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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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SCHOLARONE™  
Manuscripts

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3 1 **Evolution of pain at 3 months by oral resveratrol in knee osteoarthritis (ARTHROL):**  
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5 2 **protocol for a multicentre randomised double-blind placebo-controlled trial**  
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## 44 Abstract

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

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

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

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3 68       **Registration details.** ClinicalTrials.gov identifier: NCT02905799. First received:  
4  
5 69       September 14, 2016. Last updated: September 16, 2016. Status: not yet recruiting.  
6

7       **Funding.** French Ministry of Health (*Programme Hospitalier de Recherche Clinique*,  
8  
9 71       project no. 15-15-0234).  
10

11       **Date and version identifier of the protocol.** V2.0 of March 20, 2017.  
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14 73  
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16 74       **Keywords.** Osteoarthritis; knee; resveratrol; oral treatment; pain; clinical trial.  
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## 75 **Strengths and limitations of the study**

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

## 86 Introduction

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

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

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



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3 111 New formulations of resveratrol have allowed for an increase in oral resveratrol  
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5 112 bioavailability<sup>24</sup>. The plasmatic peak is 10-fold increased and blood concentration remains at  
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7 113 significant levels for several hours. We hypothesized that oral resveratrol in a new  
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9 114 formulation could reduce knee pain at 3 months as compared with placebo in people with  
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11 115 knee OA.  
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## 16 17 117 **Methods and analysis**

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19 118 **Design overview.** This is a prospective, parallel-group, double-blind, randomised  
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21 119 controlled multicentre study. Duration of follow-up for each participant will be 6 months  
22  
23 120 post-randomisation. The study will be reported according to the CONSORT statement<sup>25</sup>.  
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26 121 **Setting and participants.** Participants will be prospectively recruited among in- and  
27  
28 122 outpatients from Rheumatology and Rehabilitation departments of 3 tertiary care centres in  
29  
30 123 France with expertise in OA management (Cochin and Saint-Antoine Hospitals, Paris; and  
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32 124 Gabriel-Montpied Hospital, Clermont-Ferrand), by advertising on the Internet and in the  
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34 125 media (newspapers, health magazines) and by using posters in each investigating centre.  
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36 126 People interested in participating in the study will be invited to contact a biomedical research  
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38 127 technician by phone or email. In addition, the computerized medical records of each  
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40 128 investigating center will be searched from 2015 to 2017, and patients with the key words  
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42 129 “knee OA” in the records will be invited to participate in the study by phone or mail by the  
43  
44 130 biomedical research technician. The number of patients treated yearly for knee OA in the  
45  
46 131 participating centers is approximately 2000. The biomedical research technician will check  
47  
48 132 for eligibility criteria, then, if appropriate, set up a face-to-face baseline visit with one of the  
49  
50 133 investigators, a senior specialist in rehabilitation and/or rheumatology. The main eligibility  
51  
52 134 criteria will be knee OA fulfilling 1986 American College of Rheumatology criteria, pain on a  
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54 135 self-administered 11-point pain numeric rating scale (NRS)  $\geq 40/100$ , symptom duration  $\geq 1$   
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3 136 month, and Kellgren and Lawrence X-ray score 1, 2 or 3. A complete description of the  
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5 137 inclusion and non-inclusion criteria is in **Appendix 1**.

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7 138 **Experimental group.** Two capsules of resveratrol (40 mg) will be administered orally  
8  
9 139 twice a day, 30 min before a meal with a glass of water, for 1 week, then 1 capsule (20 mg)  
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11 140 twice a day for a total of 6 months. Resveratrol will be freely supplied by the Yvery  
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13 141 laboratory (Marseille, France). Resveratrol is considered a dietary supplement and is available  
14  
15 142 over the counter. No marked toxicity has been reported<sup>26</sup>. The capsules used in this study will  
16  
17 143 be exactly the same as those already available on the French market. They will be stored in  
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19 144 their original packaging at room temperature, protected from humidity, light and excessive  
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21 145 heat. A box containing 7 pillboxes of 60 capsules each of resveratrol will be provided to each  
22  
23 146 person randomised to the experimental group. Individuals will be asked to return the pillboxes  
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25 147 for capsule counts at the 3- and 6-month visits and to self-report adherence by completing a  
26  
27 148 booklet. However, no specific measures will be taken to enhance adherence.

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31 149 **Control group.** The Yvery laboratory will supply the placebo and ensure that it has a  
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33 150 similar condition and taste as resveratrol. Two capsules of placebo will be administered orally  
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35 151 twice a day for 1 week, then 1 capsule twice a day for a total of 6 months. A box containing 7  
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37 152 pillboxes of 60 capsules each of placebo will be provided to each person randomised to the  
38  
39 153 control group and stored under the same conditions as resveratrol.

