



**A Prospective Non-Interventional Study
on STRUctum[®] in Adult Patients with
oSTeoarthritis**

TRUST

Version 4

Date 21/12/2023

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Coordinating Physician and member of Scientific Committee	PPD [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
Scientific Committee	PPD [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

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INVESTIGATOR SIGNATURE PAGE

Study title: **A Prospective Non-Interventional Study on STRUctum® in Adult Patients with oSTeoarthritis (TRUST)**

Protocol version and date: V4.0 21-DEC-2023

I have read and understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signing this agreement I confirm that the study will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to good pharmacoepidemiology practices (GPP), and the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel under my responsibility, who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the study. I am aware that this protocol will need to be approved by an appropriate institutional review board (IRB) or independent ethics committee (IEC) prior to any patients being enrolled and that I am responsible for ensuring that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

Print name

Signature

Date

Print name of Institution or Practice, and Location

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PROTOCOL APPROVAL SIGNATURE PAGE

This protocol, version V4.0 and dated 21/12/2023, has been reviewed and approved by:

PPD

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HISTORY OF CHANGES

VERSIONS

Date	version N°	Reason for change
23/02/2023	V1.0	Initial version
04/04/2023	V2.0	Addition of Protocol approval signature page and investigator signature page, modification of contact presentation first page. Modifications of the information collected in the eCRF: - Updated types of treatment before inclusion; - Definition of timepoint newly diagnosed; - Updated assessment of severity of knee OA by saying the Kellgren and Lawrence radiologic assessment will be done on both knees and the Lequesne algofunctional index only for the most painful knee; - Updated exclusion criteria (patient having received intraarticular injections of corticosteroids, hyaluronic acid, and platelet-rich plasma in the last 3 months rather than 2); - Added among the information collected which inclusion criteria was used for the patient (a) knee pain lasting for at least 3 months; b) patient in the active phase of knee OA disease (knee pain score $\geq$ 40mm at inclusion on the Visual Analog Scale [VAS] 0-100 mm); or c) knee radiographs showing knee joint narrowing and/or osteophytes), - Added the WOMAC and satisfaction questionnaires in the Appendices.
19/06/2023	V3.0	Addition of Professor Piotr Wiland as Coordinating Physician
18/12/2023	V4.0	Updates of: - The age of inclusion, changed from 50 to 80 into 50 to 85 years old; - The period of inclusion, changed from 6 to 9 months, and the total length of the study, changed from 12 to 15 months; - The proposed dates of the study timeline in Table 1; - The specialties of the investigators to whom the study will be proposed, to add general practitioners/family doctors, and internists. - Addition of BEGHAD Farida as one of Pierre Fabre's representative.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
BMI	Body Mass Index
BONe'S	Burden Osteoarthritis News Scale
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Chondroitin Sulphate
CSR	Clinical Study Report
EC	Ethics Committee
ECM	Extracellular Matrix
eCRF	electronic Case Report Form
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practices
GPPs	Good Pharmacoepidemiology Practices
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MRI	Magnetic Resonance Imaging
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
PRO	Patient Reported Outcome questionnaire
PV	Pharmacovigilance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SF-12	12-Item Short Form QoL Survey
SYSADOAs	Symptomatic Slow-Acting Drugs for OA
TMF	Trial Master File
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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1 SYNOPSIS

STUDY TITLE	A Prospective Non-interventional study on Structum® in Adult Patients with Osteoarthritis
SPONSOR	Pierre Fabre Médicament
SCIENTIFIC COMMITTEE	PPD
STUDY RATIONALE	A variety of therapies are available for managing pain related to osteoarthritis (OA). Currently available pharmacological agents are analgesics, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), glucocorticoids, opioids, anti-cytokines, and SYmptomatic Slow-Acting Drugs for OA (SYSADOAs). SYSADOAs are chondroprotective substances that have also been found to improve clinical symptoms of OA. They are expected to slow down, block or shift back the pathological changes in osteoarthritic joints, limiting the progression of the disease, and are associated with favorable safety profiles [1]. Chondroitin sulfate (CS) is a SYSADOA and a natural biomacromolecule belonging to the class of glycosaminoglycans. CS is a major component of the extracellular matrix (ECM), where it constitutes an essential component of proteoglycans. To this date, no real-world studies have been conducted to precisely describe the burden associated with OA among patients treated with CS.
STUDY OBJECTIVES	Primary objective: To describe the baseline clinical profile and baseline OA symptom severity (pain, stiffness and function) as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, for patients with knee OA and treated with Structum®, a pharmaceutical grade CS. Secondary objectives: 1. To describe the knee OA symptoms severity (pain, stiffness, and function) as assessed by the WOMAC questionnaire (Appendix 1) in patients treated with Structum® over the 6-month follow-up period. 2. To describe the burden associated with knee OA in daily life (independence, interaction & recreation, psychological, budget, hygiene and beauty) as assessed by the Burden of Osteoarthritis New Scale (BONe'S) questionnaire (Appendices 2a & 2b) in patients treated with Structum® over the 6-month follow-up period. 3. To describe general health (physical and mental) assessed by the Short Form 12 items (SF-12) questionnaire (Appendix 3) as a quality-of-life measure in patients treated with Structum® over the 6-month follow-up period.

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	4. To describe treatment persistence in patients treated with Structum® over the 6-month follow-up period. 5. To describe the global assessment of the patients treated with Structum® over the 6 months follow-up period (Appendix 4). Exploratory objectives (ancillary analyses): To assess the correlation between the results of the BONE'S questionnaire and the SF-12 and WOMAC questionnaires, in participating patients over the 6-month follow-up period. To describe the evolution of the use of NSAIDs and other analgesics over the 6-month follow-up period and compare with the use of NSAIDs and other analgesics during the last 6 months before inclusion
STUDY OUTCOMES	Primary outcome: The primary outcome cannot be conveyed as a single stand-alone measure but will instead entail a comprehensive description of all source data collected, to characterize the clinical profile of included patients treated with Structum®. The description of symptom severity (pain, stiffness, and function) as assessed by the WOMAC questionnaire at baseline will complete the description of the clinical profiles. Secondary outcomes: The following secondary outcomes will be described for each timepoint (baseline, 3 months, 6 months): 1) Secondary WOMAC outcomes: - mean global score of symptoms' severity - mean score of each dimension - mean differences in symptoms' severity scores at 3 and 6 months (compared to baseline) 2) BONE'S outcomes (from the patient's questionnaire): - mean global score of OA burden - mean score of each dimension - mean differences in OA burden scores at 3 and 6 months (compared to baseline) 3) SF-12 outcomes: - mean global score of general health - mean score of each dimension (physical and mental) - mean differences in general health scores at 3 and 6 months (compared to baseline) 4) Persistence outcomes: - proportion of patients with ongoing Structum® treatment at 3 months - proportion of patients with ongoing Structum® treatment at 6 months

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	5) Personal global assessment: - proportion of patients with a positive assessment of Structum® as assessed by the Structum® treatment satisfaction questionnaire at inclusion and at 3 and 6 months. Exploratory outcomes: Spearman correlation coefficient and <i>P</i> value for the correlation between the BONE'S questionnaire and the SF-12 questionnaire at inclusion, 3 and 6 months. Spearman correlation coefficient and <i>P</i> value for the correlation between the BONE'S questionnaire and the WOMAC questionnaire at inclusion, 3 and 6 months. Proportion of patients with changes in the prescription of NSAIDs and other analgesics 6 months before inclusion, at inclusion, and at 3 and 6 months.
STUDY DESIGN	National, multicenter, prospective, observational, descriptive, longitudinal study
STUDY POPULATION	Adult patients aged 50 to 85 years at inclusion with a confirmed diagnosis of knee osteoarthritis, with a new prescription for Structum®, as treated by participating centers in Poland.
INCLUSION AND EXCLUSION CRITERIA	Patients will be eligible for inclusion if they fulfill <u>ALL</u> of the following criteria: • Male or female patients aged 50 to 85 years at inclusion. • Diagnosis of knee OA (either a patient newly diagnosed or with history of knee OA), based on at least the following items 1 and/or 2: 1. knee pain lasting for at least 3 months; 2. patient in the active phase of knee OA disease (knee pain score $\geq$ 40mm at inclusion on the Visual Analog Scale [VAS] 0-100 mm); 3. knee radiographs showing knee joint narrowing and/or osteophytes. • Patients who have been prescribed, for the first time or not, Structum®. • If patient is taking any NSAIDs or other analgesics, patient could be on stable dose at least one week before inclusion to the study. • Patients able to visit the clinic and attend follow-up visits. • Patients having signed an informed consent form, according to local regulations. Patients will NOT be eligible for inclusion if they fulfil ANY of the following criteria: • Patients with any ongoing chondroitin sulfate treatment at inclusion or during the last 3 months. Patients having received or planning to

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	receive any OA comedication, including SYSADOAs¹ (in the last 3 months), and intraarticular injections of corticosteroids, hyaluronic acid, and platelet-rich plasma (in the last 3 months). No glucocorticoids administration in the last 3 months before inclusion. That does not include NSAIDS, paracetamol and other analgesic medications (e.g. tramadol). • Patients with an artificial knee joint, including unilateral. • Patients scheduled to undergo knee replacement surgery in the next 6 months. • Patients with a severe general condition that prevents them from being included in the study as assessed by the investigator. • Patients participating in interventional trials on investigational drugs at the time of inclusion.
SAMPLE SIZE	150 patients.
STATISTICS	Statistical analyses will be fully described in a written and validated Statistical Analysis Plan. The study outcomes will be analyzed for all subjects included by subgroup(s) of interest, if the sample size allows it. Analyses will be descriptive in nature, and no hypothesis will be tested. In general, missing data will not be imputed (exceptions may be detailed in the statistical analysis plan). All variables will be described using summary statistics. Categorical variables will be summarized by frequencies and percentages. Continuous variables will be summarized by descriptive statistics (mean and standard deviation, median, 25th and 75th percentiles, minimum and maximum). The number of missing observations for each variable will also be reported.

¹ These include cytokine modulators (i.e., diacerein), cartilaginous matrix precursors (i.e., glucosamine, and hyaluronic acid), and other types of drugs such as bisphosphonates.

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2 BACKGROUND AND RATIONALE

2.1 BACKGROUND

According to the Global Burden of Disease 2017 Study, osteoarthritis (OA) affects more than 300 million adults globally, with incidence rates increasing during the period surveyed from 1990 to 2017 [2]. The remarkable impact of OA on individual well-being, work productivity, and medication use [3] carries over to become a major burden on healthcare systems [4]. Indeed, mobility loss due to lower limb OA has even been linked to a significantly increased risk in mortality (hazard ratio: 1.93; 95% CI ([1.59 – 2.36]) [5].

Characterized by the degeneration and loss of articular cartilage, OA disrupts the mechanical properties of cartilage and subchondral bone, leading to modifications in the surrounding soft tissue [6]. Although this process can develop in all osteoarticular structures, the knee is the most affected joint [2] and the one for which many specific evaluation criteria are available [7].

Prevalence of OA increases with age and is greater among women [2], with dietary habits also being an important risk factor [8, 9]. In addition, both preclinical studies in animal models and clinical studies in patients have shown a direct link between OA and metabolic syndrome, a multifactorial disorder including type 2 diabetes mellitus, high blood pressure, dyslipidemia, and obesity [10]. Development of OA has also been linked to misalignment of the joint, joint injury, and mutations in genes encoding components of the extracellular matrix (ECM) [6]. Although the pathophysiology of OA has yet to be fully elucidated, disease progression has been attributed to signaling molecules such as proinflammatory cytokines [11]. These have been suggested to induce the concomitant production of ECM degrading enzymes while suppressing ECM synthesis [12]. Moreover, the metabolism of chondrocytes – cells that inhabit cartilage and produce the different components of the ECM – has been hypothesized to revert to a dedifferentiated or immature state, or alternatively, to become hypertrophic and undergo cell death [6, 13].

Diagnosis of OA is generally symptomatic, followed by confirmation through structural changes that may be seen by X-ray. Radiological imagery results, however, may be discordant for some patients who present radiologic findings without experiencing any symptoms [14]. Although more sensitive imaging modalities such as Magnetic Resonance Imaging (MRI) can detect the earliest phases of cartilage damage, early detection of OA remains a clinical challenge. Pain is the disease characteristic that most often determines whether patients will seek medical attention, as it negatively affects multiple aspects of a patient's life, expanding beyond mobility to include sleep, mood, and their overall health-related quality of life (HRQoL) [15].

At present, there is no specific cure for OA. However, a variety of therapies are available for managing OA-related pain, including non-pharmacologic approaches (e.g., physical therapy, weight management, orthopedic aids, and orthoses, up to surgery and rehabilitation) and pharmacologic agents. Among these, analgesics, NonSteroidal Anti-Inflammatory Drugs (NSAIDs), glucocorticoids, opioids, anti-cytokines, and SYmptomatic Slow-Acting Drugs for OA (SYSADOAs) are currently available. Analgesic and NSAID are used in chronic treatments of the symptoms of OA but do not act on disease modification and may eventually be limited by their deleterious side effects. On the other hand, SYSADOAs are chondroprotective substances that have also been found capable of improving the clinical symptoms of OA. They are expected to slow down, block or shift back the pathological changes in osteoarthritic joints, limiting the progression of the disease, and are associated with high safety profiles [1]. SYSADOAs include cytokine modulators (i.e., diacerein), cartilaginous matrix precursors (i.e., chondroitin sulfate, glucosamine, and hyaluronic acid), as well as other types of drugs such as bisphosphonates [16, 17].

