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Evolution of pain at 3 months by oral resveratrol in knee osteoarthritis (ARTHROL): protocol for a multicentre randomised double-blind placebo-controlled trial

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Abstract

Introduction. Osteoarthritis (OA) pathophysiology is driven in part by joint inflammation. Resveratrol has *in vitro* anti-inflammatory properties. We aim to assess the efficacy of oral resveratrol for knee pain at 3 months in people with knee OA.

Methods and analysis. We will conduct a randomised double-blind placebo-controlled trial. Overall, 164 individuals with knee OA fulfilling the 1986 ACR criteria will be recruited in 3 tertiary care centres in France and randomised to receive oral resveratrol, 40 mg twice a day for 1 week, then 20 mg twice a day or a matching placebo for 6 months. Randomisation will be centralized and stratified by centre. The allocation ratio of assignments will be 1:1. The primary outcome will be the mean change from baseline in knee pain on a self-administered 11-point pain numeric rating scale at 3 months. Secondary outcomes will be the mean change in knee pain at 6 months, the function subscore of the WOMAC score, patient global assessment, proportion of responders according to the OARSI-OMERACT criteria at 3 and 6 months, and self-reported number of intra-articular injections of corticosteroids or hyaluronic acid and consumption of analgesics and non-steroidal anti-inflammatory drugs since the last contact. Other interventions will be allowed and self-reported. Adherence will be monitored by capsule counts and a booklet and adverse events recorded at 3 and 6 months. Statisticians, treating physicians and participants will be blinded to the allocated treatment.

Ethics and dissemination. The ARTHROL trial has been authorised by the *Agence Nationale de Sécurité du Médicament et des Produits de Santé* and ethics were approved by the *Comité de Protection des Personnes Île-de-France* III. The findings of the study will be published in a peer-reviewed journal and disseminated at conferences. The design of ARTHROL will warrant the translation of its findings into clinical practice.

Registration details. ClinicalTrials.gov identifier: NCT02905799. First received: September 14, 2016. Last updated: September 16, 2016. Status: not yet recruiting.

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Date and version identifier of the protocol. V2.0 of March 20, 2017.

Keywords. Osteoarthritis; knee; resveratrol; oral treatment; pain; clinical trial.

Strengths and limitations of the study

- First randomised controlled trial to assess the effects of oral resveratrol on pain in knee osteoarthritis.
- A design to facilitate the translation of findings into clinical practice.
- Innovative new formulation of oral resveratrol to improve its bioavailability.
- Selection of primary and secondary efficacy outcomes in accordance with Outcome Measures in Rheumatology (OMERACT) recommendations and Core Outcome Measures in Effectiveness Trials (COMET) initiative for phase III clinical trials in knee osteoarthritis.
- Participants will be recruited from tertiary care centres and may not be fully representative of the population with knee osteoarthritis in France.

Introduction

In the 2015 Global Burden of Disease Study, musculoskeletal disorders were identified among the 5 main contributors to disability-adjusted life-years [1]. Knee osteoarthritis (OA) is one of the most disabling joint disorders in Western countries [2] and OA is the first cause of disability in people over 40 years old in France [3].

OA pathophysiology is in part driven by local joint inflammation leading to severe tissue damage. No efficient treatment exists for structural changes in OA; the only treatments are for painful symptoms and are mainly acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids. Unfortunately, acetaminophen is weakly effective, with a poor effect size of 0.10, and recent data highlighted its potential cardiovascular adverse effects [4 5]. For NSAIDs, serious cardiovascular and digestive side effects do not support their prescription for long duration. An optimized treatment for OA should be efficient for both pain and inflammation, with minimal adverse effects.

Resveratrol is a molecule of interest because it has *in vitro* an *in vivo* anti-inflammatory and chondroprotective properties [6 7]. Resveratrol is available over the counter in France as a dietary supplement. No serious toxicity has been reported. In the field of rheumatic diseases, *in vitro* evidence supports anti-inflammatory, anti-catabolic, anti-apoptotic and anti-oxidative properties of resveratrol in various articular cell types, along with immunomodulation properties for T and B lymphocytes [8-20]. Consistently, resveratrol administered intra-articularly has shown chondroprotective effects in pre-clinical models of OA, mediated by decreased production of pro-inflammatory and pro-degradative soluble factors, and modulation of cellular and humoral responses [21-23]. In clinical research, resveratrol has been evaluated in ageing, cancer, neurodegenerative diseases, menopausal conditions, and cardiovascular and liver diseases [6]. The doses used in these trials were variable and not adjusted to the low bioavailability of oral formulations.

New formulations of resveratrol have allowed for an increase in oral resveratrol bioavailability [24]. The plasmatic peak is 10-fold increased and blood concentration remains at significant levels for several hours. We hypothesized that oral resveratrol in a new formulation could reduce knee pain at 3 months as compared with placebo in people with knee OA.

Methods and analysis

Design overview. This is a prospective, parallel-group, double-blind, randomised controlled multicentre study. Duration of follow-up for each participant will be 6 months post-randomisation. The study will be reported according to the CONSORT statement [25].

Setting and participants. Participants will be prospectively recruited among in- and outpatients from Rheumatology and Rehabilitation departments of 3 tertiary care centres in France with expertise in OA management (Cochin and Saint-Antoine Hospitals, Paris; and Gabriel-Montpied Hospital, Clermont-Ferrand), by advertising on the Internet and in the media (newspapers, health magazines) and by using posters in each investigating centre. People interested in participating in the study will be invited to contact a biomedical research technician by phone or email. In addition, the computerized medical records of each investigating center will be searched from 2015 to 2017, and patients with the key words "knee OA" in the records will be invited to participate in the study by phone or mail by the biomedical research technician. The number of patients treated yearly for knee OA in the participating centers is approximately 2000. The biomedical research technician will check for eligibility criteria, then, if appropriate, set up a face-to-face baseline visit with one of the investigators, a senior specialist in rehabilitation and/or rheumatology. The main eligibility criteria will be knee OA fulfilling 1986 American College of Rheumatology criteria, pain on a self-administered 11-point pain numeric rating scale (NRS) ≥ 40/100, symptom duration ≥ 1

month, and Kellgren and Lawrence X-ray score 1, 2 or 3. A complete description of the inclusion and non-inclusion criteria is in **Appendix 1**.

Experimental group. Two capsules of resveratrol (40 mg) will be administered orally twice a day, 30 min before a meal with a glass of water, for 1 week, then 1 capsule (20 mg) twice a day for a total of 6 months. Resveratrol will be freely supplied by the Yvery laboratory (Marseille, France). Resveratrol is considered a dietary supplement and is available over the counter. No marked toxicity has been reported [26]. The capsules used in this study will be exactly the same as those already available on the French market. They will be stored in their original packaging at room temperature, protected from humidity, light and excessive heat. A box containing 7 pillboxes of 60 capsules each of resveratrol will be provided to each person randomised to the experimental group. Individuals will be asked to return the pillboxes for capsule counts at the 3- and 6-month visits and to self-report adherence by completing a booklet. However, no specific measures will be taken to enhance adherence.