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42 154 **Co-interventions.** Pharmacological and non-pharmacological treatments usually  
43  
44 155 prescribed for knee OA will be authorised. Rescue medications (analgesics and NSAIDs),  
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46 156 joint injections (hyaluronic acid and corticosteroids), symptomatic slow acting drugs for OA  
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48 157 (SYSADOA) and non-pharmacological co-interventions including brace, insoles, walking  
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50 158 aids, physiotherapy, home-based therapeutic exercises and weight loss will be assessed by  
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52 159 using a standardized checklist and recorded in the electronic case report form (eCRF).  
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3 160 **Outcomes.** Primary and secondary efficacy outcomes have been selected in  
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5 161 accordance with OMERACT recommendations <sup>27</sup> and the Core Outcome Measures in  
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7 162 Effectiveness Trials (COMET) initiative for phase III clinical trials of knee OA. As  
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10 163 recommended, the outcomes include those for pain, physical function and patient global  
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12 164 assessment. The primary efficacy outcome is the mean change from baseline in mean knee  
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14 165 pain in the previous 48 hr on a self-administered 11-point pain NRS (0, no pain, to 100,  
15  
16 166 maximal pain) at 3 months. The secondary efficacy outcomes are the mean change in mean  
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18 167 knee pain on a pain NRS at 6 months, the mean change in the function subscore of the self-  
19  
20 168 administered Western Ontario and McMaster Universities Arthritis Index (WOMAC)  
21  
22 169 questionnaire at 3 and 6 months (the French version of the questionnaire) <sup>28</sup>, the mean change  
23  
24 170 in patient global assessment at 3 and 6 months on a self-administered 11-point global  
25  
26 171 assessment NRS (0, worst possible, to 100, best possible), the proportion of responders  
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28 172 according to the Osteoarthritis Research Society International (OARSI)-(Outcome Measures  
29  
30 173 in Rheumatology) OMERACT at 3 and 6 months <sup>29</sup>, the self-reported number of intra-  
31  
32 174 articular injections of corticosteroids or hyaluronic acid and the self-reported consumption of  
33  
34 175 analgesics (non-opioid, weak and strong opioids) and NSAIDs since the last contact on a self-  
35  
36 176 administered 4-class scale (never, several times a month, several times a week, daily) at 3 and  
37  
38 177 6 months. Information about the WOMAC questionnaire and OARSI-OMERACT response  
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40 178 are in **Appendix 2**. For participants who discontinue or deviate from intervention protocols,  
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42 179 the same outcome data will be collected if possible.  
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47 **Randomisation and allocation concealment.** Individuals who meet the inclusion  
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49 180 criteria and agree to participate will be randomly assigned to the resveratrol or placebo group  
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51 181 at the inclusion visit. The allocation ratio of assignments will be 1 :1. Participants, care  
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53 182 providers, data collectors, outcome assessors and statisticians will be blinded to the allocated  
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55 183 group. The randomisation sequence will be computer-generated by a statistician of the *Centre*  
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3 185 *d'Épidémiologie Clinique*. The list will be stratified by centres with variable block sizes. The  
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5 186 randomisation process will be centralized at the coordinating office (*Unité de Recherche*  
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7 187 *Clinique*, Cochin Hospital), which will have no involvement in the enrollment, follow-up, or  
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9 188 assessment of participants. Only the independent statistician of the *Centre d'Épidémiologie*  
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11 189 *Clinique*, the computer programmer at the coordinating office who will implement the  
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13 190 sequence assignment in the secure eCRF, and the Yvery company will have access to the  
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15 191 randomisation list. The Yvery Company will label the resveratrol and placebo capsules and  
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17 192 provide them with strictly identical presentations to each centre for the whole research  
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19 193 duration. In each centre, the investigator will blindly deliver the medication to patients  
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21 194 enrolled according to their randomisation number, at once, for the whole research duration.  
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23 195 The sequence will be concealed by use of a computer interface implemented in the eCRF.  
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25 196 Treatment administration and clinical monitoring of the experimental products will be the  
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27 197 same in the experimental and control groups.  
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32 198 Blinding can be broken only if the investigator deems it necessary for the safe  
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34 199 management of a specific medical condition of a subject, and whenever possible, the  
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36 200 methodologist and sponsor will be consulted before breaking the blind. If the blind is broken  
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38 201 for any reason during the study, the moment at which the blind was broken and all other  
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40 202 relevant information will be documented by the investigative site and other sponsor designees,  
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42 203 as appropriate. The reason for breaking the blind will be indicated and justified in the source  
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44 204 documentation and in the eCRF.  
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47 205 **Statistical aspects.** The sample size is estimated at 164 patients. We have predicted a  
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49 206 difference in mean change from baseline of 15 mm on the pain NRS between resveratrol and  
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51 207 placebo groups, with a standard deviation of 27 mm, and a power of 90%, corresponding to  
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53 208 69 patients in each arm. Considering a 15% lost to follow-up, we will need to enroll an  
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55 209 estimated 82 patients for each arm. Fifteen points on pain NRS is considered the minimal  
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3 210 clinically perceived difference in pain for patients with knee OA. All analyses will be  
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5 211 performed on an intent-to-treat basis, in that all patients will be considered in the analysis and  
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7 212 will be analysed in the group to which they had been assigned. For descriptive analyses,  
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9 213 qualitative variables will be reported with absolute and relative frequencies and quantitative  
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11 214 variables with median (interquartile range). To compare differences in changes in values  
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13 215 between the 2 groups for quantitative variables, a constrained longitudinal data analysis will  
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15 216 be used. In this model, both the baseline and post-baseline values will be modelled as  
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17 217 dependent variables, and the true baseline means will be constrained to be the same for the 2  
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19 218 treatment groups. This analysis provides an adjustment for the observed baseline difference in  
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21 219 estimating the treatment effects. The differences in change from week 0 will be estimated at  
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23 220 each time in each group by the time-by-treatment interaction. Random effects at patient and  
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25 221 centre levels will be added to these models. Qualitative outcomes will be analysed by a mixed  
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27 222 logistic regression model with a random effect at centre levels. Data analysis will involve use  
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29 223 of SAS 9.4 (SAS Institute, Cary, NC). Blinded statisticians will perform the statistical  
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31 224 analyses at an independent centre (*Centre d'Épidémiologie Clinique*, Paris Descartes, Hôpital  
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33 225 Hôtel-Dieu). The statistical analysis will be further detailed in a dedicated Statistical Analysis  
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35 226 Plan before any analysis is undertaken.

#### 227 **Participant timeline (Figure 1).**

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

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3 235 including Kellgren and Lawrence grade and OA location [i.e., femorotibial medial,  
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5 236 femorotibial lateral and/or patellofemoral OA]), medications in the previous 3 months  
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7 237 (analgesics, NSAIDs and intra-articular injections of hyaluronic acid and/or corticosteroids  
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9 238 and SYSADOA) and current non-pharmacological co-interventions (brace, insoles, walking  
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11 239 aids, physiotherapy, home-based therapeutic exercises and weight loss) will be recorded in the  
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13 240 eCRF by using a standardized checklist. Baseline values for prespecified assessment criteria  
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15 241 will be collected by using printed self-administered questionnaires and data will be entered in  
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17 242 the eCRF by a biomedical research technician. The investigator will deliver the experimental  
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19 243 product to the participants according to their randomisation number and give them a  
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21 244 participating card in a clinical trial. Participants will be asked to keep and return the pillboxes  
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23 245 for capsule counts at the 3- and 6-month visits and to self-report adherence by completing a  
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25 246 booklet.