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Chondroitin sulfate (CS) is a natural biomacromolecule belonging to the class of glycosaminoglycans and is an unbranched complex polysaccharide consisting of a repeating disaccharide structure of glucuronic acid and N-acetyl-D-glucosamine [18]. It is a major component of the extracellular matrix (ECM), where it constitutes an essential component of proteoglycans. Oral bioavailability of CS has been demonstrated [19], and its use for the treatment of OA has been established in animal models [20], as well as in clinical trials [21, 22]. CS, is available as a pharmaceutical grade drug (Structum®), meaning that the product is manufactured under Good Manufacturing Practices (GMP) conditions, and is in excess of 99% purity with no binders, fillers, excipients, dyes, or unknown substances. According to the Instructions for Use (IFU), the recommended posology for Structum® is 500 mg twice daily.

2.2 RATIONALE

To this date, no real-world studies have been conducted to precisely describe the burden associated with OA among patients treated with Structum®. Therefore, an observational, descriptive, prospective, national study will be conducted to describe the burden associated with OA and the quality of life of patients treated with Structum® in Poland.

This study's ancillary exploratory objective will be to evaluate further the BONE'S questionnaire (Burden of Osteoarthritis New Scale), developed as a patient-centered multidimensional assessment of OA-associated burden in daily life [23]. This will be done by assessing the correlations between the BONE'S questionnaire and the SF-12 and WOMAC questionnaires in participating patients over the 6-month follow-up period. Moreover, the evolution of the use of NSAIDs and other analgesics over the 6-month follow-up period will be described and compared with the use of NSAIDs and other analgesics during the last 6 months before inclusion.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

To describe the baseline clinical profile and baseline OA symptom severity (pain, stiffness, and function), as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, of patients with knee OA and treated with Structum®.

3.2 SECONDARY OBJECTIVES

1. To describe knee OA symptoms severity (pain, stiffness, and function), as assessed by the WOMAC questionnaire, in patients treated with Structum®, over the 6-month follow-up period.
2. To describe the burden associated with knee OA in daily life (independence, interaction & recreation, psychological, budget, and hygiene & beauty), as assessed by the BONE'S questionnaire, in patients treated with Structum® over the 6-month follow-up period.
3. To describe general health (physical and mental health) assessed by SF-12 (Short Form 12 items) as a quality-of-life measure in patients treated with Structum® over the 6-month follow-up period.
4. To describe treatment persistence in patients treated with Structum® over the 6-month follow-up period.

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- To describe the global assessment of the patients treated with Structum® over the 6-month follow-up period.

3.3 EXPLORATORY OBJECTIVES (ancillary analyses)

- To assess the correlation between the results of the BONE'S questionnaire and the SF-12 and WOMAC questionnaires, in participating patients over the 6-month follow-up period.
- To describe the evolution of the use of NSAIDs and other analgesics from 6 months before inclusion and over the 6-month follow-up period.

4 RESEARCH METHODS

4.1 STUDY DESIGN

This is an observational, descriptive, national, multicentric, prospective, longitudinal study, which will be conducted over a 6-month follow-up period for each patient. The study will not provide or recommend any specific treatment or procedures. All decisions regarding treatment of included patients will be made by the treating physician in accordance with local best clinical practice and as per local product information of Structum®. All patients will be treated and monitored according to the local clinical practice, and no specific visit dates will be mandated for this study.

All patients affected by OA in the knee, for whom Structum® is prescribed in a participating center, will be screened in a consecutive manner for eligibility. The study will focus exclusively on patients with OA in the knee as this is the joint most frequently affected and most easily assessed for OA patients.

Two additional data collections can be anticipated for these patients as part of their standard of care follow-up visits, which will usually occur around 3 and 6 months after the initial study visit.

The patient enrolment period is expected to be 9 months, with a total study duration of 15 months. If enrolment period or total study duration are modified, the present study protocol will be amended accordingly. All available data for each enrolled patient will be collected from study inclusion until the end of their follow-up period at 6 months, or death, study withdrawal or loss to follow-up (whichever comes first).

The study timeline is provided in Table 1 below.

The target country for patient enrollment will be Poland. Adult patients between 50 and 85 years old at inclusion with a confirmed diagnosis of knee OA, and with a prescription for Structum® will be invited to participate from the participating centers. Only eligible patients who provide informed consent to data collection, as per local regulations, will be enrolled.

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Table 1: Study timeline

Milestone	Proposed dates
Patient recruitment	July 2023 to April 2024
Last follow-up visit	October 2024
Database lock	December 2024
Statistical analysis	December 2024 - January 2025
Final results	March 2025

4.2 POPULATION

4.2.1 Study population

The study population will include adult patients aged 50 to 85 years with a confirmed diagnosis of knee osteoarthritis and a new prescription for Structum®, as treated by participating centers in Poland.

4.2.1.1 Inclusion criteria

Patients will be eligible for inclusion if they fulfill ALL the following criteria:

- Male or female patients aged 50 to 85 years at inclusion
- Diagnosis of knee OA (either a patient newly diagnosed [at inclusion] or with history of knee OA) based on at least the following items 1 and/or 2:
 1. knee pain lasting for at least 3 months;
 2. patient in the active phase of knee OA disease (knee pain score $\geq$ 40mm at inclusion on the Visual Analog Scale [VAS] 0-100 mm);
 3. knee radiographs showing knee joint narrowing and/or osteophytes.
- Patients who have been prescribed, for the first time or not, Structum®.
- If patient is taking any NSAIDs or other analgesics, patient could be on stable dose at least one week before inclusion to the study.
- Patients able to visit the clinic and attend follow-up visits.
- Patients having signed an informed consent form, according to local regulations.

4.2.1.2 Exclusion criteria

Patients will NOT be eligible for inclusion if they fulfill ANY of the following criteria:

- Patients with any ongoing chondroitin sulfate treatment at inclusion or during the last 3 months.
Patients having received or planning to receive any OA comedication, including SYSADOAs² (in the last 3 months), and intraarticular injections of corticosteroids, hyaluronic acid, and platelet-rich plasma (in the last 3 months). No glucocorticoids administration in the last 3 months before inclusion. That does not include NSAIDs, paracetamol and other analgesic medications (e.g. tramadol).
- Patients with an artificial knee joint, including unilateral.

² These include cytokine modulators (i.e., diacerein), cartilaginous matrix precursors (i.e., glucosamine, and hyaluronic acid), and other types of drugs such as bisphosphonates.

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- Patients scheduled to undergo knee replacement surgery in the next 6 months.
- Patients with a severe general condition that prevents them from being included in the study as assessed by the investigator.
- Patients participating in interventional trials on investigational drugs at the time of inclusion.

4.2.2 Participant recruitment and follow-up

4.2.2.1 Recruitment of Study sites

The selection of sites must assure representativeness of the patient sample. An extensive list of eligible sites to be invited (rheumatology, orthopedic practices, sports clinics, general practitioners/family doctors, internists) will be established. Then a feasibility assessment will be performed for each site and the number of sites to be selected will be adapted to reach the target sample size, with respect to the predefined period of enrolment.

The sponsor will evaluate potential participating sites to ensure that the investigator has the adequate experience, potential for inclusion, facilities, and the required resources. The target country for study participation will be Poland.

A registry of all sites invited to participate (whether they accept or refuse to participate) will be implemented to document the representativeness of the sites included. Site-specific data collected in the registry may include, but will not be limited to, site location, specialization of the invited investigator, and type of healthcare establishment.

Participating sites will receive the necessary Ethics Committee (EC) approvals and/or other regulatory approvals as per applicable local regulations and be authorized by the Sponsor to enroll patients. Study investigators must agree to comply with this protocol, EC requirements, and all applicable laws and regulations.

4.2.2.2 Participant recruitment

- The investigator will screen all consecutive patients who have a confirmed diagnosis of knee OA, and who are newly prescribed Structum® (initial or non-initial prescriptions), for their eligibility to participate in the study.
- The investigator will complete a patient enrolment log to register all eligible patients invited to participate and who were not included (together with reasons for non-inclusion) as well as all included patients. The enrolment log will be used to assess the representativeness of the study sample, and the data to be collected in that log may include (but will not be limited to): patient's sex, age, occupation, and reason for non-inclusion.
- Upon invitation to participate, the investigator will inform patients of the nature and purpose of their participation. Patients will be provided with an EC approved Patient Information Note to read, and any questions that may arise will be addressed.
- Patients will be duly informed of the study's objectives and the possibility of refusing or stopping their participation in the study without any prejudice to their relationship with the investigator

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and their medical management. Patients will also be informed about their rights concerning the processing of their personal data.

- All applicable local laws, regulations and EC requirements will be strictly applied. An informed consent form will be signed and dated by the patient.
- After agreement of participation from the patient (as evidenced by a signed informed consent form) the investigator will be able to collect required baseline data into the electronic Case Report Form (eCRF).

The patients' data that will be collected upon inclusion in the study are detailed in section 4.3 below.

4.2.2.3 Participant follow-up

All patients will be treated and monitored according to each center's standard clinical practice. Follow-ups at 3 and 6 months following the inclusion visit can be anticipated.

At the end of the inclusion visit, all patients will be provided with adequate instructions to complete a patient diary in paper format. Patients will be encouraged to complete the patient diary during visits, according to the following schedule:

- WOMAC questionnaire: at inclusion, at 3-month follow-up and at 6-month follow-up (Appendix 1).
- BONE'S questionnaires: questions for the healthcare professional at inclusion are included in the eCRF (Appendix 2a), while the patient will fill in the patient version of the questionnaire at inclusion, at 3-month follow-up and at 6-month follow-up (Appendix 2b).
- SF-12 questionnaire: at inclusion, at 3-month follow-up and at 6-month follow-up (Appendix 3).
- Structum® treatment satisfaction questionnaire: at 3-month follow-up and at 6-month follow-up (Appendix 4). This questionnaire will also have to be completed after the first dose of Structum® (first dose after inclusion in the study). Thus, for this particular timepoint, the questionnaire will have to be completed at home by the patient and sent back to their center by mail with the provided pre-paid envelop.

Patients will be explained the importance of these questionnaires and will be encouraged to be compliant with the completion of the patient diaries as instructed.

Table 2: Data collection schedule for patients enrolled in the TRUST study

All available data will be collected for study patients at three time points in the study: upon study inclusion, and at the 3-month and 6-month follow-up visits.

<i>Data for:</i>	Inclusion Visit	First follow-up visit (3 months)	Second follow-up visit (6 months)
Patient eligibility criteria and informed consent	X		

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<i>Data for:</i>	Inclusion Visit	First follow-up visit (3 months)	Second follow-up visit (6 months)
Patient demographics and clinical characteristics (Section 4.3.1.1)	X		
Treatment history before index Structum® initiation (Section 4.3.1.1)	X		
Index Structum® treatment details (Section 4.3.1.1)	X	X	X
BONe'S (healthcare professional's form; Appendix 2a) questions in the eCRF	X		
AE form in the eCRF (if applicable)	X	X	X
Patient Questionnaires			
WOMAC questionnaire (Appendix 1)	X	X	X
BONe'S questionnaire (patient's form; Appendix 2b)	X	X	X
SF-12 questionnaire (Appendix 3)	X	X	X
Structum® treatment satisfaction questionnaire (Appendix 4)	X*	X	X

*Completion of the questionnaire after the first dose of Structum®

4.2.2.4 Data collection process in case of consent withdrawal or treatment discontinuation.

In the case of withdrawal of patient consent, any data that was collected up to the date of withdrawal will be retained. No data will be collected after the date of his/her consent withdrawal.

If patient discontinues his/her treatment with Structum® during the course of the study, patient data will still have to be collected in the eCRF until the end of the follow-up period. However, the patient will be asked not to complete the questionnaires at subsequent visits.

4.2.2.5 Risks and benefits

This is an observational study that does not deviate from the local standard of care for enrolled patients. As such, there will be no additional risks for patients who participate (or not) in this study.

Potential risks associated with the ongoing COVID-19 pandemic were assessed and no additional risks were identified for patients included prospectively. All patients will follow the standard of care (in-person or remote monitoring, to be decided by the investigator if any local sanitary restrictions have been implemented), with no additional steps required that could potentially increase the risk of

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contracting the virus. This risk assessment will be a continuous process throughout the study and actions will be taken at the site level if circumstances change due to the pandemic.

There are no individual benefits from participating in the study, and patients refusing to participate will be managed identically to those enrolled.

4.3 STUDY OUTCOMES

The outcomes of this prospective, observational and longitudinal study are purely descriptive. They aim to describe the patient profile and symptom severity of patients receiving Structum® for the treatment of OA of the knee.

4.3.1 Primary outcome

The primary objective of this study is to collect comprehensive data to describe the clinical profile of knee OA patients for whom Structum® has been prescribed. Hence, the primary outcome cannot be conveyed as a single stand-alone measure but will instead entail a comprehensive description of all source data collected to characterize the clinical profile of included patients. The description of symptom severity (pain, stiffness and function) as assessed by the WOMAC at baseline will complete the description of the clinical profiles.