Control group. The Yvery laboratory will supply the placebo and ensure that it has a similar condition and taste as resveratrol. Two capsules of placebo will be administered orally twice a day for 1 week, then 1 capsule twice a day for a total of 6 months. A box containing 7 pillboxes of 60 capsules each of placebo will be provided to each person randomised to the control group and stored under the same conditions as resveratrol.

Co-interventions. Pharmacological and non-pharmacological treatments usually prescribed for knee OA will be authorised. Rescue medications (analgesics and NSAIDs), joint injections (hyaluronic acid and corticosteroids), symptomatic slow acting drugs for OA (SYSADOA) and non-pharmacological co-interventions including brace, insoles, walking aids, physiotherapy, home-based therapeutic exercises and weight loss will be assessed by using a standardized checklist and recorded in the electronic case report form (eCRF).

Outcomes. Primary and secondary efficacy outcomes have been selected in accordance with OMERACT recommendations [27] and the Core Outcome Measures in Effectiveness Trials (COMET) initiative for phase III clinical trials of knee OA. As recommended, the outcomes include those for pain, physical function and patient global assessment. The primary efficacy outcome is the mean change from baseline in mean knee pain in the previous 48 hr on a self-administered 11-point pain NRS (0, no pain, to 100, maximal pain) at 3 months. The secondary efficacy outcomes are the mean change in mean knee pain on a pain NRS at 6 months, the mean change in the function subscore of the self-administered Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire at 3 and 6 months (the French version of the questionnaire) [28], the mean change in patient global assessment at 3 and 6 months on a self-administered 11-point global assessment NRS (0, worst possible, to 100, best possible), the proportion of responders according to the Osteoarthritis Research Society International (OARSI)-(Outcome Measures in Rheumatology) OMERACT at 3 and 6 months [29], the self-reported number of intra-articular injections of corticosteroids or hyaluronic acid and the self-reported consumption of analgesics (non-opioid, weak and strong opioids) and NSAIDs since the last contact on a self-administered 4-class scale (never, several times a month, several times a week, daily) at 3 and 6 months. Information about the WOMAC questionnaire and OARSI-OMERACT response are in **Appendix 2**. For participants who discontinue or deviate from intervention protocols, the same outcome data will be collected if possible.

Randomisation and allocation concealment. Individuals who meet the inclusion criteria and agree to participate will be randomly assigned to the resveratrol or placebo group at the inclusion visit. The allocation ratio of assignments will be 1 :1. Participants, care providers, data collectors, outcome assessors and statisticians will be blinded to the allocated group. The randomisation sequence will be computer-generated by a statistician of the *Centre*

d'Épidémiologie Clinique. The list will be stratified by centres with variable block sizes. The randomisation process will be centralized at the coordinating office (*Unité de Recherche Clinique*, Cochin Hospital), which will have no involvement in the enrollment, follow-up, or assessment of participants. Only the independent statistician of the *Centre d'Épidémiologie Clinique*, the computer programmer at the coordinating office who will implement the sequence assignment in the secure eCRF, and the Yvery company will have access to the randomisation list. The Yvery Company will label the resveratrol and placebo capsules and provide them with strictly identical presentations to each centre for the whole research duration. In each centre, the investigator will blindly deliver the medication to patients enrolled according to their randomisation number, at once, for the whole research duration. The sequence will be concealed by use of a computer interface implemented in the eCRF. Treatment administration and clinical monitoring of the experimental products will be the same in the experimental and control groups.

Blinding can be broken only if the investigator deems it necessary for the safe management of a specific medical condition of a subject, and whenever possible, the methodologist and sponsor will be consulted before breaking the blind. If the blind is broken for any reason during the study, the moment at which the blind was broken and all other relevant information will be documented by the investigative site and other sponsor designees, as appropriate. The reason for breaking the blind will be indicated and justified in the source documentation and in the eCRF.

Statistical aspects. The sample size is estimated at 164 patients. We have predicted a difference in mean change from baseline of 15 mm on the pain NRS between resveratrol and placebo groups, with a standard deviation of 27 mm, and a power of 90%, corresponding to 69 patients in each arm. Considering a 15% lost to follow-up, we will need to enroll an estimated 82 patients for each arm. Fifteen points on pain NRS is considered the minimal

clinically perceived difference in pain for patients with knee OA. All analyses will be performed on an intent-to-treat basis, in that all patients will be considered in the analysis and will be analysed in the group to which they had been assigned. For descriptive analyses, qualitative variables will be reported with absolute and relative frequencies and quantitative variables with median (interquartile range). To compare differences in changes in values between the 2 groups for quantitative variables, a constrained longitudinal data analysis will be used. In this model, both the baseline and post-baseline values will be modelled as dependent variables, and the true baseline means will be constrained to be the same for the 2 treatment groups. This analysis provides an adjustment for the observed baseline difference in estimating the treatment effects. The differences in change from week 0 will be estimated at each time in each group by the time-by-treatment interaction. Random effects at patient and centre levels will be added to these models. Qualitative outcomes will be analysed by a mixed logistic regression model with a random effect at centre levels. Data analysis will involve use of SAS 9.4 (SAS Institute, Cary, NC). Blinded statisticians will perform the statistical analyses at an independent centre (*Centre d'Épidémiologie Clinique*, Paris Descartes, Hôpital Hôtel-Dieu). The statistical analysis will be further detailed in a dedicated Statistical Analysis Plan before any analysis is undertaken.

Participant timeline (Figure 1).

Baseline visit. Inclusion and non-inclusion criteria will be validated at baseline by the investigator during a face-to-face visit. The individual will be informed and the written consent collected by the investigator. Then the participant will be enrolled and randomised. Specific additional clinical examination, laboratory tests or imaging will not be required for the purpose of the study. Information regarding demographics (age, gender, body mass index, education, employment status), medical history (date of diagnosis, symptoms duration, side affected, medical history, surgery and trauma history of the affected knee, X-ray findings

including Kellgren and Lawrence grade and OA location [i.e., femorotibial medial, femorotibial lateral and/or patellofemoral OA]), medications in the previous 3 months (analgesics, NSAIDs and intra-articular injections of hyaluronic acid and/or corticosteroids and SYSADOA) and current non-pharmacological co-interventions (brace, insoles, walking aids, physiotherapy, home-based therapeutic exercises and weight loss) will be recorded in the eCRF by using a standardized checklist. Baseline values for prespecified assessment criteria will be collected by using printed self-administered questionnaires and data will be entered in the eCRF by a biomedical research technician. The investigator will deliver the experimental product to the participants according to their randomisation number and give them a participating card in a clinical trial. Participants will be asked to keep and return the pillboxes for capsule counts at the 3- and 6-month visits and to self-report adherence by completing a booklet.

Three- and 6-month visits. The investigator will assess participants during a face-to-face visit. Values for prespecified assessment criteria will be collected at 3 and 6 months by using printed self-administered questionnaires, and data will be recorded in the eCRF by a biomedical research technician. In addition, the investigator will record adverse events (AEs) since the last contact by asking an open-ended question ("Did you have any adverse events since the last contact?"), count the capsules remaining in the pillboxes, check the self-reported adherence booklet and assess non-pharmacological co-interventions by using a standardized checklist. In the event that the participant missed the appointment, self-administered questionnaires, AEs, capsule counts and non-pharmacological co-interventions will be collected by mail, email or phone by a biomedical research technician and recorded. To reduce the amount of missing data, promote participant retention and complete the follow-up, reminder newsletters will be sent once a month by mail or email to inform participants of the progression of the study.