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29 247 Three- and 6-month visits. The investigator will assess participants during a face-to-  
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31 248 face visit. Values for prespecified assessment criteria will be collected at 3 and 6 months by  
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33 249 using printed self-administered questionnaires, and data will be recorded in the eCRF by a  
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35 250 biomedical research technician. In addition, the investigator will record adverse events (AEs)  
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37 251 since the last contact by asking an open-ended question (“Did you have any adverse events  
38  
39 252 since the last contact?”), count the capsules remaining in the pillboxes, check the self-reported  
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41 253 adherence booklet and assess non-pharmacological co-interventions by using a standardized  
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43 254 checklist. In the event that the participant missed the appointment, self-administered  
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45 255 questionnaires, AEs, capsule counts and non-pharmacological co-interventions will be  
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47 256 collected by mail, email or phone by a biomedical research technician and recorded. To  
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49 257 reduce the amount of missing data, promote participant retention and complete the follow-up,  
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51 258 reminder newsletters will be sent once a month by mail or email to inform participants of the  
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53 259 progression of the study.  
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3 260 End of the research. At the end of the research, patients will be advised to continue  
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5 261 their usual medical follow-up with their treating physician. Ending a subject's participation  
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7 262 will not affect the normal medical management in any way. No exclusion period for another  
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9 263 biomedical research will be required. At the end of the study, participants will be informed of  
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11 264 the results upon request.

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14 265 **Role of the funding source.** The study is funded by a research grant from the French  
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16 266 Ministry of Health (*Programme Hospitalier de Recherche Clinique*, project no. 15-15-0234)  
17  
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19  
20 268 the *Assistance Publique-Hôpitaux de Paris* (AP-HP) (Hôpital Saint-Louis, 1, Avenue Claude  
21  
22 269 Vellefaux, 75010 Paris, FRANCE, tel: +33 1 44 49 59 69, fax: +33 1 44 84 17 99). The Yvery  
23  
24 270 laboratory will supply the resveratrol and the placebo. The funding source and the Yvery  
25  
26 271 laboratory will not be involved in the study design; collection, management, analysis, and  
27  
28 272 interpretation of data; or writing of the report; nor decision to publish the results.

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30  
31 273 **Data management**

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33  
34 274 Data collection. Data will be entered into an eCRF, completed by the investigator  
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36 275 during each visit. Data from printed self-administered questionnaires will be entered in the  
37  
38 276 eCRF by a biomedical research assistant after the visits. The investigator must give an  
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40 277 explanation for each missing data. Changes in the data in the eCRF will be tracked.  
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42 278 Discordant data in the eCRF will be corrected by queries.

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45 279 Data monitoring. In accordance with the French Good Clinical Practices, the sponsor,  
46  
47 280 DRCD, is responsible for obtaining the permission of all parties involved in the research to  
48  
49 281 guarantee direct access to all locations where the research is carried out, the source data, the  
50  
51 282 source documents and the reports, with the goal of quality control and audit by the sponsor. In  
52  
53 283 accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and  
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55 284 R.5121-13 of the French Public Health Code), the investigators will make available to those



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3 285 in charge of monitoring, quality control and audit relating to the biomedical research the  
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5 286 documents and personal data strictly necessary for these controls. Source documents are  
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7 287 defined as any original document or object that can prove the existence or accuracy of a piece  
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10 288 of information or a fact recorded during the research.

11 289 Quality control. A clinical research associate appointed by the sponsor will be  
12  
13  
14 290 responsible for the proper conduct of the research and for collecting and documenting,  
15  
16 291 recording and reporting the data generated in writing, in accordance with the Standard  
17  
18 292 Operating Procedures applied within the DRCD and in accordance with French Good Clinical  
19  
20 293 Practices as well as with the legislative and regulatory provisions in force. The investigator  
21  
22 294 and the members of the investigator's team agree to make themselves available during quality  
23  
24 295 control visits carried out at regular intervals by the clinical research associate. During these  
25  
26 296 visits, the following elements will be reviewed: written consent, compliance with the research  
27  
28 297 protocol and with the procedures defined therein, quality of the data collected in the eCRF  
29  
30 298 including accuracy, missing data, consistency of the data with the source documents (medical  
31  
32 299 files, appointment books, original copies of laboratory results, etc.), and management of the  
33  
34 300 treatments used.  
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## 302 **Ethics and dissemination**

### 303 **Ethical considerations**

304 Methods for obtaining information and consent from research participants. In  
305  
306 accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research  
307  
308 can be carried out on a person without free and informed consent obtained in writing after the  
309  
310 person has been given the information specified in Article L.1122-1 of said Code. The  
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312 investigator or a doctor representing the investigator obtains the free and informed consent, in  
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314 writing, of the individual before their inclusion in the research. The information sheet and a



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3 310 copy of the consent form signed and dated by the research participant and by the investigator  
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5 311 or the doctor representing the investigator, are given to the individual before their  
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7 312 participation in the research. In addition, the investigator will specify in the research  
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9 313 participant's medical file the methods used for obtaining consent as well as the methods used  
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11 314 for providing information with the goal of obtaining consent. The investigator will retain the  
12  
13 315 original signed and dated copy of the participant's consent form.

16 316 Data confidentiality. Those responsible for biomedical research quality control  
17  
18 317 (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to  
19  
20 318 ensure the confidentiality of information about the experimental medications, the research, the  
21  
22 319 research subjects and in particular the identity of the participants and the results obtained.  
23  
24 320 Investigators are subject to professional secrecy (in accordance with the conditions set out in  
25  
26 321 Articles 226-13 and 226-14 of the Penal Code). During or after the biomedical research, the  
27  
28 322 data collected for the research participants and sent to the sponsor by the investigators (or any  
29  
30 323 other specialised parties) will be made non-identifying. Anonymization of the patients will be  
31  
32 324 ensured by using a code number and initials, reported on each needed document for the  
33  
34 325 research, or by erasing nominative data on copies of source documents. Under no  
35  
36 326 circumstances should the names and addresses of the subjects involved be shown. The  
37  
38 327 sponsor will ensure that each research participant has given permission in writing for access  
39  
40 328 to their personal information that is strictly necessary for the quality control of the research.  
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42 329 Access to the eCRF will be restricted by an access code and a personal and unique password  
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44 330 system for each user. Each investigator will, in addition, have access to a specific profile that  
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46 331 attributes or withholds access to certain functions of the system (entering data, or simply  
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48 332 viewing the data of the enrolled participant or all the study data, possibility of change and  
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50 333 validation by the clinical research associate, etc.). Data will be stored on a secure server, with  
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52 334 data encrypted during transmission and automatic internal saving of a copy on the server that  
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3 335 will host the eCRF. This research falls under the *Méthodologie de référence* according to the  
4  
5 336 provisions of Article 54, paragraph 5 of modified Law No. 78-17 of January 6, 1978 relating  
6  
7 337 to information technology, data files and privacy. This change was approved in a decision on  
8  
9 338 January 5, 2006. AP-HP, the research sponsor, has signed a commitment to comply with the  
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11 339 *Méthodologie de référence*. Specific documents for biomedical research will be archived by  
12  
13 340 the investigator and the sponsor for 15 years after the end of the research.

