3 minutes in a relaxed position. Patient's arm lies on the table/desk with open palm. Place cuff on the upper arm with the arrow pointing down (indicates artery). Cuff needs to be put at mid-sternal height. Make sure you use the correct cuff size (i.e. not too loose or tight). The patient is not allowed to talk during the measurement.
  Automatic blood pressure measurement:
    - *Selection of either left or right arm (only at inclusion)*

  Measure blood pressure on the right arm. Register SBP/DBP. Repeat measurement on the left arm. When difference is >10mmHg SBP or >5mmHg DBP, select and register arm with highest pressure. When there is no relevant difference in pressure between arms, the right arm should be selected.
    - *Blood pressure assessment*

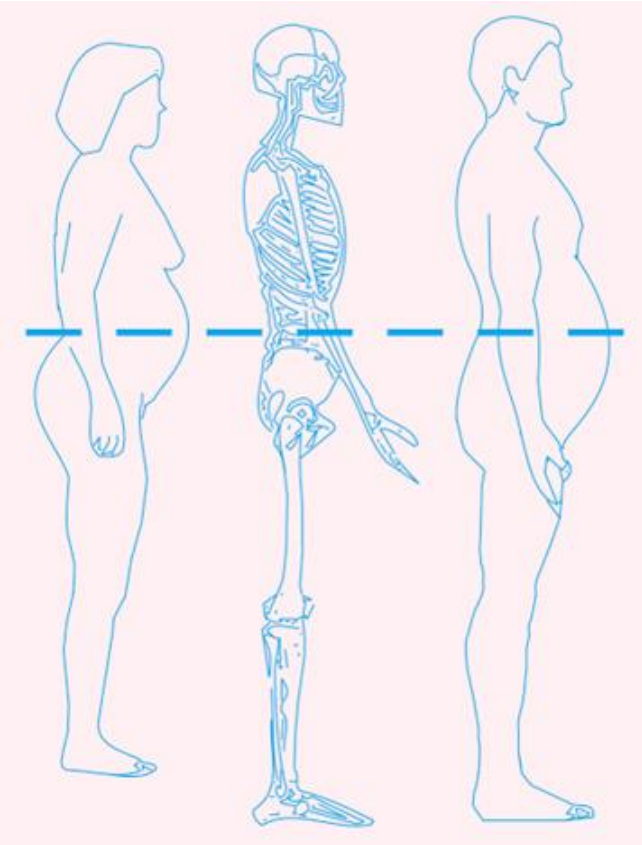
  Repeat measurement on selected arm twice. Report these two measurements in eCRF (average will be calculated). Use the same arm at every visit.

- **Pulse (in bpm)**
  Automatic blood pressure monitor: measures pulse automatically. Again both measurements should be registered in the eCRF.

- **Height (only at screening, in cm)**
  Patient is asked to ***take off his/her shoes*** and stand upright against the wall ruler.

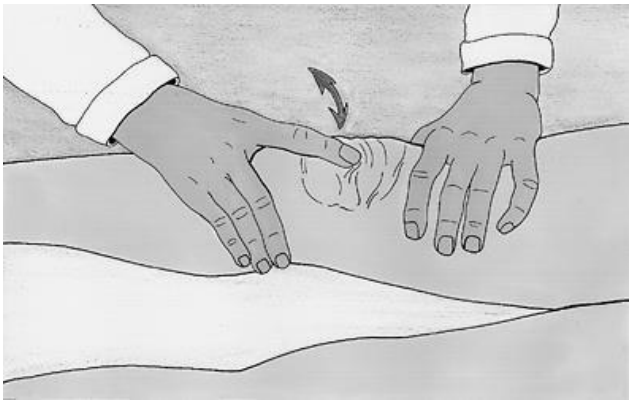
- **Weight – undressed (in kg)**
  Patient is asked to take place on a scale.

- **Waist circumference – undressed (in cm)**
  Waist circumference: locate top of iliac crest. Place measuring tape in a horizontal plane plane around the abdomen at the level of iliac crests. Ensure that tape is tight-fitting, without compressing the skin, and is parallel to the floor. Ask the patient to breath out normally and measure at end of normal expiration.