End of the research. At the end of the research, patients will be advised to continue their usual medical follow-up with their treating physician. Ending a subject's participation will not affect the normal medical management in any way. No exclusion period for another biomedical research will be required. At the end of the study, participants will be informed of the results upon request.

Role of the funding source. The study is funded by a research grant from the French Ministry of Health (*Programme Hospitalier de Recherche Clinique*, project no. 15-15-0234) and sponsored by the *Département de la Recherche Clinique et du Développement* (DRCD) of the *Assistance Publique-Hôpitaux de Paris* (AP-HP) (Hôpital Saint-Louis, 1, Avenue Claude Vellefaux, 75010 Paris, FRANCE, tel: +33 1 44 49 59 69, fax: +33 1 44 84 17 99). The Yvery laboratory will supply the resveratrol and the placebo. The funding source and the Yvery laboratory will not be involved in the study design; collection, management, analysis, and interpretation of data; or writing of the report; nor decision to publish the results.

Data management

Data collection. Data will be entered into an eCRF, completed by the investigator during each visit. Data from printed self-administered questionnaires will be entered in the eCRF by a biomedical research assistant after the visits. The investigator must give an explanation for each missing data. Changes in the data in the eCRF will be tracked. Discordant data in the eCRF will be corrected by queries.

Data monitoring. In accordance with the French Good Clinical Practices, the sponsor, DRCD, is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research is carried out, the source data, the source documents and the reports, with the goal of quality control and audit by the sponsor. In accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code), the investigators will make available to those

in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls. Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research.

Quality control. A clinical research associate appointed by the sponsor will be responsible for the proper conduct of the research and for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with French Good Clinical Practices as well as with the legislative and regulatory provisions in force. The investigator and the members of the investigator's team agree to make themselves available during quality control visits carried out at regular intervals by the clinical research associate. During these visits, the following elements will be reviewed: written consent, compliance with the research protocol and with the procedures defined therein, quality of the data collected in the eCRF including accuracy, missing data, consistency of the data with the source documents (medical files, appointment books, original copies of laboratory results, etc.), and management of the treatments used.

Ethics and dissemination

Ethical considerations

Methods for obtaining information and consent from research participants. In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code. The investigator or a doctor representing the investigator obtains the free and informed consent, in writing, of the individual before their inclusion in the research. The information sheet and a

copy of the consent form signed and dated by the research participant and by the investigator or the doctor representing the investigator, are given to the individual before their participation in the research. In addition, the investigator will specify in the research participant's medical file the methods used for obtaining consent as well as the methods used for providing information with the goal of obtaining consent. The investigator will retain the original signed and dated copy of the participant's consent form.

Data confidentiality. Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the participants and the results obtained. Investigators are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code). During or after the biomedical research, the data collected for the research participants and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying. Anonymization of the patients will be ensured by using a code number and initials, reported on each needed document for the research, or by erasing nominative data on copies of source documents. Under no circumstances should the names and addresses of the subjects involved be shown. The sponsor will ensure that each research participant has given permission in writing for access to their personal information that is strictly necessary for the quality control of the research. Access to the eCRF will be restricted by an access code and a personal and unique password system for each user. Each investigator will, in addition, have access to a specific profile that attributes or withholds access to certain functions of the system (entering data, or simply viewing the data of the enrolled participant or all the study data, possibility of change and validation by the clinical research associate, etc.). Data will be stored on a secure server, with data encrypted during transmission and automatic internal saving of a copy on the server that

will host the eCRF. This research falls under the *Méthodologie de référence* according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of January 6, 1978 relating to information technology, data files and privacy. This change was approved in a decision on January 5, 2006. AP-HP, the research sponsor, has signed a commitment to comply with the *Méthodologie de référence*. Specific documents for biomedical research will be archived by the investigator and the sponsor for 15 years after the end of the research.

Legal obligations. AP-HP is the sponsor of this research and by delegation, the DRCD performs the research's missions in accordance with Article L.1121-1 of the French Public Health Code. For this biomedical research relating to a medication for human use and prior to starting the research, AP-HP has obtained the favourable opinion of the *Comité de Protection des Personnes Île-de-France* III (CPP), within the scope of its authority and in accordance with the legislative and regulatory provisions in force. AP-HP has also obtained authorisation from the *Agence Nationale de Sécurité du Médicament et des produits de santé* (ANSM [French Health Products Safety Agency]; registration no. RCB 2016-A01310-51). AP-HP has signed a commitment to comply with the *Méthodologie de reference*. AP-HP will make a standard declaration to the *Commission Nationale de l'Informatique et des Libertés*.

Modifications to the research. Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, before starting the research, a favourable opinion from the CPP and authorisation from the ANSM within the scope of their respective authorities. The information sheet and the consent form can be revised if necessary, particularly with substantial modification to the research or if adverse reactions occur.

Safety considerations. The investigator will record all serious AEs (SAEs) and non-SAEs since the last contact by asking an open-ended question ("Did you have any adverse events since last contact?") during face-to-face visits at 3 and 6 months. In the event that the

participant missed the appointment, AEs will be requested by mail, email or phone by a biomedical research technician and recorded. All SAEs and non-SAEs will be recorded in the "Adverse events" section of the eCRF by the investigator.

Notification of an SAE. The investigator will notify the sponsor, immediately on the day when he/she becomes aware, of any serious SAE, except those that are prespecified (see below). The investigator must report all SAEs that occur in research participants on the date of the first administration of an investigational product and throughout the period when the participant is monitored. SAEs that do not require immediate notification to the sponsor are recorded in the "Adverse events" section of the eCRF. They include events associated with 1) the normal and natural evolution of the pathology including scheduled medical visits for the follow-up of knee OA, scheduled hospitalisations for the routine treatment of knee OA (joint injection, rehabilitation), and not related to a worsening of the condition, and expected symptoms secondary to knee OA worsening such as joint pain, joint effusion, OA flare, walking difficulties, or surgical knee joint replacement for OA; 2) special circumstances including hospitalisations for pre-existing conditions, surgery scheduled prior to the research, social or administrative purposes or admission to the emergency room less than 12 hr; and 3) AEs likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research, including AEs related to rescue medications (analgesics and NSAIDs) or joint injections (hyaluronic and corticosteroids) that include increased pain, joint swelling, mild joint effusion that can last a few days, skin flush following corticosteroid injections that can last a few hours, and exceptionally, septic arthritis or allergic reaction.

Investigation of an SAE. The investigator will document the SAE as thoroughly as possible and provide the medical diagnosis by using a specific SAE form. The investigator will assess the severity of the SAE: 1) mild, tolerated by the participant, does not interfere with daily activities; 2) moderate, sufficiently uncomfortable to affect daily activities; and 3)

serious, preventing daily activities. The investigator will assess the causality relation between the SAE and the clinical trial. The method the investigator uses will be based on the World Health Organisation–Uppsala Monitoring Centre (WHO-UMC) method and will include the following 4 causality terms: 1) certain, 2) probable/likely, 3) possible, and 4) unlikely (not excluded). Their comprehensive definition is provided in **Appendix 3**. The sponsor represented by the Vigilance department will continuously assess the safety of the clinical trial throughout the trial. The sponsor is responsible for assessing 1) the seriousness of all AEs reported and 2) the causality relation between the SAE and the acts/procedures/tests added by the clinical trial.