4.3.1.1 Variables pertaining to the primary outcome

The following key items will be collected at baseline (during the inclusion visit) for all patients:

1) *Patient demographics and clinical characteristics*

- a. Year of birth (YYYY): patient age at inclusion
- b. Sex (Male or Female)
- c. Employment status (full-time employment, part-time employment, retired, full-time student, homemaker, unemployed, incapacity to work, and other) and occupational categories (according to the International Standard Classification of Occupations ISCO-08: 1) managers, 2) professional, 3) technicians and associate professionals, 4) clerical support workers, 5) service and sales workers, 6) skilled agricultural, forestry and fishery workers, 7) craft related trades workers, 8) plant and machine operators, and assemblers, 9) elementary occupations, or 10) armed forces occupations)
- d. Lifestyle (more than 2h/day of physical activity, less than 1h/day, twice a week, once a week, occasionally, never)
- e. Weight (in kgs)
- f. Height (in cm) – the BMI will be derived from weight and height.
- g. Relevant co-morbidities (including the Charlson Comorbidity Index, and presence of a metabolic syndrome, which is an information indirectly linked to ethnicity [see Appendix 5])
- h. Date of initial diagnosis of knee OA (MM/YYYY)
- i. Severity of knee OA, as assessed by the investigator using the Kellgren and Lawrence radiologic assessment on both knees [7] and the Lequesne algofunctional index for the most painful knee
- j. OA environment: whether the knee OA is unilateral or bilateral, and whether it is accompanied by an OA of the hip, cervical, lumbar, of the fingers, or other

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2) *Treatment history*

- a. With which criteria was the patient included in the study (a) knee pain lasting for at least 3 months; b) patient in the active phase of knee OA disease (knee pain score $\geq$ 40mm at inclusion on the Visual Analog Scale [VAS] 0-100 mm); or c) knee radiographs showing knee joint narrowing and/or osteophytes)
- b. Prior treatments for knee OA over the previous 6 months
 - i. Type (SYSADOAs [specify], oral NSAIDs, topical NSAIDs, paracetamol, analgesics other than paracetamol [specify], glucocorticoids, intra-articular corticosteroid injection, intra-articular hyaluronic acid injection, forearm crutch, home self-exercising programs, and joint overwork reduction advice)
 - ii. Start date and end date
 - iii. Dose and frequency
- c. Ongoing and concomitant treatments for knee OA (Type, start date, end date, dose and frequency)
- d. Index Structum® prescription details
 - i. Planned duration
 - ii. Starting posology
 - iii. Initial Structum® treatment (Yes/No)
 - iv. Any change to Structum® treatment (during subsequent follow-up visits, and until study end) and reason of change.
- e. Treatment compliance (measured in the number of missed tablets during the follow-up period)
 - i. No missed tablets
 - ii. < 18 missed tablets
 - iii. 18 – 36 missed tablets
 - iv. > 36 missed tablets
 - v. I don't know

3) *Knee OA symptom severity description per the WOMAC questionnaire at inclusion*

Please refer to Appendix 1 for a sample of the complete questionnaire.

4.3.2 Secondary outcomes

The following secondary outcomes will be described:

1) **Secondary WOMAC outcomes at 3-month and 6-month follow-up**

- Mean global score of symptoms' severity
- Mean score of each dimension
- Mean differences in symptoms' severity scores at 3 and 6 months (compared to baseline)

Please refer to Appendix 1 for a sample of the complete questionnaire.

2) **BONe'S outcomes at baseline, 3-month and 6-month follow-up (from the patient questionnaire)**

- Mean global score of the OA burden
- Mean score of each dimension
- Mean differences in OA burden scores at 3 and 6 months (compared to baseline)

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Please refer to Appendices 2b for a sample of the complete questionnaire.

3) SF-12 outcomes at baseline, 3-month and 6-month follow-up

- Mean global score of general health
- Mean score of each dimension (physical and mental)
- Mean differences in general health scores at 3 and 6 months (compared to baseline)

Please refer to Appendix 3 for a sample of the complete questionnaire.

4) Persistence outcomes at 3-month and 6-month follow-up

- Proportion of patients with ongoing Structum® at 3 months
- Proportion of patients with ongoing Structum® at 6 months

5) Personal global assessment, after first dose of Structum®, at 3-month and at 6-month follow-up:

- Proportion of patients with a positive assessment of Structum®, as assessed by Structum® treatment satisfaction questionnaire

Please refer to Appendix 4 for a sample of the complete questionnaire.

4.3.3 Exploratory outcomes

Spearman correlation coefficient and *P* value for the correlation between the BONE'S questionnaire and the SF-12 questionnaire at inclusion, 3 and 6 months.

Spearman correlation coefficient and *P* value for the correlation between the BONE'S questionnaire and the WOMAC questionnaire at inclusion, 3 and 6 months.

Variables of interest for the assessment of this exploratory outcome will originate from the BONE'S, SF-12 and WOMAC questionnaires (Appendices 2a, 2b, 3 and 1).

Proportion of patients with changes in the prescription of NSAIDs and other analgesics 6 months before inclusion, at inclusion, and at 3 and 6 months.

4.3.4 Subgroups of interest

If sample size allows it, subgroup analyses will be done by:

- Sex (Male/Female),
- Time since diagnosis of knee OA: Newly diagnosed / previously diagnosed (6 months and 12 months cut off),
- Severity of knee OA (Severe / moderate),
- Knee OA localization (Unilateral / bilateral),
- Initial Structum® treatment at baseline (1st prescription vs not 1st prescription),
- Metabolic syndrome (as defined in Alberti, Zimmet & Shaw, 2005) diagnosed based on the criteria in the Appendix 5 [24].

4.4 DATA SOURCES

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The source of collected data will include all data available in the patient's medical charts and responses from patient-reported outcomes (PRO) questionnaires (the WOMAC, BONE'S, SF-12 and Structum® satisfaction questionnaires). The site investigator will be responsible for ensuring that all the required data are collected and appropriately entered in the eCRF.

Key data items that will be collected for each outcome and for the specified timepoints are listed in section 4.3, Study outcomes.

4.5 STUDY SIZE

Given the descriptive nature of the primary outcome and since no predefined clinical assumptions underlie this study, neither a sample size nor a power calculation may be conducted. We estimate the number of patients to be included to be approximately 150, to obtain a reasonably representative sample.

In Table 3 below, the precision estimates for a 95% confidence interval were calculated around proportions ranging from 10% to 50% for the estimated sample size.

Table 3: Precision estimates for a 95% confidence interval

Proportion \ Sample size	10%	20%	30%	40%	50%
150 patients	4.8%	6.4%	7.3%	7.8%	8.0%

In conclusion, a sample size of 150 patients will enable to provide 95% confidence intervals of the primary outcomes with a precision not exceeding 8%. In other words, a sample size of 150 patients would allow to assess a category of primary objective (clinical profile description of eligible patients) of 50% of patients with a precision of $\pm 8\%$ i.e., 50% with 95% CI [42% - 58%].

4.6 DATA MANAGEMENT

4.6.1 Entry of collected data

The study data will be collected by the investigator and/or qualified designee using and eCRF accessible via the internet, in accordance with a provided user manual. Only authorized and trained staff at each study site will be allowed to enter data in the eCRF. The eCRF will be developed and managed by ClinSearch. Additionally, patients will be given instructions by site staff on how to complete the patient diary in paper format.

The qualified designee for eCRF data entry will ensure that:

- Data entry is performed in a timely manner
- Data entry is complete
- All eCRF data are verifiable in the source documentation
- Data queries are resolved and documented by authorized study staff

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- All completed eCRFs are validated with an electronic signature (changes to data previously submitted will require a new electronic signature to acknowledge or approve the changes).

The investigator or qualified designee is responsible for recording and verifying the accuracy of patient data. By validating the eCRF, the investigator confirms that all recorded data have been verified as accurate.

A unique patient ID will be assigned to each enrolled patient, which will consist of two letters, corresponding to the ISO code of the country, followed by 5 digits: the first 2 will correspond to the site number and the following 3 will be unique to the patient (for instance PL02-017 will correspond to patient 17 from site 02 located in Poland). For the adverse event forms, the first three letters of the patients' last name and the first letter of their first name will be collected.

4.6.2 Quality control

After formal agreement of participation, sites will be trained at protocol procedures by a designated Clinical Research Associate (CRA). The frequency of subsequent contacts (monitoring on site visits, phone or e-mail) with the centers will be decided with the Sponsor and will be adapted if specific difficulties will be identified during the training. A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented. Data quality control will be performed remotely and at the site level, where permissible according to local regulations, by qualified designated personnel under professional secrecy.

Quality assurance department representatives from Pierre Fabre and/or Contract Research Organization (CRO - ClinSearch) may visit a study site to conduct quality assurance audit and ensure the study is conducted in compliance with protocol, Standard Operating Procedures (SOP) and all applicable legal requirements.

Taking into account the context of the COVID-19 pandemic, no additional sanitary restrictions will be necessary other than the measures already set up at participating centers to ensure patient's safety.

4.6.3 Data management

A data management plan will be created before the start of data collection and will describe all functions, processes, and specifications for data collection, cleaning and validation to ensure that the data are as clean and accurate as possible when presented for analysis. Data collection and validation procedures will be detailed in the appropriate operational documents.

All medical data will be confidential. Pierre Fabre, as the Sponsor of the study and data controller, is responsible for the processing of personal data in accordance with the provisions of Regulation 2016/679/EU of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and the free movement of such data (GDPR), the data collected being for research purposes in the field of health, the legal basis of the processing being the legitimate interest of the data controller.

ClinSearch will be responsible for the management of collected data. Data entered into the eCRF will be reviewed for consistency by the data manager using both automated logical checks (issuing in automatic queries generated by the system) and manual review (issuing in manual checks set by the

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data manager or the monitor into the eCRF). For each detected inconsistency, a CRF specific query will be generated (automatic or manual) and the investigator or data entry specialist will be responsible to correct or update any information that is incorrect or incomplete. To minimize the number of missing data, a specific query will be generated (automatic or manual) in order to confirm that data is truly missing rather than being an overlooked entry in the eCRF. An audit trail within the system will track all changes made to the data.

4.7 DATABASE LOCKING AND STORAGE

All data collected within the eCRF will be approved and electronically signed and dated by the investigator or designee. This approval will acknowledge the Investigator's review and acceptance of the data as being complete and accurate.

At study end and before the final statistical analysis, the eCRF and other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

Statistical processing will only take place once the database has been locked, i.e., the totality of the data is validated and a final quality control has been performed according to the Data Validation Plan documented by ClinSearch. Upon data validation, the database will be transferred to the statistical department of ClinSearch for analysis.

4.8 PROCEDURES FOR DATA RETENTION

The investigator must agree to keep the following documents for at least 25 years: the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms when applicable according to local regulations, electronic copy of eCRFs, and to allow evaluations or audits from regulatory authorities, the sponsor or its designees.

These documents will be kept for all participants for a period of time specified by local regulations or specified in the Clinical Study Site Agreement between the investigator and the sponsor. The Trial Master File (TMF) and the eCRF data will be retained at Pierre Fabre for 25 years.

4.9 DATA ANALYSIS

4.9.1 General considerations

All statistical analyses will be performed by ClinSearch using Statistical software (SAS), version 9.4 or a later version. A detailed Statistical Analysis Plan (SAP) will be validated by the Sponsor before the first database lock. Should there be any major changes in the planned analyses, an amendment to the SAP will be made prior to database lock. Deviations from the SAP after database lock will be outlined in the Clinical Study Report (CSR) and/or statistical analysis report.

Scoring of validated questionnaires will be applied strictly in accordance with each associated guideline.

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The study being single arm (i.e., non-comparative) and for descriptive purposes only, no *a priori* hypothesis will be tested.

Study outcomes will be analyzed for the full analysis set (comprising of all patients enrolled in the study who did not withdraw their consent to participate). Further details will be provided in the SAP.

4.9.2 Descriptive analysis

Appropriate summary statistics will be used depending on the nature of the variables, and the number of available and missing data will be specified for each variable. Categorical variables will be presented as frequencies and proportions, and continuous data will be expressed as median, mean, standard deviation, range and quartiles (Q1 and Q3). The 95% Confidence Intervals (CI) will be presented upon relevance to the analysis.

Sample representativeness assessment and patient flow chart will be outlined in the SAP.

If sample size allows it, subgroup analyses will be performed for the subgroups described in section 4.3.4.

4.9.3 Outcomes analysis

Primary and secondary outcomes will be analyzed using descriptive statistics (see section 4.9.2).

For the exploratory outcomes, in addition to descriptive statistics, Spearman correlation coefficient and *P* value will be used to analyze the correlations between the different questionnaires.

4.9.4 Missing data

Missing data will be considered missing without any imputation performed and described appropriately. For validated instruments, missing data will be handled as recommended in associated guidelines.

4.10 STUDY MANAGEMENT

Pierre Fabre is the sponsor of the study. The Sponsor will be responsible, among others, for:

- Initiating, managing, and financing the study
- Selecting qualified investigators
- Providing necessary information to the study sites to allow them to successfully conduct the study
- Obtaining investigator agreement from all participating study sites
- Ensuring that the required regulatory approvals / favorable opinions are received
- Ensuring that any modifications required by the EC or regulatory authority are implemented
- Performing and documenting root cause analysis and implementing appropriate corrective and preventive actions if non-compliance significantly affects or has the potential to significantly affect subject protection or reliability of clinical study results
- Ensuring that study procedures comply with applicable regulation for data protection.

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4.11 STRENGTHS AND LIMITATIONS OF THE RESEARCH METHODS

One of the strengths of this study is that patient-reported data will be collected to assess the burden of knee OA on patients who are treated with Structum®.

An observational study comes with its limitations which are as follows:

- 1) Selection bias: Patients who refuse to participate may limit the representativeness of the study results. Even though an enrolment log would be established to record the details of patients who were prescribed CS for their knee OA, irrespective of study inclusion status, it would only record the most basic patient demographic characteristics. Investigators will be asked to prospectively enroll consecutive patients who meet the eligibility criteria.
- 2) Patient drop-out: Patients lost to follow-up and patients who withdraw their consent will be the main source of attrition bias in this observational study. This can threaten sample representativeness if too many patients are lost to follow-up or if they differ from those who are continuing follow-up. Should the proportion of patients lost to follow-up be non-negligible, the target precision will not be reached. To minimize any risks and potential impact, efforts will be undertaken to collect the data from the lost-to-follow up patient's most recent visit. Baseline characteristics of patients lost-to-follow up/withdrawn and those who completed the study may be compared, to evaluate representativeness.
- 3) Missing data: Depending on physician practices, some data might not be systematically measured or available (such as certain clinical data or tests). Missing data can bias the descriptions if it is not completely random. Even in cases where missing data is truly random, a potential impact on the precision of the estimates cannot be overlooked. Remote Monitoring procedures will be implemented, wherein it will be ensured that the eCRFs have been comprehensively filled.
- 4) Heterogeneity between study centers: since this is an observational study prescription modality can vary widely based on standard practices in each investigating site. Where deemed appropriate subgroup analyses could be performed for certain outcomes or variables of interest.