Measuring-tape position for waist circumference in adults - ***National Heart, Lung, and Blood Institute. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart Lung and Blood Institute, Bethesda, MD, October 2000.***

- **Knee – undressed. Examine both knees.**
  - **Warmth:** Feel warmth with back of your hand. Register absence or presence of warmth.
  - **Effusion (patellar tap)**:

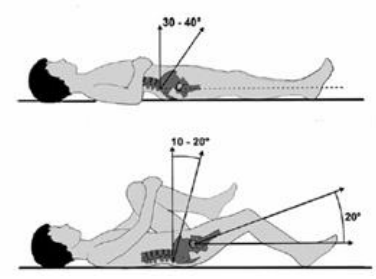


Patellar tap: Bouncing patella indicates presence of an effusion

Slide down one hand from patient's thigh and slide up the other hand from patient's lower leg so that any effusion is collected under the patella. Use the index (and middle) finger of your lowest hand to swiftly but briskly tap the patella. If the patella bounces (patellar tap) this indicates the presence of an effusion. Register absence or presence of patellar tap.

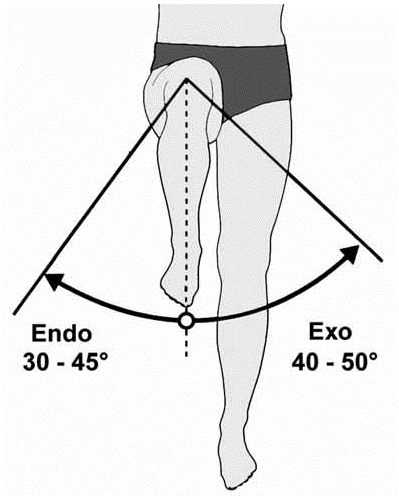
- **Passive range of flexion**: Measure with goniometer. Register as either <90º, 90º-120º, or >120º
- **Passive range of extension**: Test for flexum. Grasp both heels with the patient lying on his or her back, with legs extended, and lift them to 10cm above the table. If leg can't be fully extended there is a knee flexum. Register presence or absence.
- **Grind test**: Place the web space of your thumb on the superior part of the patella, then ask patient to gradually contract the quadriceps muscle while pushing your hand downwards. Positive when grinding AND pain are present. Register presence or absence.

- **Hip – undressed. Examine both hips**
  - **Passive range of flexion:** Measure with goniometer. Register as either <90º, 90º-120º, or >120º
  - **Passive range of extension:** Test for flexum. Thomas test: Flex one hip to the maximum. When the contralateral leg cannot be held in full extension and in contact with the table, there is a flexum in the hip of that leg



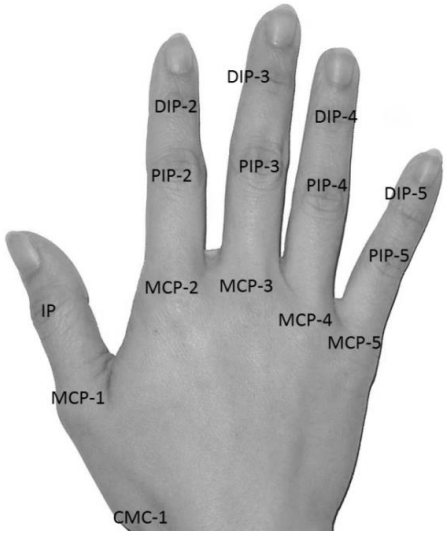
Thomas test: There is a flexum in the right hip

  - **Passive internal rotation**: Measure with goniometer with hip and knee both flexed at 90 degrees. Register as either <30º, 30º-45º, or >45º
  - **Passive external rotation:** Measure with goniometer with hip and knee both flexed at 90 degrees. Register as either <30º, 30º-45º, or >45º