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16 341 Legal obligations. AP-HP is the sponsor of this research and by delegation, the DRCD  
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18 342 performs the research's missions in accordance with Article L.1121-1 of the French Public  
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20 343 Health Code. For this biomedical research relating to a medication for human use and prior to  
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22 344 starting the research, AP-HP has obtained the favourable opinion of the *Comité de Protection*  
23  
24 345 *des Personnes Île-de-France* III (CPP), within the scope of its authority and in accordance  
25  
26 346 with the legislative and regulatory provisions in force. AP-HP has also obtained authorisation  
27  
28 347 from the *Agence Nationale de Sécurité du Médicament et des produits de santé* (ANSM  
29  
30 348 [French Health Products Safety Agency]; registration no. RCB 2016-A01310-51). AP-HP has  
31  
32 349 signed a commitment to comply with the *Méthodologie de référence*. AP-HP will make a  
33  
34 350 standard declaration to the *Commission Nationale de l'Informatique et des Libertés*.

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37 351 Modifications to the research. Any substantial modification to the protocol by the  
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39 352 coordinating investigator must be sent to the sponsor for approval. After approval is given, the  
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41 353 sponsor must obtain, before starting the research, a favourable opinion from the CPP and  
42  
43 354 authorisation from the ANSM within the scope of their respective authorities. The information  
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45 355 sheet and the consent form can be revised if necessary, particularly with substantial  
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47 356 modification to the research or if adverse reactions occur.

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50 357 **Safety considerations.** The investigator will record all serious AEs (SAEs) and non-  
51  
52 358 SAEs since the last contact by asking an open-ended question (“Did you have any adverse  
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54 359 events since last contact?”) during face-to-face visits at 3 and 6 months. In the event that the  
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3 360 participant missed the appointment, AEs will be requested by mail, email or phone by a  
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5 361 biomedical research technician and recorded. All SAEs and non-SAEs will be recorded in the  
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7 362 "Adverse events" section of the eCRF by the investigator.  
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9  
10 363 Notification of an SAE. The investigator will notify the sponsor, immediately on the  
11  
12 364 day when he/she becomes aware, of any serious SAE, except those that are prespecified (see  
13  
14 365 below). The investigator must report all SAEs that occur in research participants on the date  
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16 366 of the first administration of an investigational product and throughout the period when the  
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18 367 participant is monitored. SAEs that do not require immediate notification to the sponsor are  
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20 368 recorded in the "Adverse events" section of the eCRF. They include events associated with 1)  
21  
22 369 the normal and natural evolution of the pathology including scheduled medical visits for the  
23  
24 370 follow-up of knee OA, scheduled hospitalisations for the routine treatment of knee OA (joint  
25  
26 371 injection, rehabilitation), and not related to a worsening of the condition, and expected  
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28 372 symptoms secondary to knee OA worsening such as joint pain, joint effusion, OA flare,  
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30 373 walking difficulties, or surgical knee joint replacement for OA; 2) special circumstances  
31  
32 374 including hospitalisations for pre-existing conditions, surgery scheduled prior to the research,  
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34 375 social or administrative purposes or admission to the emergency room less than 12 hr; and 3)  
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36 376 AEs likely to be associated with the treatments prescribed as part of the patient's care during  
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38 377 the monitoring of the research, including AEs related to rescue medications (analgesics and  
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40 378 NSAIDs) or joint injections (hyaluronic and corticosteroids) that include increased pain, joint  
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42 379 swelling, mild joint effusion that can last a few days, skin flush following corticosteroid  
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44 380 injections that can last a few hours, and exceptionally, septic arthritis or allergic reaction.  
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49 381 Investigation of an SAE. The investigator will document the SAE as thoroughly as  
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51 382 possible and provide the medical diagnosis by using a specific SAE form. The investigator  
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53 383 will assess the severity of the SAE: 1) mild, tolerated by the participant, does not interfere  
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55 384 with daily activities; 2) moderate, sufficiently uncomfortable to affect daily activities; and 3)  
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3 385 serious, preventing daily activities. The investigator will assess the causality relation between  
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5 386 the SAE and the clinical trial. The method the investigator uses will be based on the World  
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7 387 Health Organisation–Uppsala Monitoring Centre (WHO-UMC) method and will include the  
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9 388 following 4 causality terms: 1) certain, 2) probable/likely, 3) possible, and 4) unlikely (not  
10  
11 389 excluded). Their comprehensive definition is provided in **Appendix 3**. The sponsor  
12  
13 390 represented by the Vigilance department will continuously assess the safety of the clinical  
14  
15 391 trial throughout the trial. The sponsor is responsible for assessing 1) the seriousness of all AEs  
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17 392 reported and 2) the causality relation between the SAE and the acts/procedures/tests added by  
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19 393 the clinical trial.  
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23 394 *Investigation of an AE.* All SAEs considered by the investigator and/or the sponsor to  
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25 395 be possibly related to the act/procedures/tests/products administered, specific to the clinical  
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27 396 trial, can be reasonably considered suspected adverse reactions (SARs). Any SAR whose  
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29 397 nature, severity or outcome is not consistent with the information related to the  
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31 398 acts/procedures/and or products administered during the clinical study is considered  
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33 399 unexpected. The sponsor represented by the Vigilance department will assess the  
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35 400 expected/unexpected nature of an SAR according to the information described in **Appendix 4**  
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37 401 <sup>26</sup>. The sponsor reports any suspected unexpected serious adverse reaction (SUSAR), within  
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39 402 the legal deadline, to the ANSM and CPP.  
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43 403 **Dissemination plan.** We aim to publish the results of ARTHROL trial in a peer-  
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45 404 review journal and present the findings to physicians who manage knee OA at national and  
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47 405 international conferences. The investigators will be involved in drafting manuscripts,  
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49 406 abstracts, press releases and any other publications arising from the trial. Authorship will be  
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51 407 determined in accordance with the International Committee of Medical Journal Editors  
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53 408 guidelines. There will be no intended use of professional writers. AP-HP is the owner of the  
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55 409 data, which cannot be used or disclosed to a third party without prior approval from the AP-  
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3 410 HP. The full original protocol in English and the full dataset will be available by contacting  
4  
5 411 the coordinating investigator, Prof François Rannou (francois.rannou@aphp.fr). Statistical  
6  
7 412 codes will be available by contacting the biostatistician of the study, Dr Gabriel Baron  
8  
9 413 (gabriel.baron@aphp.fr).