5 PROTECTION OF HUMAN SUBJECTS AND LOCAL REGULATORY ASPECTS

5.1 GENERAL PRINCIPLES

The study will be conducted in accordance with the ethical principles of the declaration of Helsinki and the General Data Protection Regulation (GDPR, EU 2016/679) and other local regulatory requirements.

The need to submit the protocol to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the requirement of informed consent will be considered in accordance with local law: in Poland, this means that a notification to the Competent Authority will be performed. Any amendments to the study protocol, as well as the associated ICF will also be sent in a notification to the Competent Authority prior to implementation.

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This observational study does not involve any changes in the local care standards of the patients participating in the study, it does not compromise their physical or psychological integrity and does not require any special follow-up visits for these patients. Only four questionnaires will have to be completed by the patients in the particular context of this study. Each patient will be fully informed before enrollment in the study and start of data collection, and their written consent will be taken, as per Polish local regulations.

5.2 PROTECTION OF PERSONS

Data will be collected and retained in a pseudonymized format, with no directly identifying values that might link the data to the corresponding participant to the study.

The Investigator must ensure that the patient's confidentiality is maintained. It is required that the Investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and the institutional ECs direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. Access to the patient's medical file is to be granted under the supervision and responsibility of the Principal Investigator or their site personnel. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to their study-related records without violating the confidentiality of the patient.

The need to submit the protocol to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the requirement of informed consent will be considered in accordance with local regulations: in Poland, this means that a notification will be sent to the Competent Authority.

Investigators shall ensure that personal identifiers will be removed from any study files that are accessible to non-study personnel in accordance with applicable laws and regulations.

In case of sub-contracting, it is the responsibility of the service provider concerned to ensure that his computerized processing is in conformity with the applicable national regulations regarding the protection of personal data and, if necessary, to carry out any formality with the supervisory authorities, and transmit the declaration date to Sponsor.

6 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

6.1 TRAINING

In order to ensure that the contractor (i.e., the CRO ClinSearch) staff receives a safety training, the project initiator transmits the contact details using the dedicated table ("Pharmacovigilance [PV] training required contact details" provided hereafter) of each person involved in the management of the study to the Training Manager, who will be responsible for the training.

The Training Manager is in charge of organizing and documenting the training provided to the ClinSearch staff.

If ClinSearch provides recent (less than one year) individual Pierre Fabre PV training certification, the training will not be mandatory.

ClinSearch should ensure that involved staff will respect the PF transmission of any safety information modalities described in the protocol/contract.

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Table 4 - PV training required contact details

Name	Surname	E-mail address	Country of residence	Position	Country where the study is performed	Possible languages for the PV Training	Name of company	Was a Pierre Fabre AE Reporting Training passed (with certification) in the last 12 months? Yes/No. If yes, date of PF training

6.2 REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

6.2.1 Definitions

Adverse event (AE); synonym: Adverse experience

An AE is any untoward medical occurrence in a patient to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment [Dir 2001/20/EC Art 2(m)].

An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator product
- Off label use, occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Product exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)

As mentioned above no causal relationship with a product is implied using the “adverse event”.

Adverse Reaction (AR); synonym: Adverse drug reaction (ADR)

An Adverse Reaction is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to product.

Serious adverse reaction:

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [DIR 2001/83/EC Art 1(12)].

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

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Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Note:

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is ‘sudden death’ where no cause has been established. In this instance, ‘sudden death’ should be regarded as the AE and ‘fatal’ as its reason for being ‘serious’.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe

Hospitalization will not be considered a SAE, if any of the following applies (however, such events are still considered as AEs):

- Hospital stays that were already pre-planned before the inclusion into the study;
- Pre-planned hospitalization to treat pre-existing diseases that are not connected to the disease or to the treatment observed in the study;
- Ambulatory treatments performed in the hospital that do not lead to hospitalization (however, in such cases it must be checked if another seriousness criterion such as “life-threatening” was fulfilled);
- Treatments in the hospital that are part of the usual treatment or surveillance of the disease investigated in this study as long as these were not urged by a worsening of the disease or by toxicities of the treatment observed in this study;
- Hospitalization due to social causes (e.g., need of nursing care) as long as this was not urged by a worsening of the patient’s general physical status or of the disease investigated in this study or by toxicities of the treatment observed in this study.

If it is currently unclear whether a hospital stay or intervention was preplanned based on any of the above-mentioned criteria, the event must be considered as a being serious.

The assessment whether an event is serious or not only depends on the fulfillment of one of the above-mentioned seriousness criteria. This assessment is independent from the question, if a causal relationship is assumed between the intake of a medicinal product and the occurrence of the SAE.

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

Congenital anomaly (birth defect), i.e., any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other reportable safety events

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Misuse of a medicinal product

Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.

Overdose

Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.

Abuse

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

Medication error

Are unintentional errors in the prescribing, dispensing, or administration of a medicine while under the control of a healthcare professional, patient or consumer. They are the most common single preventable cause of adverse events in medication practice.

Occupational exposure

For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation.

Quality complaint

Quality complaints include defects of the product itself (e.g., crack of tablets, empty blisters, etc.), defects of the package (e.g., deformation), problems with the product handling (e.g., difficulty to open the blister) as well as defects with regard to the labelling (e.g., wrong or missing patient leaflet, wrong or missing variable data) or intermixture with "alien" product (e.g., alien blister in the package), as well as the suspicion of product falsification. In addition, any expression of dissatisfaction with the quality, stability, reliability, performance and handling of a Pierre Fabre product will also be classified as a quality complaint.

Despite pure quality complaints, mixed complaints including (S)AEs and/or other safety events combined with quality complaints are possible. These especially include (S)AEs, where – based on the event description – an underlying quality complaint is to be expected. Of note: Only such combined events (i.e., combination of safety events and quality complaints) must be reported within the study.

Day 0

The clock for the submission of a valid adverse event starts as soon as the information containing the minimum criteria has been brought to the attention the investigator. This date should be considered as day zero. It is the first day when an investigator gets knowledge of an adverse event, irrespective of whether the information is received during a weekend or public holiday. The timelines for submission are based on calendar days.

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Investigator's causality assessment

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF and AE form. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are:

- "Yes"

or

- "No".

An assessment of "No" would include:

The existence of a clear alternative explanation (e.g., mechanical bleeding at surgical site)

Non-plausibility (e.g., the subject is struck by an automobile when there is no indication that the product caused disorientation that may have caused the event; cancer developing a few days after the first product administration)

An assessment of "Yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from product administration: The event should occur after the product is given. The length of time from product exposure to event should be evaluated in the clinical context of the event.
- Recovery on product discontinuation (de-challenge), recurrence on product re-introduction (re-challenge): Subject's response after de-challenge or subject's response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other products the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

Intensity Assessment

The intensity/severity of AEs will be assessed by the treating physician based on the definitions of the grades given in Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

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6.2.2 Reporting of adverse events/ adverse reactions

From the start to the end of observation of the respective patient, any AEs occurring **in context with the exposure to a Pierre Fabre product (i.e., Structum®)**, must be reported as solicited AEs to Pierre Fabre's PV department.

Newly events occurring after the end of the observation period will only be reported if causal relationship to a Pierre Fabre product cannot be excluded by the treating physician and will be considered as spontaneous reports.

The investigator conducting the study is required to provide the following information* that has been brought to his attention about a Pierre Fabre product:

- Any serious AEs: within 24 hours after becoming aware of the information:
- Any non-serious AEs (whatever the causal relationship): within 24 hours after becoming aware of the information;
- Other reportable safety events: within 24 hours after becoming aware of the information
 - o Any information concerning paternal exposure or maternal exposure during pregnancy or breastfeeding;
 - o Any information concerning an overdose, medication error, misuse, off-label use, abuse, lack of effectiveness or occupational exposure, whether or not these situations are associated to an AE;
 - o Any drug interaction;
 - o Any suspected adverse reactions related to quality defect or falsified medicinal products;
 - o Any unexpected beneficial effect

If any follow-up information becomes available, follow-up AE forms (AE information updates) are required. Follow-up AE form must also be generated within **24 hours for SAEs, non-serious AEs and other reportable safety events** after becoming aware of the respective information. In case such follow-up information should become available, the documented safety event will be updated and – after saving – reported as described above. The fact that a report is a follow-up of an already existing event is clearly specified in the safety report. Generally, all (S)AEs potentially related to a Pierre Fabre product as well as the other reportable safety events (mentioned above) occurring within the individual observation timeframe of a patient must be followed until a final outcome or a stable situation is reached.

The above information is to be entered by qualified site staff into the respective safety reporting form of the eCRF in English language. After the creation of an AE form in the eCRF, one email alert containing the completed electronic AE form will be automatically and immediately sent to ClinSearch and to Pierre Fabre PV Local Safety Officer contact: email: pharmacovigilance.poland@pierre-fabre.com.

The Adverse event form is adapted as per Pierre Fabre current applicable solicited adverse event collection form with the reference FORM_CVI_0231.

The above reporting procedure applies as long as the study is ongoing.

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After completion of this individual observation timeframe of a patient and generally after completion of the study, newly occurring AEs potentially related to a Pierre Fabre product should be reported as spontaneous reports to the Pierre Fabre local PV department; a corresponding reporting form can be requested via these contact data (pharmacovigilance.poland@pierre-fabre.com).

6.3 RECONCILIATION

The reconciliation of the safety information between ClinSearch and Pierre Fabre local PV department is performed and documented at least every 3 months and at the end of the study (modalities and timelines should be indicated in the corresponding reconciliation guideline).

For this purpose, the ClinSearch will initiate the reconciliation by sending to Pierre Fabre local PV department a request for a reconciliation listing. After having received the corresponding reconciliation listing as a basis, ClinSearch will provide Pierre Fabre local PV department with the tracking table listing of all obtained safety reports specifying potential missing and inconsistent data (see Table 5).

Table 5. Reconciliation Data

Date of receipt
Transmission date to PF
Country
Site ID
Patient ID
Year of birth
Treatment start date
Treatment end date
AE Description
Preferred Terms
Seriousness criteria
Event start date
Event outcome
Event end date, including deaths (if applicable)
Investigator's assessment of causality

7 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The statistical analysis will give rise to a CSR, which will be submitted to the Sponsor for validation. This report will enable the preparation of one or more publications.

Any written or oral communication of the research results will receive prior consent of the Sponsor and, if necessary, of any committee formed for the research. All publications will follow the International Committee of Medical Journal Editors (ICMJE, 2010) guidelines. Additionally, communication in appropriate scientific meetings will be considered.

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8 APPENDICES

Appendix 1 – WOMAC Questionnaire

Appendix 2a – BONE's Questionnaire (healthcare professional's form)

Appendix 2b – BONE's Questionnaire (patient's form)

Appendix 2c – BONE's Questionnaire (original publication by Rannou *et al.*)

Appendix 3 – SF-12 Questionnaire

Appendix 4 – Structum® treatment satisfaction questionnaire

Appendix 5 – Metabolic syndrome diagnosis (according to Alberti *et al.*)

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APPENDIX 1 – WOMAC questionnaire

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WOMAC OSTEOARTHRITIS INDEX VERSION VA3.1

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions will be asked in the following format. You should give your answers by putting an "X" on the horizontal line.

EXAMPLES:

1. If you put your "X" at the left of the line as shown below, then you are indicating that you have **no** pain.

No Pain  Extreme Pain

2. If you put your "X" at the right end of the line as shown below, then you are indicating that your pain is **extreme**.

No Pain  Extreme Pain

3. Please note:

- a) that the further to the right you place your "X" the **more** pain you are experiencing.
- b) that the further to the left you place your "X" the **less** pain you are experiencing.
- c) **please do not** place your "X" **past the end of the line**.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.

You should think about your _____ (study joint) when answering the questionnaire. Indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your _____ (study joint).

Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.

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WOMAC VA3.1 QUESTIONNAIRE

WOM_A

Section A

PAIN

Think about the pain you felt in your _____ (study joint)
due to your arthritis during the last 48 hours.

(Please mark your answers with an "X".)

QUESTION: How much pain do you have?	Study Coordinator Use Only
1. Walking on a flat surface. No Pain ----- Extreme Pain	PAIN1 _____
2. Going up or down stairs. No Pain ----- Extreme Pain	PAIN2 _____
3. At night while in bed. No Pain ----- Extreme Pain	PAIN3 _____
4. Sitting or lying. No Pain ----- Extreme Pain	PAIN4 _____
5. Standing upright. No Pain ----- Extreme Pain	PAIN5 _____

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WOMAC VA3.1 QUESTIONNAIRE

WOM_B

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your _____ (study joint) due to your arthritis during the last 48 hours.

Stiffness is a sensation of **decreased ease** in moving your joint.

(Please mark your answers with an "X".)

6. How severe is your stiffness after first awakening in the morning? No Stiffness ----- Extreme Stiffness 7. How severe is your stiffness after sitting, lying or resting later in the day? No Stiffness ----- Extreme Stiffness	Study Coordinator Use Only STIFF6 _____ STIFF7 _____
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WOMAC VA3.1 QUESTIONNAIRE

WOMC1-3

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself**. (Please mark your answers with an "X".)