Investigation of an AE. All SAEs considered by the investigator and/or the sponsor to be possibly related to the act/procedures/tests/products administered, specific to the clinical trial, can be reasonably considered suspected adverse reactions (SARs). Any SAR whose nature, severity or outcome is not consistent with the information related to the acts/procedures/and or products administered during the clinical study is considered unexpected. The sponsor represented by the Vigilance department will assess the expected/unexpected nature of an SAR according to the information described in **Appendix 4** [26]. The sponsor reports any suspected unexpected serious adverse reaction (SUSAR), within the legal deadline, to the ANSM and CPP.

Dissemination plan. We aim to publish the results of ARTHROL trial in a peer-review journal and present the findings to physicians who manage knee OA at national and international conferences. The investigators will be involved in drafting manuscripts, abstracts, press releases and any other publications arising from the trial. Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines. There will be no intended use of professional writers. AP-HP is the owner of the data, which cannot be used or disclosed to a third party without prior approval from the AP-

HP. The full original protocol in English and the full dataset will be available by contacting the coordinating investigator, Prof François Rannou (francois.rannou@aphp.fr). Statistical codes will be available by contacting the biostatician of the study, Dr Gabriel Baron (gabriel.baron@aphp.fr).

Conclusions

The ARTHROL study will be the first to assess the clinical effects of oral resveratrol in knee OA. If the results are positive, resveratrol will represent an interesting and safe alternative for treating painful knee OA.

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Author's contributions

Conception and design of the study. CN, IB, GB, EC, FB, SP, FR.

Drafting of the original protocol. CN, IB, GB, SP, FR.

Coordination of the study. CN, FR.

Design of the statistical analysis plan. IB, GB.

Drafting of the present manuscript. CN, IB.

Final approval. CN, IB, GB, EC, FB, FR.

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Competing interests statement

None to declare.

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Figure 1. Schedule of enrolment, interventions, and assessments.

	STUDY PERIOD		
	Enrolment	**Post-allocation**	**Close-out**
TIMEPOINTS	***Month 0***	***Month 3***	***Month 6***
Eligibility screen	X	-	-
Informed consent	X	-	-
Allocation	X	-	-
Delivery of the experimental product	X	-	-
Delivery of a participating card	X	-	-
Instructions to keep and return the pillboxes	X	-	-
INTERVENTIONS			
Oral resveratrol	♦—	—	—♦
Oral placebo	♦—	—	—♦
ASSESSMENTS			
Baseline variables			
Demographics	X	-	-
Medical history	X	-	-
Outcome measures (analyses planned)			
Knee pain	X	X	X
WOMAC function subscore	X	X	X
Patient global assessment	X	X	X
OARSI-OMERACT response	-	X	X
Analgesics and NSAIDs consumption	X	X	X
Injections of hyaluronic acid and/or corticosteroids	X	X	X
Collected variables (no analyses planned)			
Symptomatic slow acting drugs for OA consumption			
Non-pharmacological co-interventions	X	X	X

Appendix 1. Additional inclusion and non-inclusion criteria.

Inclusion criteria
Age ≥ 40 years-old
Written consent obtained
Health insurance coverage
Non-inclusion criteria
History of symptomatic crystal or inflammatory arthritis
Knee surgery ≤ 1 year
Knee intra-articular injection of corticosteroids and/or hyaluronic acid ≤ 2 months
Knee trauma ≤ 2 months
Neurologic disorders involving the lower limbs
Inability to speak, write or read French language
Participation in another biomedical research
Contraindication to resveratrol or hypersensitivity to any of its constituents

Appendix 2. Information about pre-specified outcomes

WOMAC questionnaire. The WOMAC questionnaire is a self-administered, disease-specific instrument validated for OA. It consists of 24 items grouped into 3 subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions), with higher scores indicating greater disease severity.
OARSI-OMERACT response. The OARSI-OMERACT response to intervention will be defined as an improvement in pain (assessed by an 11-point pain NRS) or in function (assessed by the WOMAC function subscore) ≥ 50% and absolute change ≥ 20, or improvement in at least 2 of the 3 following: 1) pain ≥ 20% and absolute change ≥ 10, 2) function ≥ 20% and absolute change ≥ 10, 3) patient global assessment (assessed by an 11-point global assessment NRS) ≥ 20% and absolute change ≥ 10.
NRS: numeric rating scale; **OARSI:** Osteoarthritis Research Society International; **OMERACT:** Outcome Measures in Rheumatology; **WOMAC:** Western Ontario and McMaster Universities Arthritis Index.

Appendix 3. World Health Organisation–Uppsala Monitoring Centre causality categories (extract).

Causality term	Assessment criteria*
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) Rechallenge satisfactory, if necessary
Probable/likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear
Unlikely (not excluded)	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations
*All points should be reasonably complied with.	

Appendix 4. Expected nature of a suspected adverse reaction.

Suspected adverse reaction
Headache
Myalgia of the lower extremities
Somnolence
Epidymitis
Dizziness
Nasopharyngitis
Erythematous
Rash
Nephrotoxicity was reported in *in vivo* animal studies
Interactions with macrolides

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 23
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6 and 7
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	8 and 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7 and 9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8 and appendix 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 9 and appendix 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 12 and figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9 and 10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9 and 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9 and 10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9 and 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 9, 11, 12, 13, 14 and appendix 2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9 and 12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 and 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10 and 11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16, 17 and 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14 and 15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15 and 16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18 and 19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12, 18 and 19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18 and 19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendices
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Evolution of pain at 3 months by oral resveratrol in knee osteoarthritis (ARTHROL): protocol for a multicentre randomised double-blind placebo-controlled trial

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Evolution of pain at 3 months by oral resveratrol in knee osteoarthritis (ARTHROL): protocol for a multicentre randomised double-blind placebo-controlled trial

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Abstract

Introduction. Osteoarthritis (OA) pathophysiology is driven in part by joint inflammation. Resveratrol has *in vitro* anti-inflammatory properties. We aim to assess the efficacy of oral resveratrol for knee pain at 3 months in people with knee OA.

Methods and analysis. We will conduct a randomised double-blind placebo-controlled trial. Overall, 164 individuals with knee OA fulfilling 1986 ACR criteria will be recruited in 3 tertiary care centres in France and randomised to receive oral resveratrol, 40 mg (2 caplets) twice a day for 1 week, then 20 mg (1 caplet) twice a day or a matching placebo for a total of 6 months. Randomisation will be centralized and stratified by centre. The allocation ratio of assignments will be 1:1. The primary outcome will be the mean change from baseline in knee pain on a self-administered 11-point pain numeric rating scale at 3 months. Secondary outcomes will be the mean change in knee pain at 6 months, the function subscore of the WOMAC score, patient global assessment, proportion of responders according to the OARSI-OMERACT criteria at 3 and 6 months, and self-reported number of intra-articular injections of corticosteroids or hyaluronic acid and consumption of analgesics and non-steroidal anti-inflammatory drugs since the last contact. Other interventions will be allowed and self-reported. Adherence will be monitored by capsule counts and a booklet and adverse events recorded at 3 and 6 months. Statisticians, treating physicians and participants will be blinded to the allocated treatment.