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## 14 415 **Conclusions**

16  
17 416 The ARTHROL study will be the first to assess the clinical effects of oral resveratrol  
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19 417 in knee OA. If the results are positive, resveratrol will represent an interesting and safe  
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21 418 alternative for treating painful knee OA.  
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For peer review only

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3 498 **Author's contributions**  
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6 499 Conception and design of the study. CN, IB, GB, EC, FB, SP, FR.  
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8 500 Drafting of the original protocol. CN, IB, GB, SP, FR.  
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10 501 Coordination of the study. CN, FR.  
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12 502 Design of the statistical analysis plan. IB, GB.  
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14 503 Drafting of the present manuscript. CN, IB.  
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16 504 Final approval. CN, IB, GB, EC, FB, FR.  
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26

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32 510 **Competing interests statement**  
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34

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**Appendix 1. Additional inclusion and non-inclusion criteria.**

<b>Inclusion criteria</b>
Age $\geq$ 40 years-old
Written consent obtained
Health insurance coverage
<b>Non-inclusion criteria</b>
History of symptomatic crystal or inflammatory arthritis
Knee surgery $\leq$ 1 year
Knee intra-articular injection of corticosteroids and/or hyaluronic acid $\leq$ 2 months
Knee trauma $\leq$ 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)  $\geq 50\%$  and absolute change  $\geq 20$ , or improvement in at least 2 of the 3 following: 1) pain  $\geq 20\%$  and absolute change  $\geq 10$ , 2) function  $\geq 20\%$  and absolute change  $\geq 10$ , 3) patient global assessment (assessed by an 11-point global assessment NRS)  $\geq 20\%$  and absolute change  $\geq 10$ .

**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*
<b>Certain</b>	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
<b>Probable/likely</b>	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
<b>Possible</b>	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
<b>Unlikely (not excluded)</b>	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 <i>in vivo</i> 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
<b>Administrative information</b>			
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



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49**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

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3	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
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6	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
7				

### 8 **Methods: Assignment of interventions (for controlled trials)**

#### 9 Allocation:

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12	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
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18	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
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22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9 and 10
23				
24				
25	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
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28		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
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### 32 **Methods: Data collection, management, and analysis**

33				
34	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
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39		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
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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



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3	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
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5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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8				
9	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
10				
11				
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
13				
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15	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
16				
17				
18	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
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20				
21	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
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	19
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18 and 19
29				
30	<b>Appendices</b>			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendices
33				
34				
35	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
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## 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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<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Rheumatology
Keywords:	Osteoarthritis, Resveratrol, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Pain

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Manuscripts

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3 1 **Evolution of pain at 3 months by oral resveratrol in knee osteoarthritis (ARTHROL):**  
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5 2 **protocol for a multicentre randomised double-blind placebo-controlled trial**  
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42 **Total word count: 4723**

43

44 **References: 30**

## 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.



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

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

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

74  
75           **Keywords.** Osteoarthritis; knee; resveratrol; oral treatment; pain; clinical trial.

## 76 **Strengths and limitations of the study**

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

## 87 Introduction

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

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

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

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3 112 New formulations of resveratrol have allowed for an increase in oral resveratrol  
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5 113 bioavailability<sup>24</sup>. The plasmatic peak is 10-fold increased and blood concentration remains at  
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7 114 significant levels for several hours. We hypothesized that oral resveratrol in a new  
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9 115 formulation could reduce knee pain at 3 months as compared with placebo in people with  
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11 116 knee OA.  
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## 16 118 **Methods and analysis**

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19 119 **Design overview.** This is a prospective, parallel-group, double-blind, randomised  
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21 120 controlled multicentre study. Duration of follow-up for each participant will be 6 months  
22  
23 121 post-randomisation. The study will be reported according to the CONSORT statement<sup>25</sup>.  
24  
25

26 122 **Setting and participants.** Participants will be prospectively recruited among in- and  
27  
28 123 outpatients from Rheumatology and Rehabilitation departments of 3 tertiary care centres in  
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30 124 France with expertise in OA management (Cochin and Saint-Antoine Hospitals, Paris; and  
31  
32 125 Gabriel-Montpied Hospital, Clermont-Ferrand), by advertising on the Internet and in the  
33  
34 126 media (newspapers, health magazines) and by using posters in each investigating centre.  
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36 127 People interested in participating in the study will be invited to contact a biomedical research  
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38 128 technician by phone or email. In addition, the computerized medical records of each  
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40 129 investigating center will be searched from 2015 to 2017, and patients with the key words  
41  
42 130 “knee OA” in the records will be invited to participate in the study by phone or mail by the  
43  
44 131 biomedical research technician. The number of patients treated yearly for knee OA in the  
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46 132 participating centers is approximately 2000. The biomedical research technician will check  
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48 133 for eligibility criteria, then, if appropriate, set up a face-to-face baseline visit with one of the  
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50 134 investigators, a senior specialist in rehabilitation and/or rheumatology. The main eligibility  
51  
52 135 criteria will be knee OA fulfilling 1986 American College of Rheumatology criteria, pain on a  
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54 136 self-administered 11-point pain numeric rating scale (NRS)  $\geq 40/100$ , symptom duration  $\geq 1$   
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3 137 month, and Kellgren and Lawrence X-ray score 1, 2 or 3. A complete description of the  
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5 138 inclusion and non-inclusion criteria is in **Appendix 1**. Patients excluded for temporary  
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7 139 reasons can be rescreened.