QUESTION: What degree of difficulty do you have?		Study Coordinator Use Only
8. Descending stairs. No Difficulty ----- Extreme Difficulty	PFTN8	_____
9. Ascending stairs. No Difficulty ----- Extreme Difficulty	PFTN9	_____
10. Rising from sitting. No Difficulty ----- Extreme Difficulty	PFTN10	_____
11. Standing. No Difficulty ----- Extreme Difficulty	PFTN11	_____
12. Bending to the floor. No Difficulty ----- Extreme Difficulty	PFTN12	_____
13. Walking on a flat surface. No Difficulty ----- Extreme Difficulty	PFTN13	_____

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WOMAC VA3.1 QUESTIONNAIRE

WOMC2-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself**. (Please mark your answers with an "X".)

QUESTION: What degree of difficulty do you have?	Study Coordinator Use Only
14. Getting in or out of a car, or getting on or off a bus. No Difficulty Extreme Difficulty	PFTN14 _____
15. Going shopping. No Difficulty Extreme Difficulty	PFTN15 _____
16. Putting on your socks or tights. No Difficulty Extreme Difficulty	PFTN16 _____
17. Rising from bed. No Difficulty Extreme Difficulty	PFTN17 _____
18. Taking off your socks or tights. No Difficulty Extreme Difficulty	PFTN18 _____
19. Lying in bed. No Difficulty Extreme Difficulty	PFTN19 _____

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WOMAC VA3.1 QUESTIONNAIRE

WOMc3-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself**. (Please mark your answers with an "X".)

QUESTION: What degree of difficulty do you have?	Study Coordinator Use Only
20. Getting in or out of the bath. No Difficulty Extreme Difficulty	PFTN20 _____
21. Sitting. No Difficulty Extreme Difficulty	PFTN21 _____
22. Getting on or off the toilet. No Difficulty Extreme Difficulty	PFTN22 _____
23. Performing heavy domestic duties. No Difficulty Extreme Difficulty	PFTN23 _____
24. Performing light domestic duties. No Difficulty Extreme Difficulty	PFTN24 _____

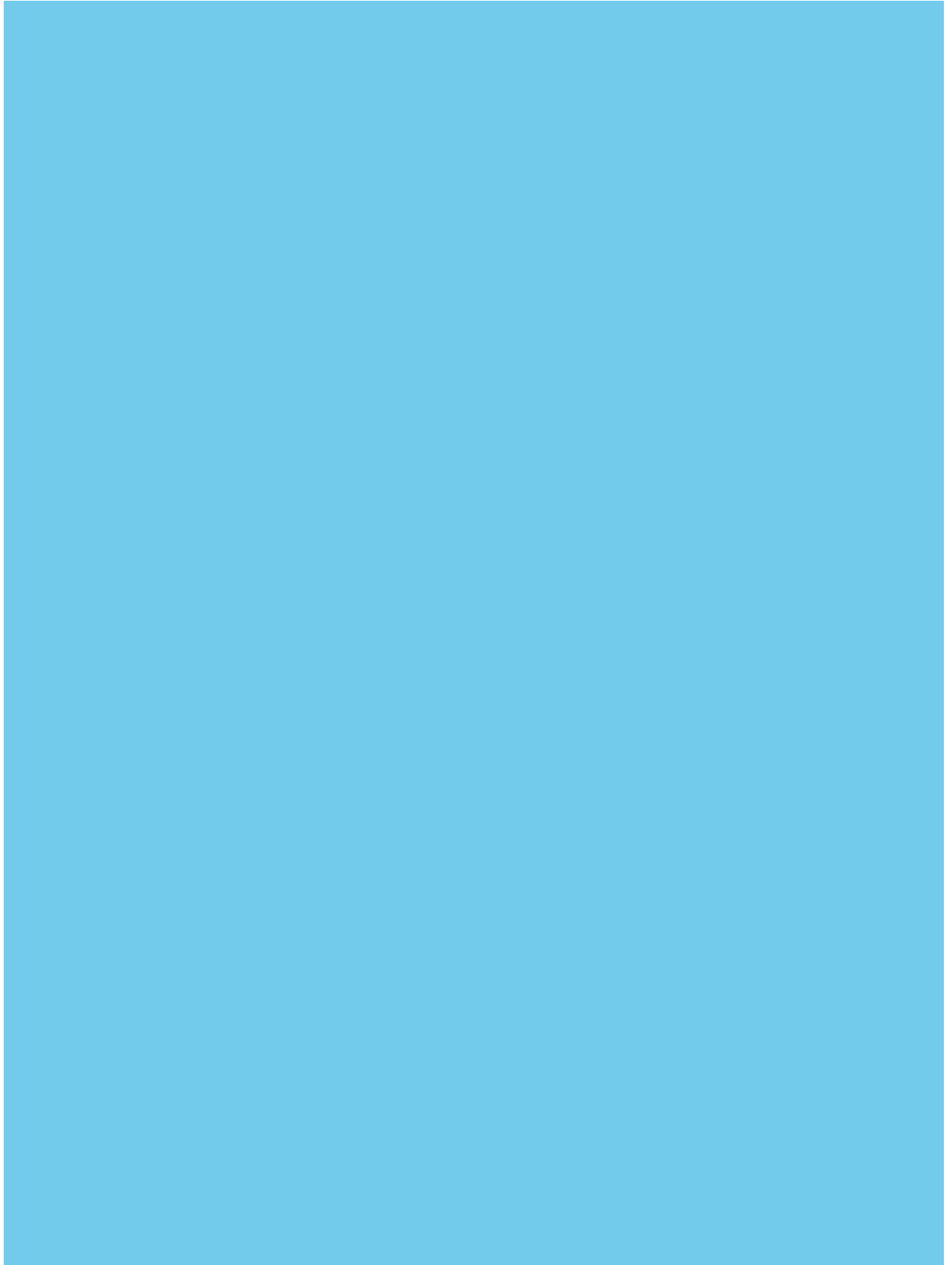
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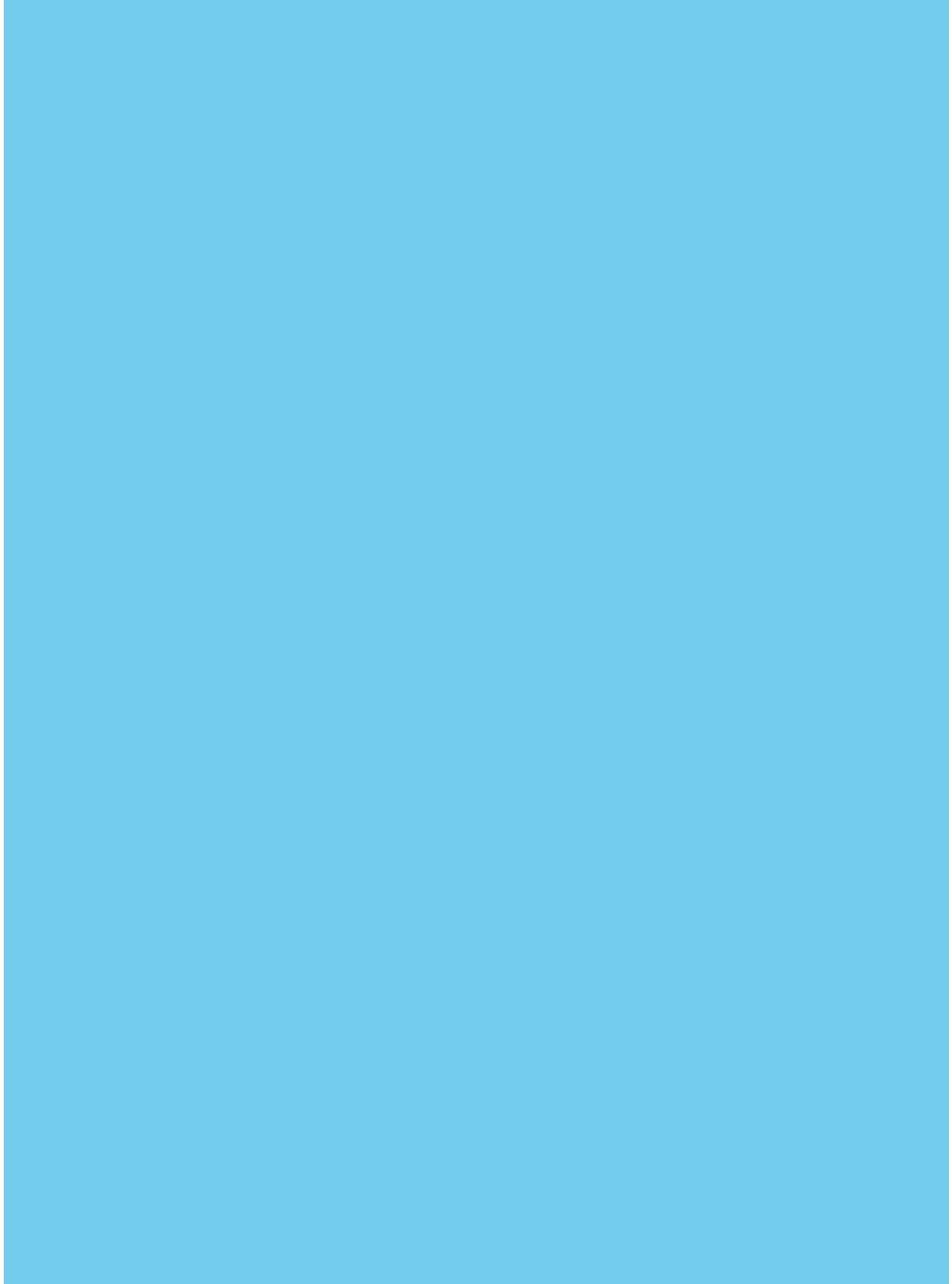
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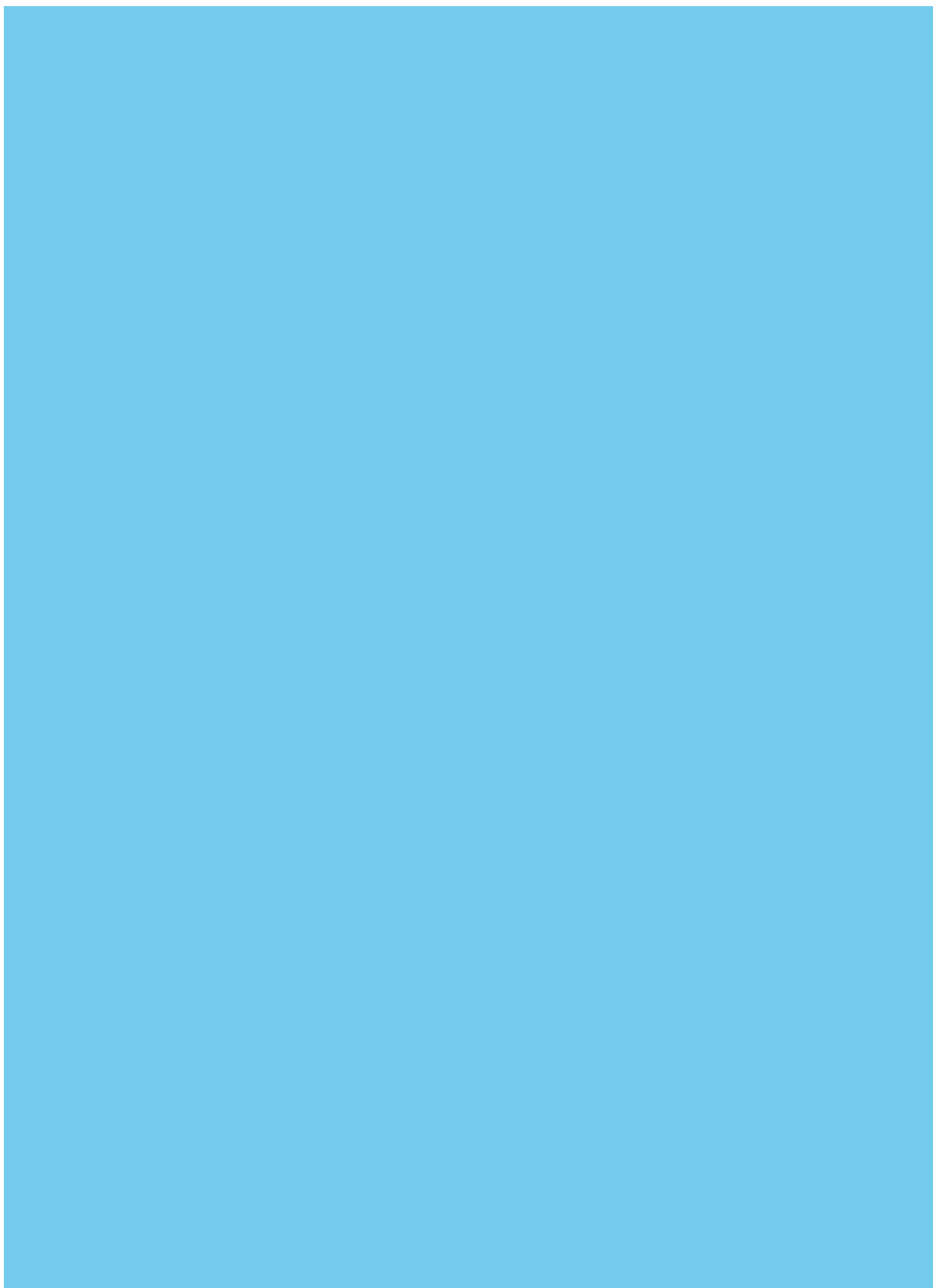
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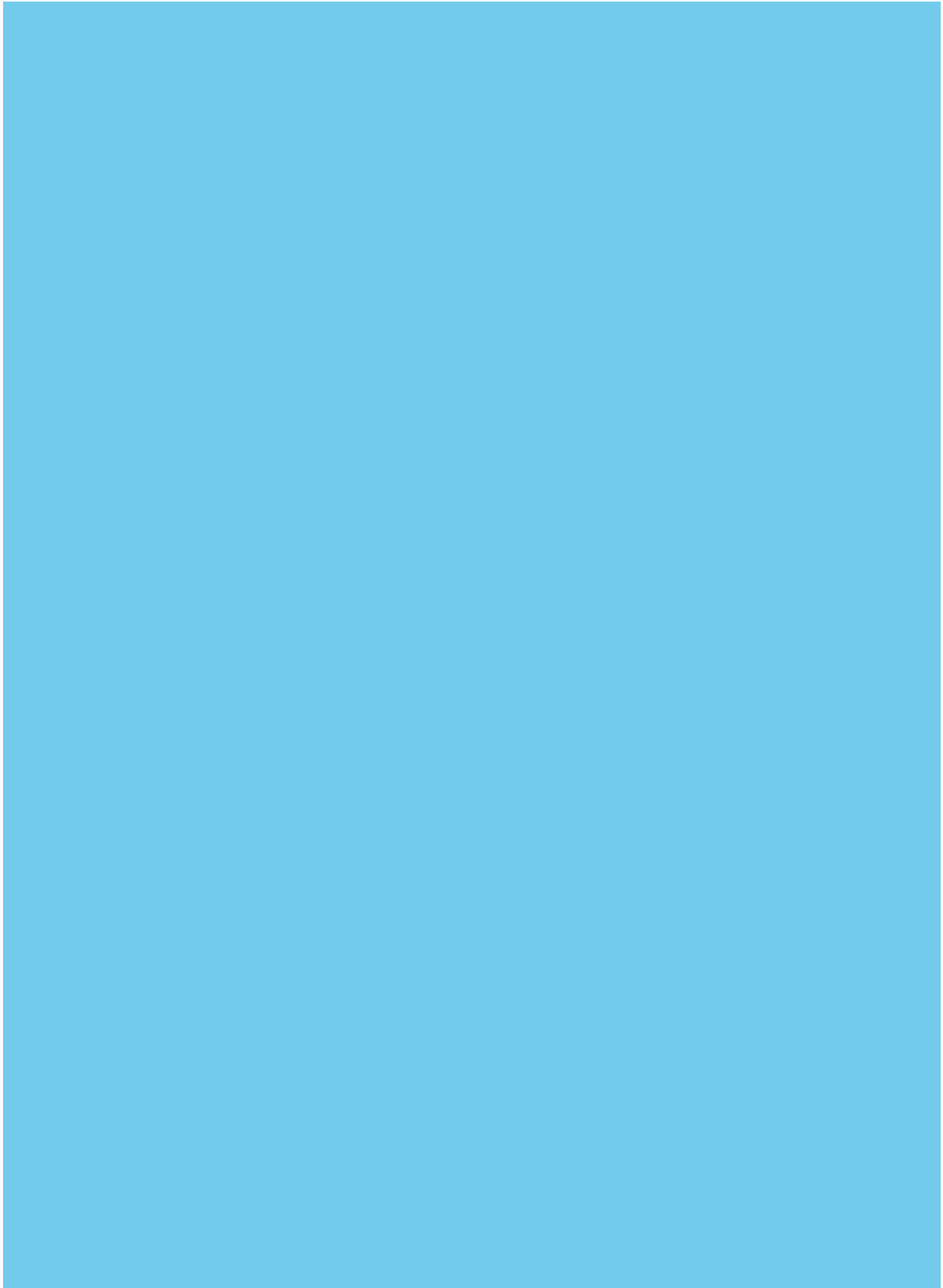
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APPENDIX 2c – BONE'S questionnaire (original publication by Rannou *et al.*)