Ethics and dissemination. The ARTHROL trial has been authorised by the *Agence Nationale de Sécurité du Médicament et des Produits de Santé* and ethics were approved by the *CPP Île-de-France* III. The findings of the study will be published in a peer-reviewed journal and disseminated at conferences. The design of ARTHROL will warrant the translation of its findings into clinical practice.

Registration details. ClinicalTrials.gov identifier: NCT02905799. First received: September 14, 2016. Last updated: September 16, 2016. Status: not yet recruiting.

Funding. French Ministry of Health (*Programme Hospitalier de Recherche Clinique*, project no. 15-15-0234).

Date and version identifier of the protocol. V2.0 of March 20, 2017.

Keywords. Osteoarthritis; knee; resveratrol; oral treatment; pain; clinical trial.

Strengths and limitations of the study

- First randomised controlled trial to assess the effects of oral resveratrol on pain in knee osteoarthritis.
- A design to facilitate the translation of findings into clinical practice.
- Innovative new formulation of oral resveratrol to improve its bioavailability.
- Selection of primary and secondary efficacy outcomes in accordance with Outcome Measures in Rheumatology (OMERACT) recommendations and Core Outcome Measures in Effectiveness Trials (COMET) initiative for phase III clinical trials in knee osteoarthritis.
- Participants will be recruited from tertiary care centres and may not be fully representative of the population with knee osteoarthritis in France.

Introduction

In the 2015 Global Burden of Disease Study, musculoskeletal disorders were identified among the 5 main contributors to disability-adjusted life-years [1]. Knee osteoarthritis (OA) is one of the most disabling joint disorders in Western countries [2] and OA is the first cause of disability in people over 40 years old in France [3].

OA pathophysiology is in part driven by local joint inflammation leading to severe tissue damage. No efficient treatment exists for structural changes in OA; the only treatments are for painful symptoms and are mainly acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids. Unfortunately, acetaminophen is weakly effective, with a poor effect size of 0.10, and recent data highlighted its potential cardiovascular adverse effects [4 5]. For NSAIDs, serious cardiovascular and digestive side effects do not support their prescription for long duration. An optimized treatment for OA should be efficient for both pain and inflammation, with minimal adverse effects.

Resveratrol is a molecule of interest because it has *in vitro* an *in vivo* anti-inflammatory and chondroprotective properties [6 7]. Resveratrol is available over the counter in France as a dietary supplement. No serious toxicity has been reported. In the field of rheumatic diseases, *in vitro* evidence supports anti-inflammatory, anti-catabolic, anti-apoptotic and anti-oxidative properties of resveratrol in various articular cell types, along with immunomodulation properties for T and B lymphocytes [8-20]. Consistently, resveratrol administered intra-articularly has shown chondroprotective effects in pre-clinical models of OA, mediated by decreased production of pro-inflammatory and pro-degradative soluble factors, and modulation of cellular and humoral responses [21-23]. In clinical research, resveratrol has been evaluated in ageing, cancer, neurodegenerative diseases, menopausal conditions, and cardiovascular and liver diseases [6]. The doses used in these trials were variable and not adjusted to the low bioavailability of oral formulations.

New formulations of resveratrol have allowed for an increase in oral resveratrol bioavailability [24]. The plasmatic peak is 10-fold increased and blood concentration remains at significant levels for several hours. We hypothesized that oral resveratrol in a new formulation could reduce knee pain at 3 months as compared with placebo in people with knee OA.

Methods and analysis

Design overview. This is a prospective, parallel-group, double-blind, randomised controlled multicentre study. Duration of follow-up for each participant will be 6 months post-randomisation. The study will be reported according to the CONSORT statement [25].

Setting and participants. Participants will be prospectively recruited among in- and outpatients from Rheumatology and Rehabilitation departments of 3 tertiary care centres in France with expertise in OA management (Cochin and Saint-Antoine Hospitals, Paris; and Gabriel-Montpied Hospital, Clermont-Ferrand), by advertising on the Internet and in the media (newspapers, health magazines) and by using posters in each investigating centre. People interested in participating in the study will be invited to contact a biomedical research technician by phone or email. In addition, the computerized medical records of each investigating center will be searched from 2015 to 2017, and patients with the key words "knee OA" in the records will be invited to participate in the study by phone or mail by the biomedical research technician. The number of patients treated yearly for knee OA in the participating centers is approximately 2000. The biomedical research technician will check for eligibility criteria, then, if appropriate, set up a face-to-face baseline visit with one of the investigators, a senior specialist in rehabilitation and/or rheumatology. The main eligibility criteria will be knee OA fulfilling 1986 American College of Rheumatology criteria, pain on a self-administered 11-point pain numeric rating scale (NRS) ≥ 40/100, symptom duration ≥ 1

month, and Kellgren and Lawrence X-ray score 1, 2 or 3. A complete description of the inclusion and non-inclusion criteria is in **Appendix 1.** Patients excluded for temporary reasons can be rescreened.

Experimental group. 40 mg (2 caplets) of resveratrol will be administered orally twice a day, 30 min before a meal with a glass of water, for 1 week, then 20 mg (1 caplet) twice a day for a total of 6 months. Pharmacokinetics, bioavailability and toxicity of trans-resveratrol formulation used in the ARTHROL trial have been previously described in a phase I clinical trial [24]. Briefly, 15 healthy volunteers received a single dose of 40 mg of oral trans-resveratrol in 2 forms (soluble galenic formulation or dry powder). The single dose of the soluble trans-resveratrol was well absorbed and elicited biologically efficient blood levels (0.1-6 μM) for several hours. The soluble formulation led to 8.8-fold higher trans-resveratrol levels in plasma versus the powder. We have made substantial modifications to the administration scheme as compared to the one tested in the phase I clinical trial: 1/ because trans-resveratrol is metabolized into glucuronide and sulfate conjugates coupled to renal elimination, we hypothesized that giving a loading dose for 1 week may allow attaining the drug effect more rapidly, and 2/ for the maintenance dose, we chose 40 mg a day as tested in the phase I clinical trial, but in 2 doses, because the half-life of the soluble galenic formulation of trans-resveratrol is 79 min only. Resveratrol will be freely supplied by the Yvery laboratory (patent n° WO 2012/007252, Marseille, France). Resveratrol is considered a dietary supplement and is available over the counter. No marked toxicity has been reported [26]. The caplets used in this study will be exactly the same as those already available on the French market. They will be stored in their original packaging at room temperature, protected from humidity, light and excessive heat. A box containing 7 pillboxes of 60 caplets each of resveratrol will be provided to each person randomised to the experimental group. Individuals will be asked to return the pillboxes for capsule counts at the 3- and 6-month visits and to

self-report adherence by completing a booklet. However, no specific measures will be taken to enhance adherence.