Endo
30 - 45°
Exo
40 - 50°

- **Hands. Examine both hands**
  - **Hard tissue enlargement/Bouchard nodules (PIPs) and Heberden nodules (DIPs):** location of affected joints
  - Number and location of **inflamed joints** as defined by soft synovial tissue swelling and/or fluctuation on palpation
  - **Doyle index**: Put thumbs on dorsal side of joint and index fingers on palmar side. Give pressure until own fingertips turn white. Grade pain in all DIP joints, PIP joints, MCP joints, IP joint of thumb and first CMC joint (Doyle 1981):
    - 0= no tenderness
    - 1= patient complains of pain
    - 2= patient complains of pain and winces
    - 3= patient complains of pain, winces and withdraws joint
  - **Subluxation MCP-1:** in relaxed position. Register as yes or no.
  - **Deformity of CMC-1, PIP-2, PIP-3, DIP-2 and DIP-3**

    Ask patient whether pain was present in hand joints during a period of more than 20 days during the last month: yes/no



PATIENT-ID

Date:
M000/M006/M012/M024

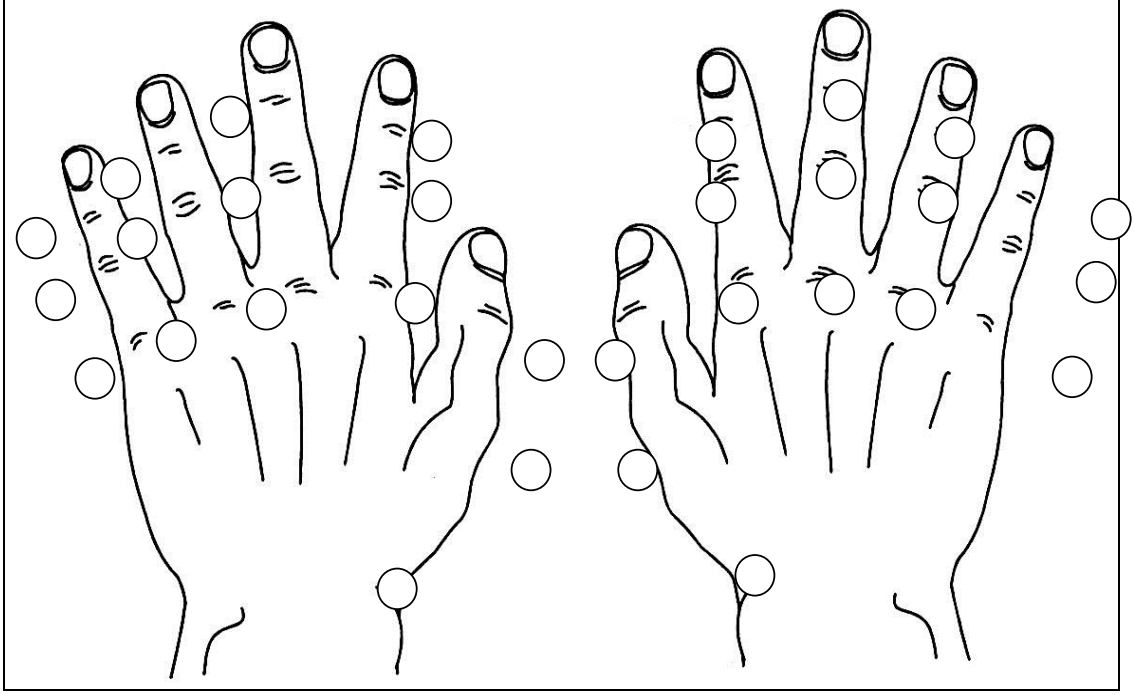
Physical examination

*** fill in a number**
**** cross wrong answer(s)**
***** answer YES/NO in general and write down which joints are affected**
****** score 0-3**