CMRO

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Original article

The burden of osteoarthritis: development and validation of a new assessment tool (BONe'S)

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Individual burden – Osteoarthritis – Questionnaire – Validation

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Abstract

Objective:

To develop and validate a specific individual burden questionnaire, BONe'S (Burden of Osteoarthritis New Scale), assessing osteoarthritis (OA) patients in the broadest sense.

Research design and methods:

Items included in BONe'S were identified by literature review, and patient/healthcare practitioner interviews, and refined via item reduction and exploratory factor analysis (EFA). Internal consistency was calculated using Cronbach's α ; concurrent validity was assessed by calculating the correlation between BONe'S and the Short Form (SF)-12 Health Survey and Psychological General Well-Being Index (PGWB). Discriminant validity was analyzed by age, gender and number of OA locations.

Results:

From an initial list of 56 items, the final BONe'S questionnaire consisted of 20 questions (5 dimensions) based on EFA. BONe'S was evaluated in patients with OA ($n = 200$; mean age 69.4 ± 7.0 years; 86% of patients aged >60 years, 91.5% women). BONe'S demonstrated excellent internal coherence (Cronbach's α : 0.86). Individual BONe'S dimensions correlated well with the overall BONe'S score (highest: 'Independence' [$r = 0.91$]; lowest: 'Hygiene & Beauty' [$r = 0.56$]), and to each other dimension, and also correlated well (inversely) with the SF-12 and, to a slightly lesser extent, the PGWB. The only exception was 'Budget', but this dimension was important and relevant in the subpopulation of active OA patients ($r = 0.40$). The mean BONe'S score for subjects with one or two affected joints was significantly lower than for subjects with three or more affected joints. The BONe'S score also differed according to gender and age. The original French BONe'S has also been adapted (linguistically and culturally) to English, Russian and Portuguese. Limitations include the fact that BONe'S was developed in a predominantly female population, in patients receiving a pharmacological intervention, has not been evaluated in a large population and has not been compared with other OA tools, including WOMAC, Lequesne and KOOS.

Conclusion:

The BONe'S questionnaire is a short (20-item) validated tool for evaluating the specific individual burden of OA in a holistic manner.

Introduction

Osteoarticular diseases, specifically osteoarthritis (OA), represent chronic conditions that have the highest impact on patient health-related quality of life (HRQoL).^{1,2} Indeed, data from the 2008–2009 Disability–Health Survey in France show that musculoskeletal impairments contributed the most to self-reported disability and musculoskeletal diseases had the second largest impact on disability¹. From a societal perspective, OA is also associated with significant economic burden³. In the United States, OA is estimated to affect nearly

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27 million individuals, approximately 12.1% of the adult population³. Recent data from the European Project on Osteoarthritis (EPOSA) estimate self-reported and clinically judged prevalence rates of up to 31% and 51%, respectively, for knee OA, and up to 19% and 36%, respectively, for hip OA⁴.

In recent years, the concept of individual burden has assumed an increasingly important place in the clinical evaluation and management of chronic disorders. The Global Burden of Disease (GBD) initiative was introduced in the 1990s by the World Health Organization (WHO) as an initiative to close the 'health gap', to quantify a population's health and determine priorities for public health action⁵. There have been regular updates to the GBD, with a comprehensive, systematic, evidence-based update from the GBD 2010 study published recently⁶. Importantly, the latest GBD update shows that the increasing global burden from mental and behavioral disorders, musculoskeletal disorders (including OA), and diabetes will impose new challenges on health systems². However, the concept of burden and the 'health gap' associated with the WHO/GBD initiatives relate to an assessment of the overall societal and economic impact of disease management, particularly from the payee perspective. More recently, the notion of burden has been extended to individuals and their families, to assess disability (e.g. HRQoL, social integration, home life, and use of medical resources such as consultations, medications), in the broadest sense of the term (psychological, social, economic and physical), related to chronic venous disorders⁶, hand-foot syndrome⁷, infantile hemangioma⁸, inherited ichthyosis⁹, and atopic dermatitis¹⁰.

Numerous specific tools are currently available for assessing HRQoL in patients with OA (e.g. Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]^{11,12}, the Measure of Intermittent and Constant Osteoarthritis Pain [ICOAP]¹³, Psychological General Well-Being Index [PGWB]¹⁴, Osteoarthritis of Knee Hip Quality Of Life [OAKHQOL]¹⁵, Knee injury and Osteoarthritis Outcome Score [KOOS]¹⁶, and Lequesne Index¹⁷), focusing on functional disability, pain, well-being, and function in sport and recreation. However, some of these assessment tools focus on a single joint (hip, knee, hand) or on pre/post prosthetics. Other tools were developed for assessing general health (e.g. Short Form 12-item [SF-12]), or for very specific diseases (e.g. rheumatoid arthritis) and are not directly relevant to patients with OA¹⁸. As recently reviewed systematically by Busija and colleagues¹⁹, available questionnaires do not cover certain fields sufficiently or at all, including individual psychological, economic and aesthetic impacts of the disease, even though the latter is one of the primary causes of complaint from patients with OA. Moreover, although the exact prevalence is

unknown, patients commonly experience polyarticular disease, affecting five or more joints²⁰. Thus we identified the need to design and develop a new questionnaire about the individual burden of overall OA.

Indeed, a recently published systematic review of adult measures of general health and HRQoL used in rheumatology, excluding measures that are specific to any disease, concluded that there is currently no single optimal assessment tool, with all evaluated tools demonstrating psychometric weaknesses²¹. The primary aim of the current study was to develop and validate a specific individual burden questionnaire in French, called BONE'S (Burden of Osteoarthritis New Scale), assessing the disability of patients with OA in the broadest sense. A secondary objective was to adapt (cultural and linguistic validation) the original BONE'S questionnaire in several other languages.

Methods

The self-administered BONE'S questionnaire was developed using standard methodology for HRQoL questionnaire development^{22,23}. The overall development of the questionnaire consisted of three stages: exploratory phase, development phase and validation phase.

To ensure clinical and scientific rigor throughout the entire methodological process, the questionnaire was developed by a multidisciplinary team, consisting of individuals with expertise in the design and development of questionnaires, healthcare professionals (e.g. rheumatologists) with expertise in the management and care of patients with OA, patient associations, and quality of life experts.

Exploratory phase of BONE'S

The initial exploratory step involved the creation of a verbatim report based on a review of relevant literature and qualitative face-to-face interviews with rheumatologists ($n = 3$), patients with OA ($n = 12$), and an expert in the design of questionnaires.

To determine and synthesize the main concerns, this first exploratory step aimed to structure a refined objective examination and deeper understanding of the difficulties experienced by patients with OA. Once the main concerns were determined, a semi-structured questionnaire (with precise themes imposed, supplemented by a more 'free speech' approach through open-ended questions) was administered to a group of 165 subjects.

In order to ensure the participation of patients with diverse profiles, it was planned to include 165 patients recruited by rheumatologists working privately (20%) or in hospitals (30%), general practitioners (20%), pharmacists working for pharmacies (20%) and patients from the

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Association Française de Lutte Anti-Rhumatismale (AFLAR) (10%).

This first step allowed us to determine the major concerns of individuals with OA, namely: consequences at work, autonomy in daily life, the impact of treatment, self-image, and aestheticism. Based on this feedback, the BONE'S questionnaire was created by the working group. Items were converted into questions. A first assessment to simplify the questionnaire and to avoid redundancies was performed by the working group. The questionnaire was created in a question and answer format. Response modalities were also determined at this point by consensus among the experts (see *Development phase of BONE'S*).

Development phase of BONE'S

During the first stage of the development phase, the wording of possible questions/answers formed in the preliminary questionnaire was subjected to an initial assessment in order to group similar items, remove indiscriminate questions (where >90% of subjects, regardless of gender or age influences, responded in the same way) and limit redundancy. The selection of items which formed the questions in the pilot questionnaire was based on content and pertinence.

The method of response to the questionnaire was fixed at this stage, using a 6 point Likert scale ('never', 'rarely', 'sometimes', 'often', 'very often', 'constantly'), with an additional response 'not applicable' included in order to limit missing data. Likert scales are often used in self-administered questionnaires^{6,7} and this method of response was identified by the working group as the most relevant method for BONE'S. The reliability of a rating scale increases with the number of response categories, to a point²⁴ and Sellitz *et al.* argue in favor of more items as long as the wording of the response categories is clear, thus reducing the likelihood of distortion scores²⁵.

In this next stage, a study aiming to validate the pilot questionnaire (psychometric properties) and to reduce the number of questions, was implemented. To ensure the participation of patients with diverse profiles, it was planned to include 200 patients with OA. Subsequently, 200 subjects were recruited randomly by a specialized company (WR Council, Paris, France). To avoid selection bias (e.g. subjects with severe OA, hospitalized individuals), subjects were recruited at the time they presented to a pharmacy to be issued with a prescription for OA treatment following a physician-confirmed diagnosis of OA. OA diagnosis was based on standard clinical examination and patient questioning under 'real life' conditions.

As a result of the pilot study, indiscriminate items were deleted. Moreover, based on advice from the expert panel, items which represented similar complaints, and for

which answers showed equivalent scores on the Likert scale, were also removed.

An exploratory factor analysis (principal factor analysis) was then performed with the number of factors left free in order to highlight the underlying constructs and to categorize each item to its respective domains. An oblique (promax) rotation was performed after an orthogonal (varimax) rotation in order to explore whether the hypothetical constructs that constitute burden were interrelated. Items were considered for deletion if they loaded on two or more factors or did not load on any of the factors.

The final questionnaire was then tested in a sample of native French-speaking subjects during an individual, cognitive debriefing interview to determine the issues related to question and answer wording (ambiguity, misunderstanding, acceptability, etc.). This pilot testing was performed in France by a specialized institution (Lionbridge, Dublin, Ireland).

Dimension scores were calculated by adding up each individual item score. A global score, the sum of all individual item scores, was transformed onto a 0–100 scale: the higher the BONE'S score, the higher the burden of OA. Dimensions included in BONE'S were 'Independence', 'Interaction & Recreation', 'Psychological', 'Budget', and 'Hygiene & Beauty'.

Psychometric analysis – validation of BONE'S

Psychometric properties were evaluated by assessing the internal consistency reliability, and the construct – concurrent and discriminant – validity of BONE'S.

For internal consistency reliability, the homogeneity of the question items in each domain was evaluated using Cronbach's α coefficient. Coefficient scores in the range 0.6–0.69 are considered acceptable, and a coefficient score >0.7 generally indicates good internal reliability²⁶.