Control group. The Yvery laboratory will supply the placebo and ensure that it has a similar condition and taste as resveratrol. Two caplets of placebo will be administered orally twice a day for 1 week, then 1 capsule twice a day for a total of 6 months. A box containing 7 pillboxes of 60 caplets each of placebo will be provided to each person randomised to the control group and stored under the same conditions as resveratrol.

Co-interventions. Pharmacological and non-pharmacological treatments usually prescribed for knee OA will be authorised. Rescue medications (analgesics and NSAIDs), joint injections (hyaluronic acid and corticosteroids), symptomatic slow acting drugs for OA (SYSADOA) and non-pharmacological co-interventions including brace, insoles, walking aids, physiotherapy, home-based therapeutic exercises and weight loss will be assessed by using a standardized checklist and recorded in the electronic case report form (eCRF).

Outcomes. Primary and secondary efficacy outcomes have been selected in accordance with Outcome Measures in Rheumatology (OMERACT) [27] and Osteoarthritis Research Society International (OARSI) recommendations [28] and the Core Outcome Measures in Effectiveness Trials (COMET) initiative for phase III clinical trials of knee OA. As recommended, the outcomes include those for pain, physical function and patient global assessment. The primary efficacy outcome is the mean change from baseline in mean knee pain in the previous 48 hr on a self-administered 11-point pain NRS (0, no pain, to 100, maximal pain) at 3 months. The secondary efficacy outcomes are the mean change in mean knee pain on a pain NRS at 6 months, the mean change in the function subscore of the self-administered Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire at 3 and 6 months (the French version of the questionnaire) [29], the mean change in patient global assessment at 3 and 6 months on a self-administered 11-point global

assessment NRS (0, worst possible, to 100, best possible), the proportion of responders according to the Osteoarthritis Research Society International (OARSI)-(Outcome Measures in Rheumatology) OMERACT at 3 and 6 months [30], the self-reported number of intra-articular injections of corticosteroids or hyaluronic acid and the self-reported consumption of analgesics (non-opioid, weak and strong opioids) and NSAIDs since the last contact on a self-administered 4-class scale (never, several times a month, several times a week, daily) at 3 and 6 months. Information about the WOMAC questionnaire and OARSI-OMERACT response are in **Appendix 2**. For participants who discontinue or deviate from intervention protocols, the same outcome data will be collected if possible.

Randomisation and allocation concealment. Individuals who meet the inclusion criteria and agree to participate will be randomly assigned to the resveratrol or placebo group at the inclusion visit. The allocation ratio of assignments will be 1 :1. Participants, care providers, data collectors, outcome assessors and statisticians will be blinded to the allocated group. The randomisation sequence will be computer-generated by a statistician of the *Centre d'Épidémiologie Clinique*. The list will be stratified by centres with variable block sizes. The randomisation process will be centralized at the coordinating office (*Unité de Recherche Clinique*, Cochin Hospital), which will have no involvement in the enrollment, follow-up, or assessment of participants. Only the independent statistician of the *Centre d'Épidémiologie Clinique*, the computer programmer at the coordinating office who will implement the sequence assignment in the secure eCRF, and the Yvery company will have access to the randomisation list. The Yvery Company will label the resveratrol and placebo caplets and provide them with strictly identical presentations to each centre for the whole research duration. In each centre, the investigator will blindly deliver the medication to patients enrolled according to their randomisation number, at once, for the whole research duration. The sequence will be concealed by use of a computer interface implemented in the eCRF.

Treatment administration and clinical monitoring of the experimental products will be the same in the experimental and control groups.

Blinding can be broken only if the investigator deems it necessary for the safe management of a specific medical condition of a subject, and whenever possible, the methodologist and sponsor will be consulted before breaking the blind. If the blind is broken for any reason during the study, the moment at which the blind was broken and all other relevant information will be documented by the investigative site and other sponsor designees, as appropriate. The reason for breaking the blind will be indicated and justified in the source documentation and in the eCRF.

Statistical aspects. The sample size is estimated at 164 patients. We have predicted a difference in mean change from baseline of 15 points on the pain NRS between resveratrol and placebo groups, with a standard deviation of 27 points, and a power of 90%, corresponding to 69 patients in each arm. Considering a 15% lost to follow-up, we will need to enroll an estimated 82 patients for each arm. Fifteen points on pain NRS is considered the minimal clinically perceived difference in pain for patients with knee OA. All analyses will be performed on an intent-to-treat basis, in that all patients will be considered in the analysis and will be analysed in the group to which they had been assigned. For descriptive analyses, qualitative variables will be reported with absolute and relative frequencies and quantitative variables with median (interquartile range). To compare differences in changes in values between the 2 groups for quantitative variables, a constrained longitudinal data analysis will be used. In this model, both the baseline and post-baseline values will be modelled as dependent variables (the constrained longitudinal data analysis model assumes that both the baseline and post-baseline measurements are jointly multivariate normally distributed because the baseline value is treated as part of the response vector). The true baseline means will be constrained to be the same for the 2 treatment groups. This analysis provides an adjustment

for the observed baseline difference in estimating the treatment effects. Random effects at patient and centre levels will be added to these models. Results are expressed as differences in mean change from baseline with 95% CI at 3 month and 6 months. The constrained longitudinal data analysis model can include all randomized subjects with a baseline or post-baseline value. Such methods based on maximum likelihood are consistent under the missing-at-random assumption. Qualitative outcomes will be analysed by a mixed logistic regression model with a random effect at centre levels. Data analysis will involve use of SAS 9.4 (SAS Institute, Cary, NC). Blinded statisticians will perform the statistical analyses at an independent centre (*Centre d'Épidémiologie Clinique*, Paris Descartes, Hôpital Hôtel-Dieu). The statistical analysis will be further detailed in a dedicated Statistical Analysis Plan before any analysis is undertaken.

Participant timeline (Table 1).

Baseline visit. Inclusion and non-inclusion criteria will be validated at baseline by the investigator during a face-to-face visit. The individual will be informed and the written consent collected by the investigator. Then the participant will be enrolled and randomised. Specific additional clinical examination, laboratory tests or imaging will not be required for the purpose of the study. Information regarding demographics (age, gender, body mass index, education, employment status), medical history (date of diagnosis, symptoms duration, side affected, medical history, surgery and trauma history of the affected knee, X-ray findings including Kellgren and Lawrence grade and OA location [i.e., femorotibial medial, femorotibial lateral and/or patellofemoral OA]), medications in the previous 3 months (analgesics, NSAIDs and intra-articular injections of hyaluronic acid and/or corticosteroids and SYSADOA) and current non-pharmacological co-interventions (brace, insoles, walking aids, physiotherapy, home-based therapeutic exercises and weight loss) will be recorded in the eCRF by using a standardized checklist. Baseline values for prespecified assessment criteria

will be collected by using printed self-administered questionnaires and data will be entered in the eCRF by a biomedical research technician. The investigator will deliver the experimental product to the participants according to their randomisation number and give them a participating card in a clinical trial. Participants will be asked to keep and return the pillboxes for capsule counts at the 3- and 6-month visits and to self-report adherence by completing a booklet.