General*		
o Blood pressure	……mmHg	
o Pulse	……bpm	
o Height	……cm (only at screening)	
o Weight	……kg	
o Waist circumference	……cm	
Knee**	**Left**	**Right**
o Warmth	YES/NO	YES/NO
o Effusion	YES/NO	YES/NO
o Passive flexion	<90º/90º-120º/>120º	<90º/90º-120º/>120º
o Passive extension: flexum	YES/NO	YES/NO
o Patellar grinding	YES/NO	YES/NO
o Presence of varus	YES/NO	YES/NO
o Presence of valgus	YES/NO	YES/NO
Hip**	**Left**	**Right**
o Passive flexion	<90º/90º-120º/>120º	<90º/90º-120º/>120º
o Passive extension: flexum	YES/NO	YES/NO
o Internal rotation	<30º/30º-45º/>45º	<30º/30º-45º/>45º
o External rotation	<30º/30º-45º/>45º	<30º/30º-45º/>45º

Hand***

- Heberden's nodes (DIP), mark as **H**
- Bouchard's nodes (PIP), mark as **B**
- Hard tissue enlargement other than Heberden or Bouchard nodules, mark as **E**
- Inflamed joints, mark as **I**



Doyle index (Doyle 1981)******	**Left**	**Right**
○ DIP-2	…	…
○ DIP-3	…	…
○ DIP-4	…	…
○ DIP-5	…	…
○ PIP-2	…	…
○ PIP-3	…	…
○ PIP-4	…	…
○ PIP-5	…	…
○ IP	…	…
○ MCP-1	…	…
○ MCP-2-5	…	…
○ CMC-1	…	…
	Total left	**Total right**
	Total (left + right)	
Subluxation MCP-1**	**Left**	**Right**
	YES/NO	YES/NO
Deformity	**Left**	**Right**
○ CMC-1	YES/NO	YES/NO
○ DIP-2	YES/NO	YES/NO
○ DIP-3	YES/NO	YES/NO
○ PIP-2	YES/NO	YES/NO
○ PIP-3	YES/NO	YES/NO
Has the patient pain present in hand joints during a period of more than 20 days during the last month?	YES/NO	

Appendix 4: Questionnaires

KOOS, reduced version, at screening

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 1

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last 48 hours** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 2

Pain

P1. How often do you experience knee pain?

Never ☐ Monthly ☐ Weekly ☐ Daily ☐ Always ☐

What amount of knee pain have you experienced the **last 48 hours** during the following activities ?

P2. Twisting/pivoting on your knee

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P3. Straightening knee fully

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P4. Bending knee fully

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P5. Walking on flat surface

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P6. Going up or down stairs

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P7. At night while in bed

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P8. Sitting or lying

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P9. Standing upright

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Function, daily living

The following questions concern your physical finction. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last 48 hours** due to your knee.

A1. Descending stairs

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A2. Ascending stairs

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 3

For each of the following activities please indicate the degree of difficulty you have experienced in the **last 48 hours** due to your knee.

A3. Rising from sitting
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A4. Standing
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A5. Bending to floor/pick up an object
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A6. Walking on flat surface
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A7. Getting in/out of car
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A8. Going shopping
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A9. Putting on socks/stockings
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A10. Rising from bed
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A11. Taking off socks/stockings
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A12. Lying in bed (turning over, maintaining knee position)
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A13. Getting in/out of bath
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A14. Sitting
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A15. Getting on/off toilet
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 4

For each of the following activities please indicate the degree of difficulty you have experienced in the **last 48 hours** due to your knee.

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

KOOS for visits other than screening

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 1

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 4

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

HOOS HIP SURVEY

HOOS HIP SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your hip. This information will help us keep track of how you feel about your hip and how well you are able to do your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are uncertain about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your hip symptoms and difficulties during the **last week**.

S1. Do you feel grinding, hear clicking or any other type of noise from your hip?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Difficulties spreading legs wide apart

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S3. Difficulties to stride out when walking

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your hip. Stiffness is a sensation of restriction or slowness in the ease with which you move your hip joint.

S4. How severe is your hip joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S5. How severe is your hip stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain
P1. How often is your hip painful?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of hip pain have you experienced the **last week** during the following activities?

P2. Straightening your hip fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

What amount of hip pain have you experienced the **last week** during the following activities?

P3. Bending your hip fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Walking on a flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Walking on a hard surface (asphalt, concrete, etc.)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P10. Walking on an uneven surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your hip.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Hip dysfunction and Osteoarthritis Outcome Score (HOOS), English version LK 2.0 3

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your hip.