With regard to validity, concurrent validity of the questionnaire was determined by calculating the Spearman coefficient (r) between the BONE'S questionnaire and the SF-12 items and PGWB. Discriminant validity (known-group validity) was analyzed according to the following subgroups: age, gender and number of OA locations, using the Wilcoxon Mann–Whitney test since the parameters studied did not show a normal distribution.

Patient sample sizes were determined based on sample sizes in recently published studies, identified by a literature review, which reported the development of patient questionnaires across a diverse range of therapeutic areas: pediatrics, dermatology, cardiovascular, oncology, and allergy^{27–33}. Our sample sizes were consistent with those in the reported literature.

Data were analyzed using SAS software version 9.3 (SAS Institute Inc., Cary, USA) for Windows.

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A significance level of 0.05 was fixed for all tests unless stated otherwise.

Test-retest analysis

In order to assess the level of OA burden over a period of several weeks, a test-retest analysis was conducted. Subjects were retested after about 2 weeks to allow for daily variations³⁴. Test-retest analysis was determined by calculating the coefficient of intra-class correlation (ICC). The estimation of this coefficient was based on an analysis of variance. A Bland-Altman assessment for agreement was used to compare the two scores. A range of agreement was defined as mean bias ± 2 SD.

Translation and cross-cultural adaptation

Although the original BONE'S questionnaire was developed in French, well-established methodology (based on Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes [PRO] Measures³⁵) was applied to generate versions in other languages, and to account for cross-cultural validation. For each language, linguistic and cross-cultural validation followed a 9-step process (Table 1). This process aims to refine the translation, taking into account the nuances of the original version. Several changes can be implemented throughout the validation process without modifying the content. The aim is to allow an improvement on the first idiomatic rendering. In addition, the scales can be changed afterwards based on cognitive debriefing, in order to be consistent with the wording of the same question in the other available languages. The linguistic and cultural adaptation was performed by a specialized institution (Lionbridge, Dublin, Ireland).

Ethical considerations

The French legislator has, by the adoption of Law No. 88-1138 dated 20 December 1988, created Advisory Committees for the Protection of Persons in Biomedical Research (CCPPRB). These committees have the mission of screening research protocols, and have two characteristics: an advisory role and autonomy of operation in compliance with legislation. The procedure for reporting *a priori* research projects and submission of a protocol to an ethics committee resulted in the *de facto* creation of a database of clinical research studies planned in the country. This database is comprehensive for all protocols that come under the scope of Huriet-Sérusclat (Act No. 94-630, dated 25 July 1994, amending Book II of the Code of Public Health concerning the protection of persons who are suitable for biomedical research)³⁶.

In our study, subjects responded anonymously to a questionnaire, which was not conducted within the framework of biomedical research. Our study did not, therefore, come under the scope of Huriet-Sérusclat. In fact, at no time did the 200 subjects perform an additional review or was their care changed. At the beginning of the interview, the practitioners who conducted the questionnaire clearly explained the purpose of the questionnaire, and informed subjects that: (i) nothing required subjects to answer the questionnaire, (ii) all answers were strictly confidential, (iii) subjects could stop the interview at any time without having to give an explanation, (iv) each subject's identity would be kept strictly confidential and never revealed. Each subject provided verbal consent to participate and the interview commenced. Verbal agreement to participate was recorded in the study database or acknowledged via saving all answers to the questions. Individuals who declined to participate were thanked, the file was closed and no information was recorded (as dictated by French law).

Table 1. Stages of the linguistic and cross-cultural validation.

Stage	Details
1. Preparation	Evaluation of the source text from a linguistic and cultural point of view including definition of concepts
2. Forward translations	Forward translation into the required target language by two independent translators
3. Reconciliation	Comparison of the two forward translations to provide the best adaptation and produce a draft version of the text
4. Back translation	Translation of the draft forward translation back into the source language without reference to the original language
5. Back-translation review	Comparison of the original text and the back translation to verify that the meaning of the draft translation is equivalent to source
6. Analysis and implementation of back-translation review report	Analysis of the back-translation review report to verify if any changes are required to the draft forward
7. Pilot testing	Clinical review and cognitive debriefing
8. Review of cognitive debriefing or clinical review results	Review of the results from the cognitive debriefing or clinical review to identify translation modifications necessary for improvement
9. Proofreading and finalization	Last stage, which aims to detect any final grammatical and formatting errors before proceeding to testing and application stages

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Results

Exploratory phase of the BONE'S questionnaire

The initial exploratory phase involved 12 patients who discussed their complaints and disabilities related to OA, as well as input from three rheumatologists and an expert in the design of questionnaires.

Following qualitative interviews, the main statements received were: 'discouragement when dealing with the condition', 'difficulty completing simple daily activities', 'changes in physical appearance', and 'the view of arthritis as a handicap'. Altered family interaction was emphasized over altered interaction with others. At this initial exploratory stage of the questionnaire development, 56 items were generated.

A total of 126/165 (76%) patients with OA (27.8% male, 72.2% female; mean age: 66 years) participated in the subsequent pilot study. The original 56 items generated during the exploratory stage were reduced to 41 questions.

Development phase of the BONE'S questionnaire

During the next phase of development, data from 200 patients with OA were analyzed. The average age was 69.4 ± 7.0 years; 86% of patients were aged >60 years and 91.5% were female; 43%, 26%, 18.5%, and 12.5% of patients had one, two, three, and four joints affected by OA, respectively; 57% of patients had OA of the knee; 34% of patients had hip osteoarthritis (Table 2).

Responses to questions about 'stopping using the stairs' and 'having trouble using public transport' were in line with those generated by the question 'having trouble in walking'. Consequently, only the latter question was retained in the questionnaire. A similar situation was observed for three original questions relating to 'work'

(the first one was about absenteeism, the second about sick leave, and the third one related to difficulties at work). The first two questions were retained in the questionnaire due to their economical dimension. From the questions 'having trouble tying my shoelaces' and 'having trouble pursuing my hobbies', only the second one, associated with higher degrees of frustration, was retained in the questionnaire because both questions were deemed to broach the concept of 'loss of independence of the hands and fingers'. Moreover, questions identified during interviews for which relevance has not been established, were also deleted.

Consequently, taking into account all these effects, the pilot version of the questionnaire consisted of 25 questions (reduced from 41 questions), making it easier to use in large-scale longitudinal studies.

The exploratory factorial analysis identified a five-group model as the most parsimonious. Of the original 25 questions in the pilot questionnaire, two questions were deleted due to cross-loadings on factors, and three questions were deleted because they did not load on any of the factors. Thus, the final version of the BONE'S questionnaire used in the psychometric analysis consisted of 20 items. Standardized regression coefficients were all higher than 0.4 on their factor except for the item about budget/expenditures (Table 3). However, this item was retained due to its relevance and importance in the individual burden questionnaire, particularly in young, active, working individuals with OA. Indeed, because of the substantial budget deficit of healthcare systems, patients' non-reimbursed portion of the management of care increases and affects their purchasing power. Moreover, the current global economic downturn and the fact that individuals are generally working and living longer create the need to factor budget/economic aspects into health-related questionnaires. In addition, as individuals live longer, the prevalence of OA is predicted to increase substantially and non-inclusion of a 'Budget' dimension in BONE'S would potentially shorten the lifespan utility of the questionnaire.

According to the standardized regression coefficients, each group of questions was assigned a dimension, with each dimension consisting of at least three items and the 'Independence' dimension having the largest number of items: 'Independence' (7 questions), 'Interaction & Recreation' (4), 'Psychological' (3), 'Budget' (3) and 'Hygiene & Beauty' (3).

As a result of cognitive debriefing, there were no major changes to the wording of questions.

Psychometric analysis – validation of BONE'S

All dimensions correlated well with the overall BONE'S score (highest correlation: 'Independence' [$r = 0.91$];

Table 2. Sociodemographic and clinical characteristics of patients ($n = 200$) with osteoarthritis (OA).

Characteristic	
Gender, n (%)	
Female	183 (91.5)
Male	17 (8.5)
Age, years (mean $\pm$ SD)	69.4 ± 7.0
No. of joints affected, n (%)	
1	86 (43.0)
2	52 (26.0)
≥ 3	62 (31.0)
OA type, n (%)	
Knee	114 (57.0)
Hip	67 (33.5)
Fingers	89 (44.5)
Other	131 (65.5)
Employment status, n (%)	
Full-time	8 (4.0)
Part-time	10 (5.0)
None	182 (91.0)

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Table 3. Standardized regression coefficients from the final rotated factor pattern. Regression coefficients shown in bold represent the individual items included in each dimension.

As a result of my osteoarthritis...	Factor 1: Independence	Factor 2: Interaction & recreation	Factor 3: Budget	Factor 4: Hygiene & Beauty	Factor 5: Psychological
...I have trouble walking	0.58629	0.13150	-0.04421	-0.11961	0.00222
...I have trouble doing my shopping	0.48816	-0.03807	0.16395	0.16685	0.11917
...I have a hard time getting up from the toilet	0.40077	0.20318	-0.01355	0.22884	-0.20054
...I have trouble pursuing my hobbies (sewing, knitting, gardening, DIY)	0.46865	-0.11593	-0.03829	0.00671	0.29827
...I cannot stand for very long	0.69932	-0.00084	0.03991	0.04705	0.05537
...I have trouble cutting my nails	0.44518	0.15026	-0.06685	-0.00250	0.00143
...I find that there has been a decline in my appearance (aesthetics, gait, build)	0.52014	0.01001	-0.03150	0.05366	-0.01055
...I do not have as many friends over to my house as I did before	-0.07226	0.67148	0.03031	0.04719	0.08326
...I cannot travel whenever I want to	0.22108	0.67379	-0.03826	-0.07877	-0.08339
...I cannot go out whenever I want to	0.28702	0.63137	-0.00600	-0.00211	-0.01508
...I may go several days without going out	-0.03455	0.60303	-0.03565	0.05733	0.18851
...I often have to leave work	-0.04014	0.02969	0.86788	0.00572	-0.05378
...I have been on sick leave several times	-0.00402	0.03987	0.89054	-0.05484	0.01129
...how much do you estimate you spent on your personal, non-reimbursed expenses for your osteoarthritis last month?	0.02426	-0.18320	0.26038	0.10238	0.06297
...I am reluctant to wash my hair	-0.09105	0.29760	-0.05864	0.53010	0.08210
...I have trouble getting dressed	0.14475	0.00845	0.07037	0.58723	0.03207
...I have trouble brushing my teeth	0.03655	-0.07222	-0.00538	0.77095	-0.03872
...I am anxious or nervous	0.00460	0.21039	0.03193	0.13041	0.43809
...I feel tired	0.25875	0.01225	0.02672	-0.05930	0.59829
...I am experiencing side effects from my treatment	-0.06765	0.02204	-0.02639	-0.00674	0.60026

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Table 4. Correlation coefficients and Cronbach's α for the different dimensions of the BONE'S questionnaire.

	Independence	Interaction & Recreation	Psychological	Budget	Hygiene & Beauty	Cronbach's α
Independence						0.79
Interaction & Recreation	0.59					0.82
Psychological	0.52	0.46				0.69
Budget	0.04*	0.05*	0.11*			0.67
Hygiene & Beauty	0.49	0.39	0.40	0.06		0.75
BONE'S score	0.91	0.74	0.71	0.19	0.56	0.86

*Non-significant.

Table 5. Correlation coefficients for the validation of the BONE'S tool versus the SF-12 and PGWBI assessment tools.

	Independence	Interaction & Recreation	Psychological	Budget	Hygiene & Beauty	BONE'S score
SF-12 – MCS	–0.33	–0.32	–0.42	–0.02*	–0.35	–0.40
SF-12 – PCS	–0.65	–0.60	–0.48	–0.02*	–0.33	–0.70
PGWBI	–0.39	–0.30	–0.47	–0.03*	–0.38	–0.45

*Non-significant.

MCS: mental health composite score; PCS: physical health composite score; PGWBI: Psychological General Well-Being Index; SF-12: Short Form 12-item health survey.

lowest correlation: 'Hygiene & Beauty' [$r = 0.56$], with the exception of 'Budget' ($r = 0.19$; Table 4). However, this dimension appeared significant and relevant in the subpopulation of active, working subjects ($r = 0.40$), thus confirming its importance. In addition, with the exception of 'Budget' ($r = 0.06$ to 0.11), all dimensions correlated well with each other (range: 0.39 to 0.59 ; Table 4).

Internal consistency reliability

Cronbach's α was 0.86 for the entire questionnaire, indicating excellent internal coherence. Intra-dimensional coherences all demonstrated acceptable reliability ($\alpha > 0.67$) with all coherence values clustered within a narrow range ($\alpha = 0.67$ – 0.82 ; Table 4).

Concurrent validity

The average PGWBI score (out of 100) was 50.5 ± 12.6 (range: 6–70). Analysis of the SF-12 demonstrated an altered HRQoL for the physical dimension (38.9 ± 9.9), but not for the mental dimension (49.9 ± 11.8). With the exception of the 'Budget' dimension, each individual dimension of BONE'S correlated well (inversely) with the SF-12 and, to a slightly lesser extent, with the PGWBI (Table 5). Given that the SF-12 and PGWBI tools do not assess budgetary aspects, the lack of correlation with the 'Budget' dimension of BONE'S is in line with expectations. The overall BONE'S score showed good inverse correlation with the physical dimension of the SF-12 ($r = -0.70$) and, to a lesser extent, with the mental dimension (-0.40), as was the case with the PGWBI score ($r = -0.45$) (Table 5).

Discriminant validity

The average BONE'S score was 21.9 ± 16.0 (median: 17.6, range: 0–79). The mean score for subjects with one or two affected joints was significantly different from the score for subjects with three or more affected joints (effect size: 11 points, Student's t -test: $p < 0.01$). The BONE'S score also differed significantly according to gender (men experienced a heavier burden than women, effect size: 6 points, $p = 0.02$), and age (patients aged < 55 years had higher scores than those aged ≥ 55 years, effect size: 8 points, $p = 0.003$).