Three- and 6-month visits. The investigator will assess participants during a face-to-face visit. Values for prespecified assessment criteria will be collected at 3 and 6 months by using printed self-administered questionnaires, and data will be recorded in the eCRF by a biomedical research technician. In addition, the investigator will record adverse events (AEs) since the last contact by asking an open-ended question ("Did you have any adverse events since the last contact?"), count the caplets remaining in the pillboxes, check the self-reported adherence booklet and assess non-pharmacological co-interventions by using a standardized checklist. In the event that the participant missed the appointment, self-administered questionnaires, AEs, capsule counts and non-pharmacological co-interventions will be collected by mail, email or phone by a biomedical research technician and recorded. To reduce the amount of missing data, promote participant retention and complete the follow-up, reminder newsletters will be sent once a month by mail or email to inform participants of the progression of the study.

End of the research. At the end of the research, patients will be advised to continue their usual medical follow-up with their treating physician. Ending a subject's participation will not affect the normal medical management in any way. No exclusion period for another biomedical research will be required. At the end of the study, participants will be informed of the results upon request.

Role of the funding source. The study is funded by a research grant from the French Ministry of Health (*Programme Hospitalier de Recherche Clinique*, project no. 15-15-0234) and sponsored by the *Département de la Recherche Clinique et du Développement* (DRCD) of the *Assistance Publique-Hôpitaux de Paris* (AP-HP) (Hôpital Saint-Louis, 1, Avenue Claude Vellefaux, 75010 Paris, FRANCE, tel: +33 1 44 49 59 69, fax: +33 1 44 84 17 99). The Yvery laboratory will supply the resveratrol and the placebo. The funding source and the Yvery laboratory will not be involved in the study design; collection, management, analysis, and interpretation of data; or writing of the report; nor decision to publish the results.

Data management

Data collection. Data will be entered into an eCRF, completed by the investigator during each visit. Data from printed self-administered questionnaires will be entered in the eCRF by a biomedical research assistant after the visits. The investigator must give an explanation for each missing data. Changes in the data in the eCRF will be tracked. Discordant data in the eCRF will be corrected by queries.

Data monitoring. In accordance with the French Good Clinical Practices, the sponsor, DRCD, is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research is carried out, the source data, the source documents and the reports, with the goal of quality control and audit by the sponsor. In accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code), the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls. Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research.

Quality control. A clinical research associate appointed by the sponsor will be responsible for the proper conduct of the research and for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with French Good Clinical Practices as well as with the legislative and regulatory provisions in force. The investigator and the members of the investigator's team agree to make themselves available during quality control visits carried out at regular intervals by the clinical research associate. During these visits, the following elements will be reviewed: written consent, compliance with the research protocol and with the procedures defined therein, quality of the data collected in the eCRF including accuracy, missing data, consistency of the data with the source documents (medical files, appointment books, original copies of laboratory results, etc.), and management of the treatments used.

Ethics and dissemination

Ethical considerations

Methods for obtaining information and consent from research participants. In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code. The investigator or a doctor representing the investigator obtains the free and informed consent, in writing, of the individual before their inclusion in the research. The information sheet and a copy of the consent form signed and dated by the research participant and by the investigator or the doctor representing the investigator, are given to the individual before their participation in the research. In addition, the investigator will specify in the research participant's medical file the methods used for obtaining consent as well as the methods used

for providing information with the goal of obtaining consent. The investigator will retain the original signed and dated copy of the participant's consent form.

Data confidentiality. Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the participants and the results obtained. Investigators are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code). During or after the biomedical research, the data collected for the research participants and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying. Anonymization of the patients will be ensured by using a code number and initials, reported on each needed document for the research, or by erasing nominative data on copies of source documents. Under no circumstances should the names and addresses of the subjects involved be shown. The sponsor will ensure that each research participant has given permission in writing for access to their personal information that is strictly necessary for the quality control of the research. Access to the eCRF will be restricted by an access code and a personal and unique password system for each user. Each investigator will, in addition, have access to a specific profile that attributes or withholds access to certain functions of the system (entering data, or simply viewing the data of the enrolled participant or all the study data, possibility of change and validation by the clinical research associate, etc.). Data will be stored on a secure server, with data encrypted during transmission and automatic internal saving of a copy on the server that will host the eCRF. This research falls under the *Méthodologie de référence* according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of January 6, 1978 relating to information technology, data files and privacy. This change was approved in a decision on January 5, 2006. AP-HP, the research sponsor, has signed a commitment to comply with the

Méthodologie de référence. Specific documents for biomedical research will be archived by the investigator and the sponsor for 15 years after the end of the research.

Legal obligations. AP-HP is the sponsor of this research and by delegation, the DRCD performs the research's missions in accordance with Article L.1121-1 of the French Public Health Code. For this biomedical research relating to a medication for human use and prior to starting the research, AP-HP has obtained the favourable opinion of the *Comité de Protection des Personnes Île-de-France* III (CPP), within the scope of its authority and in accordance with the legislative and regulatory provisions in force. AP-HP has also obtained authorisation from the *Agence Nationale de Sécurité du Médicament et des produits de santé* (ANSM [French Health Products Safety Agency]; registration no. RCB 2016-A01310-51). AP-HP has signed a commitment to comply with the *Méthodologie de reference*. AP-HP will make a standard declaration to the *Commission Nationale de l'Informatique et des Libertés*.

*Modifications to the research***.** Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, before starting the research, a favourable opinion from the CPP and authorisation from the ANSM within the scope of their respective authorities. The information sheet and the consent form can be revised if necessary, particularly with substantial modification to the research or if adverse reactions occur.

Safety considerations. The investigator will record all serious AEs (SAEs) and non-SAEs since the last contact by asking an open-ended question (“Did you have any adverse events since last contact?”) during face-to-face visits at 3 and 6 months. In the event that the participant missed the appointment, AEs will be requested by mail, email or phone by a biomedical research technician and recorded. All SAEs and non-SAEs will be recorded in the "Adverse events" section of the eCRF by the investigator.

Notification of an SAE. The investigator will notify the sponsor, immediately on the day when he/she becomes aware, of any serious SAE, except those that are prespecified (see below). The investigator must report all SAEs that occur in research participants on the date of the first administration of an investigational product and throughout the period when the participant is monitored. SAEs that do not require immediate notification to the sponsor are recorded in the "Adverse events" section of the eCRF. They include events associated with 1) the normal and natural evolution of the pathology including scheduled medical visits for the follow-up of knee OA, scheduled hospitalisations for the routine treatment of knee OA (joint injection, rehabilitation), and not related to a worsening of the condition, and expected symptoms secondary to knee OA worsening such as joint pain, joint effusion, OA flare, walking difficulties, or surgical knee joint replacement for OA; 2) special circumstances including hospitalisations for pre-existing conditions, surgery scheduled prior to the research, social or administrative purposes or admission to the emergency room less than 12 hr; and 3) AEs likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research, including AEs related to rescue medications (analgesics and NSAIDs) or joint injections (hyaluronic and corticosteroids) that include increased pain, joint swelling, mild joint effusion that can last a few days, skin flush following corticosteroid injections that can last a few hours, and exceptionally, septic arthritis or allergic reaction.