A5. Bending to the floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on a flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining hip position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your hip.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Twisting/pivoting on loaded leg

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Walking on uneven surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your hip problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid activities potentially damaging to your hip?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your hip?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your hip?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

A Measure of Intermittent and constant osteoarthritis Pain, ICOAP Knee version and Hip version

{merge ID here}

A Measure of Intermittent and Constant Osteoarthritis Pain, ICOAP: KNEE Version

People have told us that they experience different kinds of pain (including aching or discomfort) in their knee. To get a better sense of the different types of knee pain you may experience, we would like to ask you about any "constant pain" (pain you have all the time) separately from any pain that you may experience less often, that is, "pain that comes and goes". The following questions will ask you about the pain that you have experienced in your knee in the PAST WEEK. Please answer ALL questions.

A) CONSTANT PAIN

For each of the following questions, please select the response that best describes, on average, your *constant knee pain* in the PAST WEEK.

1. **In the past week, how intense has your *constant knee pain* been?**

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant knee pain	Mildly	Moderately	Severely	Extremely

2. **In the past week, how much has your *constant knee pain* affected your sleep?**

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant knee pain	Mildly	Moderately	Severely	Extremely

3. **In the past week, how much has your *constant knee pain* affected your overall quality of life?**

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant knee pain	Mildly	Moderately	Severely	Extremely

4. **In the past week, how frustrated or annoyed have you been by your *constant knee pain?***

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant knee pain	Mildly	Moderately	Severely	Extremely

5. **In the past week, how upset or worried have you been by your *constant knee pain*?**

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant knee pain	Mildly	Moderately	Severely	Extremely

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{merge ID here}

B) PAIN THAT COMES AND GOES

For each of the following questions, please select the response that best describes your *knee pain that comes and goes*, *on average*, in the PAST WEEK.

6. In the past week, how intense has your most severe *knee pain that comes and goes* been?

☐0	☐1	☐2	☐3	☐4
Not at all/ No knee pain that comes and goes	Mildly	Moderately	Severely	Extremely

7. In the past week, how frequently has this *knee pain that comes and goes* occurred?

☐0	☐1	☐2	☐3	☐4
Never/ No knee pain that comes and goes	Rarely	Sometimes	Often	Very Often

8. In the past week, how much has your *knee pain that comes and goes* affected your sleep?

☐0	☐1	☐2	☐3	☐4
Not at all/ No knee pain that comes and goes	Mildly	Moderately	Severely	Extremely

9. In the past week, how much has your *knee pain that comes and goes* affected your overall quality of life?

☐0	☐1	☐2	☐3	☐4
Not at all/ No knee pain that comes and goes	Mildly	Moderately	Severely	Extremely

10. In the past week, how frustrated or annoyed have you been by your *knee pain that comes and goes*?

☐0	☐1	☐2	☐3	☐4
Not at all/ No knee pain that comes and goes	Mildly	Moderately	Severely	Extremely

11. In the past week, how upset or worried have you been by your *knee pain that comes and goes*?

☐0	☐1	☐2	☐3	☐4
Not at all/ No knee pain that comes and goes	Mildly	Moderately	Severely	Extremely

THANK YOU!

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{merge ID here}

A Measure of Intermittent and Constant Osteoarthritis Pain, ICOAP: HIP Version

People have told us that they experience different kinds of pain (including aching or discomfort) in their hip. To get a better sense of the different types of hip pain you may experience, we would like to ask you about any "constant pain" (pain you have all the time) separately from any pain that you may experience less often, that is, "pain that comes and goes". The following questions will ask you about the pain that you have experienced in your hip in the PAST WEEK. Please answer ALL questions.

A) CONSTANT PAIN

For each of the following questions, please select the response that best describes, on average, your *constant hip pain* in the PAST WEEK.