Test–retest analysis

The test–retest reliability of BONE'S was confirmed; an ICC of 0.87 (95% CI, 0.73 , 0.94) was obtained, demonstrating very good reproducibility. The ICC of each dimension was > 0.73 . A Bland–Altman plot for the test–retest analysis is presented in Figure 1.

Translation and cross-cultural adaptation

The original French version of BONE'S has been translated and undergone linguistic and cultural adaptation into English (US), Portuguese and Russian. The psychometric properties of the translated questionnaires were not performed; cognitive debriefing was performed for each validation.

Discussion

The recent concept of individual burden of disease, introduced to assess individual disease-related patient

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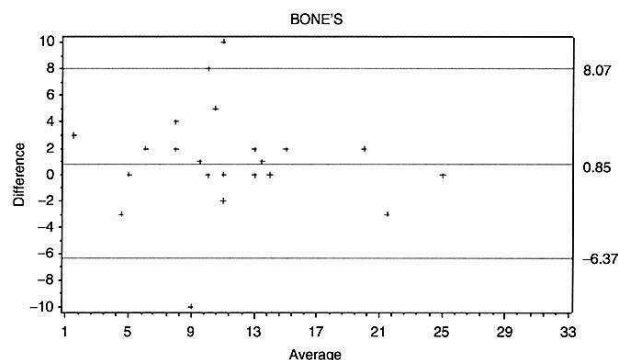


Figure 1. Test-retest analysis of the BONE'S questionnaire, presented as a Bland-Altman plot. Variable means are plotted on the horizontal axis with differences between the two BONE'S scores plotted on the vertical axis.

disability (covering, in the broadest sense, psychological, social, physical and economic burden), extends the more conventional concept of societal burden as generally applied to populations/healthcare systems^{2,5}.

OA is associated with significant impairment that impacts on the daily HRQoL of patients, particularly elderly patients^{12,37,38}. Moreover, there is increasing recognition that OA also has a significant impact on younger patients. In a recent analysis of data (from individuals aged ≥ 20 years) from the 2009 US National Health and Wellness Survey, individuals with OA pain were less likely to be employed and the impact of OA and arthritic pain was shown to reduce workplace productivity, and was associated with significantly impaired health status and higher total healthcare resource utilization costs (indirect and direct) compared with individuals not experiencing OA and arthritic pain³⁹.

Many assessment tools commonly used to determine QoL in patients with OA are general health indices that have not been developed specifically to determine specific disease burden¹⁷. Indeed, only tools that assess functional disability have been developed specifically for patients with OA; in most cases, the effects of OA on large joints of the lower limbs tend to be assessed, rather than a more global assessment of all affected joints¹⁸. In recognition of these current deficiencies, our objective was to develop and validate a specific individual burden questionnaire (BONE'S) for assessing the disability of patients with OA in the broadest sense. Other researchers have also recently reported conceptual models of the personal and social burden of osteoarthritis that may assist in the future management of individuals with OA and the wider society⁴⁰.

The new BONE'S questionnaire has been developed with the goal of providing an assessment tool that can measure the individual burden of OA on patients' daily life (covering psychological, social, economic and physical aspects). Based on Cronbach's α , the overall questionnaire had excellent internal coherence ($\alpha = 0.86$); furthermore, intra-dimensional correlations were all well correlated (>0.67). Of note, the BONE'S score was higher when patients had more joints affected by OA, with a significant difference between one or two affected joints and three or more joints.

With regard to external validity, the BONE'S score showed good inverse correlation with the physical dimension of the SF-12 ($r = -0.70$) and, to a lesser extent, with the mental dimension (-0.40), as was the case with the PGWBI score ($r = -0.45$). Evidence suggests that a decline in physical functioning with advancing age is independent of mental health, which appears to remain relatively stable; furthermore, patients with chronic diseases, such as OA, also experience a decline in physical function while mental health remains relatively stable^{41,42}.

Limitations associated with the current study include the fact that the psychometric analysis was conducted in a relatively small sample of patients (predominantly females, potentially limiting the generalizability of our data to the general population) and did not test for reproducibility, measurement error, responsiveness, or interpretability; larger confirmatory studies using the BONE'S questionnaire are warranted. Test-retest analysis of the BONE'S questionnaire demonstrated good reliability; however, since measures were obtained over an approximate 2 week interval, it is theoretically possible that memory resulted in an overestimation of the reliability⁴³. Nevertheless, since it is difficult to recall a large number of

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scores (such as in BONE'S)⁴³, the ratings can be considered practically independent of each other and it is unlikely that memory significantly influenced the second evaluation. Patients with OA who were evaluated in the BONE'S validation study had a mean age of 69.4 ± 7.0 years; an assessment of the BONE'S questionnaire in a younger population of patients with OA would be valuable. Although body mass index and comorbidities can impact on the burden of OA, the current study to develop and validate the BONE'S questionnaire did not evaluate these parameters; these characteristics will be evaluated in future studies. It is also important to note that we recruited subjects who presented to a pharmacy to be issued a treatment. However, this selection procedure does not account for patients with OA who are not treated; consequently, as currently developed, the questionnaire is relevant in patients receiving pharmacological interventions, possibly limiting the generalizability of our findings. In addition, the BONE'S questionnaire was validated with SF-12 and PGWBI but was not compared with other specific tools used in the assessment of OA, including WOMAC, Lequesne and KOOS. Furthermore, the original BONE'S questionnaire was developed and validated in French only. In order to ensure that the BONE'S questionnaire can be utilized across wider geographic populations, linguistic and cultural adaptations have subsequently made it possible for BONE'S to be available in US English, Portuguese and Russian, based on the guidance of the International Society for Pharmacoeconomics and Outcomes Research Principles of Good Practice for Translation³⁵. Two prospective studies using the BONE'S questionnaire are currently planned in France and Portugal in 2000 and 1200 individuals, respectively.

In order to assess the interpretability of BONE'S, it would be interesting to evaluate the questionnaire's sensitivity to clinically meaningful change, or minimal-important difference²², in a prospective cohort study. Also, a confirmatory factorial analysis on another sample of patients with OA may be necessary to confirm the factorial structure of BONE'S. At this stage in the development of BONE'S, item response theory (IRT) has not yet been conducted. IRT provides a collection of supportive techniques for modeling the analysis of item level data obtained to measure interindividual variation^{44,45}. Finally, missing data represent a problem in most epidemiological studies and, although numerous methods are currently available for handling missing data, some methods have the potential to introduce serious bias into study results⁴⁶; it is planned that the design of future studies to confirm the utility of BONE'S will incorporate appropriate methodology for handling missing data.

Increasing importance is being placed on PRO by regulatory authorities^{47,48}. Indeed, the term PRO covers a range of patient-centered items including single- and multiple-dimension measures of disease symptoms,

HRQoL, health status, and satisfaction with treatment⁴⁸. The BONE'S questionnaire aligns with the PRO concept and provides supplementary information by taking into account the burden of OA in the broadest sense.

Conclusion

The BONE'S questionnaire is a short (20-item) and easy to use tool for evaluating the burden of OA. Although BONE'S has not been evaluated against a range of other currently available OA tools, such as WOMAC or Lequesne, many of the currently available QoL questionnaires generally only assess a single affected joint (upper or lower body limb) and do not assess the economic impact of OA on an individual's daily life. The BONE'S questionnaire allows an evaluation of the individual burden of OA in a more holistic manner.

Transparency

Declaration of funding

This study was funded by Pierre Fabre Laboratories.

Declaration of financial/other relationships

C.T. and S.B. are employed by Pierre Fabre Laboratories. F.R., P.B. and L.G. have received consulting fees from Pierre Fabre Laboratories for their contribution to this project. J.-N.D. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article.

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Note: a copy of the BONE'S questionnaire and the algorithm used to calculate the BONE'S score are available, on written request, from MAPI.

Author contribution

Conception and design of the study – F.R., P.B., L.G., S.B., J.-N.D., C.T. Acquisition of data – F.R., P.B., L.G., S.B., J.-N.D., C.T. Analysis and interpretation of data – S.B., C.T. Drafting the article or revising it critically for important intellectual content – F.R., P.B., L.G., S.B., J.-N.D., C.T. Final approval of the version to be submitted – F.R., P.B., L.G., S.B., J.-N.D., C.T. Responsibility for the integrity of the work as a whole, from inception to finished article – C.T.

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APPENDIX 3 – Short-Form questionnaire (SF-12)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

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

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

2. The following questions 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
			
a	<u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....		
	☐ 1	☐ 2	☐ 3
b	Climbing <u>several</u> flights of stairs		
	☐ 1	☐ 2	☐ 3

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3. During the past 4 weeks, how much of the time have you had any of the

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

a Accomplished less than you would like 1..... 2..... 3..... 4..... 5

b Were limited in the kind of work or other activities 1..... 2..... 3..... 4..... 5

following problems with your work or other regular daily activities as a result of your physical health

4. During the past 4 weeks, how much of the time 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)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

a Accomplished less than you would like ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5

b Did work or other activities less carefully than usual..... ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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6. 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	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. During the past 4 weeks, how much of the time has your physical health or

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

Thank you for completing these questions!

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APPENDIX 4 – Structum® treatment satisfaction questionnaire

After the inclusion visit

1. How easy or difficult is to take the medication by mouth?	☐ Very Easy ☐ Easy ☐ Somewhat Easy ☐ Difficult ☐ Very Difficult
2. How convenient or inconvenient is it to take the medication as instructed?	☐ Very Convenient ☐ Convenient ☐ Somewhat Convenient ☐ Inconvenient ☐ Very Inconvenient

At the 3-month follow up visit

1. How easy or difficult is it to take the medication by mouth?	☐ Very Easy ☐ Easy ☐ Somewhat Easy ☐ Difficult ☐ Very Difficult
2. How convenient or inconvenient is it to take the medication as instructed?	☐ Very Convenient ☐ Convenient ☐ Somewhat Convenient ☐ Inconvenient ☐ Very Inconvenient
3. Since the last visit (3 months ago), how satisfied or dissatisfied are you with the way the medication relieves your symptoms?	☐ Very Satisfied ☐ Satisfied ☐ Somewhat Satisfied ☐ Dissatisfied ☐ Very Dissatisfied
4. Since the last visit (3 months ago), how satisfied or dissatisfied are you with the amount of time it takes the medication to start working?	☐ Very Satisfied ☐ Satisfied ☐ Somewhat Satisfied ☐ Dissatisfied ☐ Very Dissatisfied
5. Taking all things into account (the ability to relieve the symptoms, the time of action, the form of administration and the convenience of taking the medication), how satisfied or dissatisfied are you with this medication?	☐ Very Satisfied ☐ Satisfied ☐ Somewhat Satisfied ☐ Dissatisfied ☐ Very Dissatisfied

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At the 6-month follow up visit

1. How easy or difficult is to take the medication by mouth?	☐ Very Easy ☐ Easy ☐ Somewhat Easy ☐ Difficult ☐ Very Difficult
2. How convenient or inconvenient is it to take the medication as instructed?	☐ Very Convenient ☐ Convenient ☐ Somewhat Convenient ☐ Inconvenient ☐ Very Inconvenient
3. Since the last visit (3 months ago), how satisfied or dissatisfied are you with the way the medication relieves your symptoms?	☐ Very Satisfied ☐ Satisfied ☐ Somewhat Satisfied ☐ Dissatisfied ☐ Very Dissatisfied
4. Since the last visit (3 months ago), how satisfied or dissatisfied are you with the effect duration of the medication?	☐ Very Satisfied ☐ Satisfied ☐ Somewhat Satisfied ☐ Dissatisfied ☐ Very Dissatisfied
5. Taking all things into account (the ability to relieve the symptoms, the time of action, the form of administration and the convenience of taking the medication), how satisfied or dissatisfied are you with this medication?	☐ Very Satisfied ☐ Satisfied ☐ Somewhat Satisfied ☐ Dissatisfied ☐ Very Dissatisfied

Reference

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APPENDIX 5 – Metabolic syndrome diagnosis (according to Alberti *et al.*)

Metabolic syndrome as defined by Alberti *et al.* is a combination of different degrees of visceral obesity, dyslipidemia, hyperglycemia and hypertension.

Diagnosis of the presence of metabolic syndrome is based on a panel of measurements. General consensus states that the patient must present Central Obesity and at least two other factors.

1. Central obesity
 - a. Ethnicity specific waist circumference (see table below)
 - b. BMI > 30 kg/m², with assumption of obesity
2. Raised triglycerides
 - a. >150mg/dL (or 1.7 mmol/L)
 - b. Undergo specific treatment for this abnormality
3. Reduced HDL-cholesterol
 - a. <40 mg/dL or 1.03 mmol/L in men
 - b. <50 mg/dL or 1.29 mmol/L in women
 - c. undergo specific treatment for this abnormality
4. Raised blood pressure
 - a. ≥ 130 mm Hg Systolic
 - b. ≥ 85 mm Hg Diastolic
 - c. previously diagnosed and treated hypertension
5. Raised fasting plasma glucose
 - a. Fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L) – (if above, the oral glucose tolerance test is strongly recommended but not obligatory for the diagnosis)
 - b. Previously diagnosed type II diabetes

Ethnicity Waist circumference	Europids	South Asians	Chinese	Japanese	Ethnic south and central Americans	Sub-Saharan Africans/Easter Mediterranean /Middle East populations
Men	≥ 94 cm	≥ 90 cm	≥ 90 cm	≥ 85 cm	Use South Asian recommendations until more specific data are available	Use European recommendations until more specific data are available
Women	≥ 80cm	≥ 80 cm	≥ 80 cm	≥90 cm		

PPD

PPD