Investigation of an SAE. The investigator will document the SAE as thoroughly as possible and provide the medical diagnosis by using a specific SAE form. The investigator will assess the severity of the SAE: 1) mild, tolerated by the participant, does not interfere with daily activities; 2) moderate, sufficiently uncomfortable to affect daily activities; and 3) serious, preventing daily activities. The investigator will assess the causality relation between the SAE and the clinical trial. The method the investigator uses will be based on the World Health Organisation–Uppsala Monitoring Centre (WHO-UMC) method and will include the

following 4 causality terms: 1) certain, 2) probable/likely, 3) possible, and 4) unlikely (not excluded). Their comprehensive definition is provided in **Appendix 3**. The sponsor represented by the Vigilance department will continuously assess the safety of the clinical trial throughout the trial. The sponsor is responsible for assessing 1) the seriousness of all AEs reported and 2) the causality relation between the SAE and the acts/procedures/tests added by the clinical trial.

Investigation of an AE. All SAEs considered by the investigator and/or the sponsor to be possibly related to the act/procedures/tests/products administered, specific to the clinical trial, can be reasonably considered suspected adverse reactions (SARs). Any SAR whose nature, severity or outcome is not consistent with the information related to the acts/procedures/and or products administered during the clinical study is considered unexpected. The sponsor represented by the Vigilance department will assess the expected/unexpected nature of an SAR according to the information described in **Appendix 4** [26]. The sponsor reports any suspected unexpected serious adverse reaction (SUSAR), within the legal deadline, to the ANSM and CPP.

Dissemination plan. We aim to publish the results of ARTHROL trial in a peer-review journal and present the findings to physicians who manage knee OA at national and international conferences. The investigators will be involved in drafting manuscripts, abstracts, press releases and any other publications arising from the trial. Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines. There will be no intended use of professional writers. AP-HP is the owner of the data, which cannot be used or disclosed to a third party without prior approval from the AP-HP. The full original protocol in English and the full dataset will be available by contacting the coordinating investigator, Prof François Rannou (francois.rannou@aphp.fr). Statistical

codes will be available by contacting the biostatician of the study, Dr Gabriel Baron (gabriel.baron@aphp.fr).

The ARTHROL study will be the first to assess the clinical effects of oral resveratrol in knee OA. If the results are positive, resveratrol will represent an interesting and safe alternative for treating painful knee OA.

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Table 1. Schedule of enrolment, interventions, and assessments.

	STUDY PERIOD		
	Enrolment	**Post-allocation**	**Close-out**
TIMEPOINTS	***Month 0***	***Month 3***	***Month 6***
Eligibility screen	X	-	-
Informed consent	X	-	-
Allocation	X	-	-
Delivery of the experimental product	X	-	-
Delivery of a participating card	X	-	-
Instructions to keep and return the pillboxes	X	-	-
INTERVENTIONS			
Oral resveratrol	♦———	———	———♦
Oral placebo	♦———	———	———♦
ASSESSMENTS			
Baseline variables			
Demographics	X	-	-
Medical history	X	-	-
Outcome measures (analyses planned)			
Knee pain	X	X	X
WOMAC function subscore	X	X	X
Patient global assessment	X	X	X
OARSI-OMERACT response	-	X	X
Analgesics and NSAIDs consumption	X	X	X
Injections of hyaluronic acid and/or corticosteroids	X	X	X
Collected variables (no analyses planned)			
Symptomatic slow acting drugs for OA consumption			

Non-pharmacological co-interventions	X	X	X
Adverse events	-	X	X
Adherence	-	X	X

NSAIDs: non-steroidal anti-inflammatory drugs; OARSI: Osteoarthritis Research Society International; OMERACT: Outcome Measures in Rheumatology; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Author's contributions

Conception and design of the study. CN, IB, GB, EC, FB, SP, FR.

Drafting of the original protocol. CN, IB, GB, SP, FR.

Coordination of the study. CN, FR.

Design of the statistical analysis plan. IB, GB.

Drafting of the present manuscript. CN, IB.

Final approval. CN, IB, GB, EC, FB, FR.

Data sharing statement

The full original protocol in English and the full dataset will be available by contacting the coordinating investigator, Prof François Rannou (francois.rannou@aphp.fr). Statistical codes will be available by contacting the biostatician of the study, Dr Gabriel Baron (gabriel.baron@aphp.fr).

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Competing interests statement

None to declare.

Checklist compliance statement

The authors confirm that their manuscript fully adheres with the SPIRIT Checklist.

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Appendix 1. Additional inclusion and non-inclusion criteria.

Inclusion criteria
Age ≥ 40 years-old
Written consent obtained
Health insurance coverage
Non-inclusion criteria
History of symptomatic crystal or inflammatory arthritis
Knee surgery ≤ 1 year
Knee intra-articular injection of corticosteroids and/or hyaluronic acid ≤ 2 months
Current use of intramuscular, intravenous or oral corticosteroids
Uncontrolled diseases that may require intramuscular, intravenous or oral corticosteroids
Knee trauma ≤ 2 months
Neurologic disorders involving the lower limbs
Inability to speak, write or read French language
Participation in another biomedical research
Contraindication to resveratrol or hypersensitivity to any of its constituents

Appendix 2. Information about pre-specified outcomes

WOMAC questionnaire. The WOMAC questionnaire is a self-administered, disease-specific instrument validated for OA. It consists of 24 items grouped into 3 subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions), with higher scores indicating greater disease severity.
OARSI-OMERACT response. The OARSI-OMERACT response to intervention will be defined as an improvement in pain (assessed by an 11-point pain NRS) or in function (assessed by the WOMAC function subscore) ≥ 50% and absolute change ≥ 20, or improvement in at least 2 of the 3 following: 1) pain ≥ 20% and absolute change ≥ 10, 2) function ≥ 20% and absolute change ≥ 10, 3) patient global assessment (assessed by an 11-point global assessment NRS) ≥ 20% and absolute change ≥ 10.
NRS: numeric rating scale; **OARSI:** Osteoarthritis Research Society International; **OMERACT:** Outcome Measures in Rheumatology; **WOMAC:** Western Ontario and McMaster Universities Arthritis Index.

Appendix 3. World Health Organisation–Uppsala Monitoring Centre causality categories (extract).

Causality term	Assessment criteria*
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) Rechallenge satisfactory, if necessary
Probable/likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear
Unlikely (not excluded)	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations
*All points should be reasonably complied with.	

Appendix 4. Expected nature of a suspected adverse reaction.

Suspected adverse reaction
Dizziness
Epidymitis
Erythematous
Headache
Interactions with macrolides
Myalgia of the lower extremities
Nasopharyngitis
Nephrotoxicity was reported in *in vivo* animal studies
Rash
Somnolence

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 23
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6 and 7
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	8 and 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7 and 9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8 and appendix 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 9 and appendix 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 12 and figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9 and 10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9 and 10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9 and 10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9 and 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 9, 11, 12, 13, 14 and appendix 2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9 and 12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13 and 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10 and 11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16, 17 and 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14 and 15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15 and 16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18 and 19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12, 18 and 19
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18 and 19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendices
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.