1. In the past week, how intense has your *constant hip pain* been?

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant hip pain	Mildly	Moderately	Severely	Extremely

2. In the past week, how much has your *constant hip pain* affected your sleep?

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant hip pain	Mildly	Moderately	Severely	Extremely

3. In the past week, how much has your *constant hip pain* affected your overall quality of life?

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant hip pain	Mildly	Moderately	Severely	Extremely

4. In the past week, how frustrated or annoyed have you been by your *constant hip pain?*

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant hip pain	Mildly	Moderately	Severely	Extremely

5. In the past week, how upset or worried have you been by your *constant hip pain*?

☐0	☐1	☐2	☐3	☐4
Not at all/ No constant hip pain	Mildly	Moderately	Severely	Extremely

{merge ID here}

B) PAIN THAT COMES AND GOES

For each of the following questions, please select the response that best describes your *hip pain that comes and goes*, *on average*, in the PAST WEEK.

6. In the past week, how intense has your most severe *hip pain that comes and goes* been?

☐0	☐1	☐2	☐3	☐4
Not at all/ No hip pain that comes and goes	Mildly	Moderately	Severely	Extremely

7. In the past week, how frequently has this *hip pain that comes and goes* occurred?

☐0	☐1	☐2	☐3	☐4
Never/ No hip pain that comes and goes	Rarely	Sometimes	Often	Very Often

8. In the past week, how much has your *hip pain that comes and goes* affected your sleep?

☐0	☐1	☐2	☐3	☐4
Not at all/ No hip pain that comes and goes	Mildly	Moderately	Severely	Extremely

9. In the past week, how much has your *hip pain that comes and goes* affected your overall quality of life?

☐0	☐1	☐2	☐3	☐4
Not at all/ No hip pain that comes and goes	Mildly	Moderately	Severely	Extremely

10. In the past week, how frustrated or annoyed have you been by your *hip pain that comes and goes*?

☐0	☐1	☐2	☐3	☐4
Not at all/ No hip pain that comes and goes	Mildly	Moderately	Severely	Extremely

11. In the past week, how upset or worried have you been by your *hip pain that comes and goes*?

☐0	☐1	☐2	☐3	☐4
Not at all/ No hip pain that comes and goes	Mildly	Moderately	Severely	Extremely

THANK YOU!

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FIHOA

Please answer the questions regarding the past 48 hours.

FIHOA

FUNCTIONAL INDEX FOR HAND ARTHROPATHIES (FIHOA)

Scoring system
0: possible without difficulty
1: possible with slight difficulty
2: possible with important difficulty
3: impossible

1.	Are you able to turn a key in a lock?	☐0 ☐1 ☐2 ☐3
2.	Are you able to cut meat with a knife?	☐0 ☐1 ☐2 ☐3
3.	Are you able to cut cloth or paper with a pair of scissors?	☐0 ☐1 ☐2 ☐3
4.	Are you able to lift a full bottle with the hand?	☐0 ☐1 ☐2 ☐3
5.	Are you able to clench your fist?	☐0 ☐1 ☐2 ☐3
6.	Are you able to tie a knot?	☐0 ☐1 ☐2 ☐3
7.	*For women* - Are you able to sew? *For men* - Are you able to use a screwdriver?	☐0 ☐1 ☐2 ☐3
8.	Are you able to fasten buttons?	☐0 ☐1 ☐2 ☐3
9.	Are you able to write for a long period of time (1 mn)?	☐0 ☐1 ☐2 ☐3
10.	Would you accept a handshake without reluctance?	☐0 ☐1 ☐2 ☐3