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10 **Experimental group.** 40 mg (2 caplets) of resveratrol will be administered orally  
11  
12 141 twice a day, 30 min before a meal with a glass of water, for 1 week, then 20 mg (1 caplet)  
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14 142 twice a day for a total of 6 months. Pharmacokinetics, bioavailability and toxicity of trans-  
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16 143 resveratrol formulation used in the ARTHROL trial have been previously described in a phase  
17  
18 144 I clinical trial <sup>24</sup>. Briefly, 15 healthy volunteers received a single dose of 40 mg of oral trans-  
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20 145 resveratrol in 2 forms (soluble galenic formulation or dry powder). The single dose of the  
21  
22 146 soluble trans-resveratrol was well absorbed and elicited biologically efficient blood levels  
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24 147 (0.1-6  $\mu$ M) for several hours. The soluble formulation led to 8.8-fold higher trans-resveratrol  
25  
26 148 levels in plasma versus the powder. We have made substantial modifications to the  
27  
28 149 administration scheme as compared to the one tested in the phase I clinical trial: 1/ because  
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30 150 trans-resveratrol is metabolized into glucuronide and sulfate conjugates coupled to renal  
31  
32 151 elimination, we hypothesized that giving a loading dose for 1 week may allow attaining the  
33  
34 152 drug effect more rapidly, and 2/ for the maintenance dose, we chose 40 mg a day as tested in  
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36 153 the phase I clinical trial, but in 2 doses, because the half-life of the soluble galenic  
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38 154 formulation of trans-resveratrol is 79 min only. Resveratrol will be freely supplied by the  
39  
40 155 Yvery laboratory (patent n° WO 2012/007252, Marseille, France). Resveratrol is considered a  
41  
42 156 dietary supplement and is available over the counter. No marked toxicity has been reported <sup>26</sup>.  
43  
44 157 The caplets used in this study will be exactly the same as those already available on the  
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46 158 French market. They will be stored in their original packaging at room temperature, protected  
47  
48 159 from humidity, light and excessive heat. A box containing 7 pillboxes of 60 caplets each of  
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50 160 resveratrol will be provided to each person randomised to the experimental group. Individuals  
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52 161 will be asked to return the pillboxes for capsule counts at the 3- and 6-month visits and to  
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3 162 self-report adherence by completing a booklet. However, no specific measures will be taken  
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5 163 to enhance adherence.  
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7 164 **Control group.** The Yvery laboratory will supply the placebo and ensure that it has a  
8  
9 165 similar condition and taste as resveratrol. Two caplets of placebo will be administered orally  
10  
11 166 twice a day for 1 week, then 1 capsule twice a day for a total of 6 months. A box containing 7  
12  
13 167 pillboxes of 60 caplets each of placebo will be provided to each person randomised to the  
14  
15 168 control group and stored under the same conditions as resveratrol.  
16

17 169 **Co-interventions.** Pharmacological and non-pharmacological treatments usually  
18  
19 170 prescribed for knee OA will be authorised. Rescue medications (analgesics and NSAIDs),  
20  
21 171 joint injections (hyaluronic acid and corticosteroids), symptomatic slow acting drugs for OA  
22  
23 172 (SYSADOA) and non-pharmacological co-interventions including brace, insoles, walking  
24  
25 173 aids, physiotherapy, home-based therapeutic exercises and weight loss will be assessed by  
26  
27 174 using a standardized checklist and recorded in the electronic case report form (eCRF).  
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30 175 **Outcomes.** Primary and secondary efficacy outcomes have been selected in  
31  
32 176 accordance with Outcome Measures in Rheumatology (OMERACT)<sup>27</sup> and Osteoarthritis  
33  
34 177 Research Society International (OARSI) recommendations<sup>28</sup> and the Core Outcome  
35  
36 178 Measures in Effectiveness Trials (COMET) initiative for phase III clinical trials of knee OA.  
37  
38 179 As recommended, the outcomes include those for pain, physical function and patient global  
39  
40 180 assessment. The primary efficacy outcome is the mean change from baseline in mean knee  
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42 181 pain in the previous 48 hr on a self-administered 11-point pain NRS (0, no pain, to 100,  
43  
44 182 maximal pain) at 3 months. The secondary efficacy outcomes are the mean change in mean  
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46 183 knee pain on a pain NRS at 6 months, the mean change in the function subscore of the self-  
47  
48 184 administered Western Ontario and McMaster Universities Arthritis Index (WOMAC)  
49  
50 185 questionnaire at 3 and 6 months (the French version of the questionnaire)<sup>29</sup>, the mean change  
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52 186 in patient global assessment at 3 and 6 months on a self-administered 11-point global  
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3 187 assessment NRS (0, worst possible, to 100, best possible), the proportion of responders  
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5 188 according to the Osteoarthritis Research Society International (OARSI)-(Outcome Measures  
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7 189 in Rheumatology) OMERACT at 3 and 6 months <sup>30</sup>, the self-reported number of intra-  
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10 190 articular injections of corticosteroids or hyaluronic acid and the self-reported consumption of  
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12 191 analgesics (non-opioid, weak and strong opioids) and NSAIDs since the last contact on a self-  
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14 192 administered 4-class scale (never, several times a month, several times a week, daily) at 3 and  
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16 193 6 months. Information about the WOMAC questionnaire and OARSI-OMERACT response  
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18 194 are in **Appendix 2**. For participants who discontinue or deviate from intervention protocols,  
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20 195 the same outcome data will be collected if possible.

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23 196 **Randomisation and allocation concealment.** Individuals who meet the inclusion  
24  
25 197 criteria and agree to participate will be randomly assigned to the resveratrol or placebo group  
26  
27 198 at the inclusion visit. The allocation ratio of assignments will be 1 :1. Participants, care  
28  
29 199 providers, data collectors, outcome assessors and statisticians will be blinded to the allocated  
30  
31 200 group. The randomisation sequence will be computer-generated by a statistician of the *Centre*  
32  
33 201 *d'Épidémiologie Clinique*. The list will be stratified by centres with variable block sizes. The  
34  
35 202 randomisation process will be centralized at the coordinating office (*Unité de Recherche*  
36  
37 203 *Clinique*, Cochin Hospital), which will have no involvement in the enrollment, follow-up, or  
38  
39 204 assessment of participants. Only the independent statistician of the *Centre d'Épidémiologie*  
40  
41 205 *Clinique*, the computer programmer at the coordinating office who will implement the  
42  
43 206 sequence assignment in the secure eCRF, and the Yvery company will have access to the  
44  
45 207 randomisation list. The Yvery Company will label the resveratrol and placebo caplets and  
46  
47 208 provide them with strictly identical presentations to each centre for the whole research  
48  
49 209 duration. In each centre, the investigator will blindly deliver the medication to patients  
50  
51 210 enrolled according to their randomisation number, at once, for the whole research duration.  
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54 211 The sequence will be concealed by use of a computer interface implemented in the eCRF.  
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3 212 Treatment administration and clinical monitoring of the experimental products will be the  
4  
5 213 same in the experimental and control groups.  
6