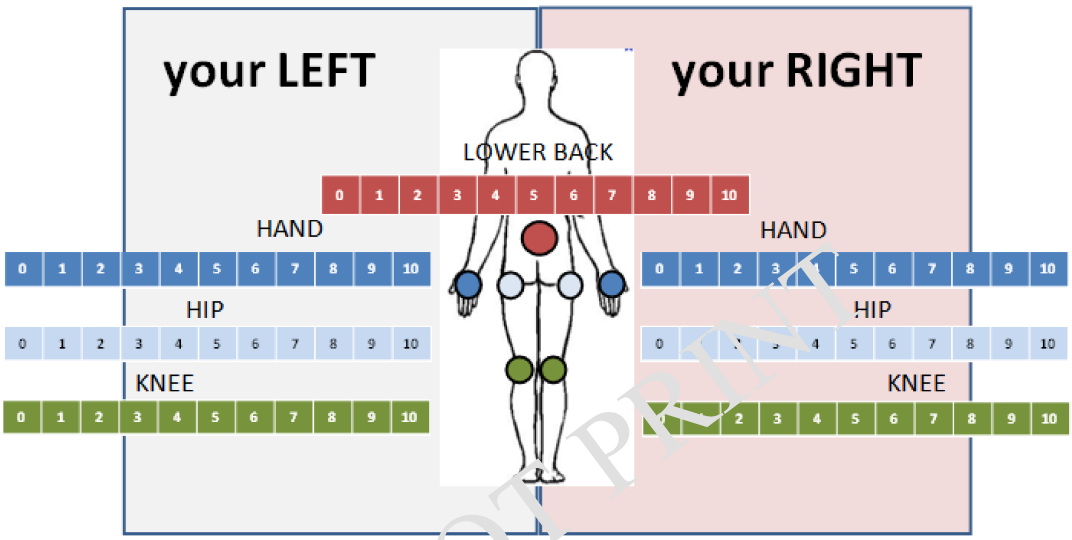
Result

Pain NRS right now in knee, hip, hand, and lower back at screening

Pain NRS (Numeric Rating Scale) for lower back, hips, hands and knees

How severe is your pain right now on the following joints?

Circle the number that Best Describes Your Pain for each joint knowing that 0 means no pain and 10 means very severe pain.

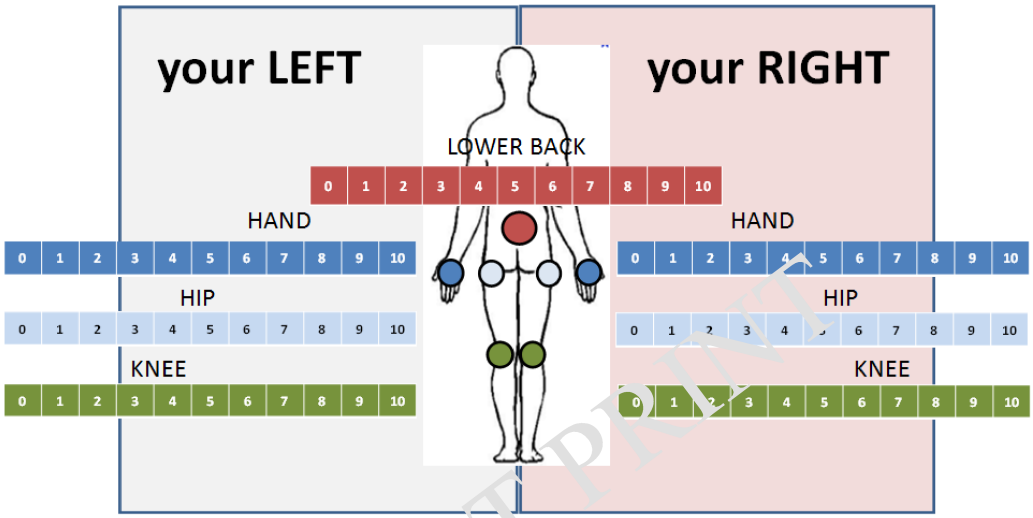


Pain NRS on the last week in knee, hip, hand, and lower back

Pain NRS (Numeric Rating Scale) for lower back, hips, hands and knees

How severe was your pain during the last week on the following joints?

Circle the number that Best Describes Your Pain for each joint knowing that 0 means no pain and 10 means very severe pain.



Pain DETECT

painDETECT PAIN QUESTIONNAIRE

Date: ..... Patient: Last name: ..... First name: .....

How would you assess your pain **now**, at this moment?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the **strongest** pain during the past 4 weeks?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the pain during the past 4 weeks **on average**?

0 1 2 3 4 5 6 7 8 9 10

none max.