7 214 Blinding can be broken only if the investigator deems it necessary for the safe  
8  
9 215 management of a specific medical condition of a subject, and whenever possible, the  
10  
11 216 methodologist and sponsor will be consulted before breaking the blind. If the blind is broken  
12  
13 217 for any reason during the study, the moment at which the blind was broken and all other  
14  
15 218 relevant information will be documented by the investigative site and other sponsor designees,  
16  
17 219 as appropriate. The reason for breaking the blind will be indicated and justified in the source  
18  
19 220 documentation and in the eCRF.  
20  
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22  
23 221 **Statistical aspects.** The sample size is estimated at 164 patients. We have predicted a  
24  
25 222 difference in mean change from baseline of 15 points on the pain NRS between resveratrol  
26  
27 223 and placebo groups, with a standard deviation of 27 points, and a power of 90%,  
28  
29 224 corresponding to 69 patients in each arm. Considering a 15% lost to follow-up, we will need  
30  
31 225 to enroll an estimated 82 patients for each arm. Fifteen points on pain NRS is considered the  
32  
33 226 minimal clinically perceived difference in pain for patients with knee OA. All analyses will be  
34  
35 227 performed on an intent-to-treat basis, in that all patients will be considered in the analysis and  
36  
37 228 will be analysed in the group to which they had been assigned. For descriptive analyses,  
38  
39 229 qualitative variables will be reported with absolute and relative frequencies and quantitative  
40  
41 230 variables with median (interquartile range). To compare differences in changes in values  
42  
43 231 between the 2 groups for quantitative variables, a constrained longitudinal data analysis will  
44  
45 232 be used. In this model, both the baseline and post-baseline values will be modelled as  
46  
47 233 dependent variables (the constrained longitudinal data analysis model assumes that both the  
48  
49 234 baseline and post-baseline measurements are jointly multivariate normally distributed because  
50  
51 235 the baseline value is treated as part of the response vector). The true baseline means will be  
52  
53 236 constrained to be the same for the 2 treatment groups. This analysis provides an adjustment  
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3 237 for the observed baseline difference in estimating the treatment effects. Random effects at  
4  
5 238 patient and centre levels will be added to these models. Results are expressed as differences in  
6  
7 239 mean change from baseline with 95% CI at 3 month and 6 months. The constrained  
8  
9 240 longitudinal data analysis model can include all randomized subjects with a baseline or post-  
10  
11 241 baseline value. Such methods based on maximum likelihood are consistent under the missing-  
12  
13 242 at-random assumption. Qualitative outcomes will be analysed by a mixed logistic regression  
14  
15 243 model with a random effect at centre levels. Data analysis will involve use of SAS 9.4 (SAS  
16  
17 244 Institute, Cary, NC). Blinded statisticians will perform the statistical analyses at an  
18  
19 245 independent centre (*Centre d'Épidémiologie Clinique*, Paris Descartes, Hôpital Hôtel-Dieu).  
20  
21 246 The statistical analysis will be further detailed in a dedicated Statistical Analysis Plan before  
22  
23 247 any analysis is undertaken.

24 248 **Participant timeline (Table 1).**

25 249 *Baseline visit.* Inclusion and non-inclusion criteria will be validated at baseline by the  
26  
27 250 investigator during a face-to-face visit. The individual will be informed and the written  
28  
29 251 consent collected by the investigator. Then the participant will be enrolled and randomised.  
30  
31 252 Specific additional clinical examination, laboratory tests or imaging will not be required for  
32  
33 253 the purpose of the study. Information regarding demographics (age, gender, body mass index,  
34  
35 254 education, employment status), medical history (date of diagnosis, symptoms duration, side  
36  
37 255 affected, medical history, surgery and trauma history of the affected knee, X-ray findings  
38  
39 256 including Kellgren and Lawrence grade and OA location [i.e., femorotibial medial,  
40  
41 257 femorotibial lateral and/or patellofemoral OA]), medications in the previous 3 months  
42  
43 258 (analgesics, NSAIDs and intra-articular injections of hyaluronic acid and/or corticosteroids  
44  
45 259 and SYSADOA) and current non-pharmacological co-interventions (brace, insoles, walking  
46  
47 260 aids, physiotherapy, home-based therapeutic exercises and weight loss) will be recorded in the  
48  
49 261 eCRF by using a standardized checklist. Baseline values for prespecified assessment criteria  
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3 262 will be collected by using printed self-administered questionnaires and data will be entered in  
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5 263 the eCRF by a biomedical research technician. The investigator will deliver the experimental  
6  
7 264 product to the participants according to their randomisation number and give them a  
8  
9 265 participating card in a clinical trial. Participants will be asked to keep and return the pillboxes  
10  
11 266 for capsule counts at the 3- and 6-month visits and to self-report adherence by completing a  
12  
13 267 booklet.

14  
15  
16 268 Three- and 6-month visits. The investigator will assess participants during a face-to-  
17  
18 269 face visit. Values for prespecified assessment criteria will be collected at 3 and 6 months by  
19  
20 270 using printed self-administered questionnaires, and data will be recorded in the eCRF by a  
21  
22 271 biomedical research technician. In addition, the investigator will record adverse events (AEs)  
23  
24 272 since the last contact by asking an open-ended question (“Did you have any adverse events  
25  
26 273 since the last contact?”), count the caplets remaining in the pillboxes, check the self-reported  
27  
28 274 adherence booklet and assess non-pharmacological co-interventions by using a standardized  
29  
30 275 checklist. In the event that the participant missed the appointment, self-administered  
31  
32 276 questionnaires, AEs, capsule counts and non-pharmacological co-interventions will be  
33  
34 277 collected by mail, email or phone by a biomedical research technician and recorded. To  
35  
36 278 reduce the amount of missing data, promote participant retention and complete the follow-up,  
37  
38 279 reminder newsletters will be sent once a month by mail or email to inform participants of the  
39  
40 280 progression of the study.

41  
42  
43 281 End of the research. At the end of the research, patients will be advised to continue  
44  
45 282 their usual medical follow-up with their treating physician. Ending a subject's participation  
46  
47 283 will not affect the normal medical management in any way. No exclusion period for another  
48  
49 284 biomedical research will be required. At the end of the study, participants will be informed of  
50  
51 285 the results upon request.  
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3 286 **Role of the funding source.** The study is funded by a research grant from the French  
4  
5 287 Ministry of Health (*Programme Hospitalier de Recherche Clinique*, project no. 15-15-0234)  
6  
7 288 and sponsored by the *Département de la Recherche Clinique et du Développement* (DRCD) of  
8  
9 289 the *Assistance Publique-Hôpitaux de Paris* (AP-HP) (Hôpital Saint-Louis, 1, Avenue Claude  
10  
11 290 Vellefaux, 75010 Paris, FRANCE, tel: +33 1 44 49 59 69, fax: +33 1 44 84 17 99). The Yvery  
12  
13 291 laboratory will supply the resveratrol and the placebo. The funding source and the Yvery  
14  
15 292 laboratory will not be involved in the study design; collection, management, analysis, and  
16  
17 293 interpretation of data; or writing of the report; nor decision to publish the results.  
18  
19