Mark the picture that best describes the course of your pain:

- **Persistent pain with slight fluctuations** ☐
- **Persistent pain with pain attacks** ☐
- **Pain attacks without pain between them** ☐
- **Pain attacks with pain between them** ☐

Please mark your **main area of pain**

Does your pain radiate to other regions of your body? yes ☐ no ☐

If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

never	hardly noticed	slightly	moderately	strongly	very strongly
x 0 = 0	x 1 =	x 2 =	x 3 =	x 4 =	x 5 =

Total score ____ **out of 35**

R. Freynhagen, R. Baron, U. Gockel,T.R. Tölle, CurrMed ResOpin Vol 22, 2006, 1911-1920 © 2005 Pfizer Pharma GmbH, Pfizerstr.1, 76139 Karlsruhe, Germany

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painDETECT

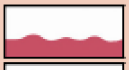
SCORING OF PAIN QUESTIONNAIRE

Date: ..... Patient: Last name: ..... First name: .....

Please transfer the total score from the pain questionnaire:

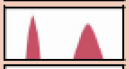
Total score ☐☐

Please add up the following numbers, depending on the marked pain behavior pattern and the pain radiation. Then total up the final score:



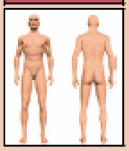
Persistent pain with slight fluctuations — 0

Persistent pain with pain attacks — -1 — if marked, or



Pain attacks without pain between them — +1 — if marked, or

Pain attacks with pain between them — +1 — if marked

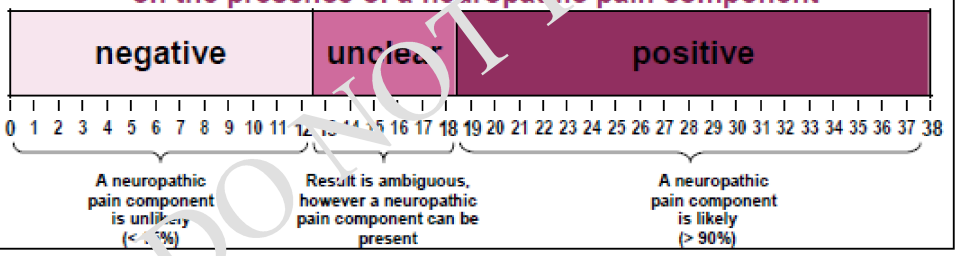


Radiating pains? — +2 — if yes

Final score ☐☐

Screening Result

on the presence of a neuropathic pain component



This sheet does not replace medical diagnostics.
It is used for screening the presence of a neuropathic pain component.

DFNS

pain

R. Freynhagen, R. Baron, U. Gockel,T.R. Tölle, CurrMed ResOpin Vol 22, 2006, 1911-1920

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SF-36 Health survey

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks.** For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks...**

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

One month pain diary

STUDY N° CL2-IMIRHU-001 COUNTRY |_x_|_x_|_x_|

CENTRE N° |__|__|__|__|__| PATIENT N° |__|__|__|__|__|__| VISIT |_x_|_x_|_x_|_x_|

One month pain diary

1-Please, start completing this diary at least 1 month before your next visit to clinical centres (for example, if your next visit is planned on 15th November, you need to start to complete this diary on 15th October)

2-It is very important to complete it every day at the end of the day. You can put it on a place where it is easy to access, for example on the door of your fridge.

3-My most affected knee is the ☐ right knee

☐ left knee

Starting date of diary completion (DD/MM/YYYY) : __/__/20__

Day	1. Do you have pain in your most affected knee?	2. Did you take painkiller or analgesics* for your most affected knee ?	3. Did you take painkiller or analgesics* for other reasons (for example headache, throatache, backache)?
D1	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D2	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D3	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D4	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D5	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D6	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D7	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D8	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D9	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D10	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D11	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D12	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D13	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D14	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D15	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D16	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D17	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D18	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D19	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D20	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D21	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D22	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D23	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D24	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D25	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D26	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D27	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D28	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D29	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D30	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
D31	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No

* painkiller or analgesicsare treatments to decrease or suppress your pain (pill, tablet, capsule, ampule…)