#### 20 21 294 **Data management**

22  
23 295 Data collection. Data will be entered into an eCRF, completed by the investigator  
24  
25 296 during each visit. Data from printed self-administered questionnaires will be entered in the  
26  
27 297 eCRF by a biomedical research assistant after the visits. The investigator must give an  
28  
29 298 explanation for each missing data. Changes in the data in the eCRF will be tracked.  
30  
31 299 Discordant data in the eCRF will be corrected by queries.  
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33

34 300 Data monitoring. In accordance with the French Good Clinical Practices, the sponsor,  
35  
36 301 DRCD, is responsible for obtaining the permission of all parties involved in the research to  
37  
38 302 guarantee direct access to all locations where the research is carried out, the source data, the  
39  
40 303 source documents and the reports, with the goal of quality control and audit by the sponsor. In  
41  
42 304 accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and  
43  
44 305 R.5121-13 of the French Public Health Code), the investigators will make available to those  
45  
46 306 in charge of monitoring, quality control and audit relating to the biomedical research the  
47  
48 307 documents and personal data strictly necessary for these controls. Source documents are  
49  
50 308 defined as any original document or object that can prove the existence or accuracy of a piece  
51  
52 309 of information or a fact recorded during the research.  
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3 310 Quality control. A clinical research associate appointed by the sponsor will be  
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5 311 responsible for the proper conduct of the research and for collecting and documenting,  
6  
7 312 recording and reporting the data generated in writing, in accordance with the Standard  
8  
9 313 Operating Procedures applied within the DRCD and in accordance with French Good Clinical  
10  
11 314 Practices as well as with the legislative and regulatory provisions in force. The investigator  
12  
13 315 and the members of the investigator's team agree to make themselves available during quality  
14  
15 316 control visits carried out at regular intervals by the clinical research associate. During these  
16  
17 317 visits, the following elements will be reviewed: written consent, compliance with the research  
18  
19 318 protocol and with the procedures defined therein, quality of the data collected in the eCRF  
20  
21 319 including accuracy, missing data, consistency of the data with the source documents (medical  
22  
23 320 files, appointment books, original copies of laboratory results, etc.), and management of the  
24  
25 321 treatments used.  
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## 32 **Ethics and dissemination**

### 34 **Ethical considerations**

35  
36  
37 325 Methods for obtaining information and consent from research participants. In  
38  
39 326 accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research  
40  
41 327 can be carried out on a person without free and informed consent obtained in writing after the  
42  
43 328 person has been given the information specified in Article L.1122-1 of said Code. The  
44  
45 329 investigator or a doctor representing the investigator obtains the free and informed consent, in  
46  
47 330 writing, of the individual before their inclusion in the research. The information sheet and a  
48  
49 331 copy of the consent form signed and dated by the research participant and by the investigator  
50  
51 332 or the doctor representing the investigator, are given to the individual before their  
52  
53 333 participation in the research. In addition, the investigator will specify in the research  
54  
55 334 participant's medical file the methods used for obtaining consent as well as the methods used  
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3 335 for providing information with the goal of obtaining consent. The investigator will retain the  
4  
5 336 original signed and dated copy of the participant's consent form.  
6

7 337 Data confidentiality. Those responsible for biomedical research quality control  
8  
9 338 (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to  
10  
11 339 ensure the confidentiality of information about the experimental medications, the research, the  
12  
13 340 research subjects and in particular the identity of the participants and the results obtained.  
14  
15 341 Investigators are subject to professional secrecy (in accordance with the conditions set out in  
16  
17 342 Articles 226-13 and 226-14 of the Penal Code). During or after the biomedical research, the  
18  
19 343 data collected for the research participants and sent to the sponsor by the investigators (or any  
20  
21 344 other specialised parties) will be made non-identifying. Anonymization of the patients will be  
22  
23 345 ensured by using a code number and initials, reported on each needed document for the  
24  
25 346 research, or by erasing nominative data on copies of source documents. Under no  
26  
27 347 circumstances should the names and addresses of the subjects involved be shown. The  
28  
29 348 sponsor will ensure that each research participant has given permission in writing for access  
30  
31 349 to their personal information that is strictly necessary for the quality control of the research.  
32  
33 350 Access to the eCRF will be restricted by an access code and a personal and unique password  
34  
35 351 system for each user. Each investigator will, in addition, have access to a specific profile that  
36  
37 352 attributes or withholds access to certain functions of the system (entering data, or simply  
38  
39 353 viewing the data of the enrolled participant or all the study data, possibility of change and  
40  
41 354 validation by the clinical research associate, etc.). Data will be stored on a secure server, with  
42  
43 355 data encrypted during transmission and automatic internal saving of a copy on the server that  
44  
45 356 will host the eCRF. This research falls under the *Méthodologie de référence* according to the  
46  
47 357 provisions of Article 54, paragraph 5 of modified Law No. 78-17 of January 6, 1978 relating  
48  
49 358 to information technology, data files and privacy. This change was approved in a decision on  
50  
51 359 January 5, 2006. AP-HP, the research sponsor, has signed a commitment to comply with the  
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3 360 *Méthodologie de référence*. Specific documents for biomedical research will be archived by  
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5 361 the investigator and the sponsor for 15 years after the end of the research.  
6

7 362 Legal obligations. AP-HP is the sponsor of this research and by delegation, the DRCD  
8  
9 363 performs the research's missions in accordance with Article L.1121-1 of the French Public  
10  
11 364 Health Code. For this biomedical research relating to a medication for human use and prior to  
12  
13 365 starting the research, AP-HP has obtained the favourable opinion of the *Comité de Protection*  
14  
15 366 *des Personnes Île-de-France* III (CPP), within the scope of its authority and in accordance  
16  
17 367 with the legislative and regulatory provisions in force. AP-HP has also obtained authorisation  
18  
19 368 from the *Agence Nationale de Sécurité du Médicament et des produits de santé* (ANSM  
20  
21 369 [French Health Products Safety Agency]; registration no. RCB 2016-A01310-51). AP-HP has  
22  
23 370 signed a commitment to comply with the *Méthodologie de référence*. AP-HP will make a  
24  
25 371 standard declaration to the *Commission Nationale de l'Informatique et des Libertés*.  
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28

29 372 Modifications to the research. Any substantial modification to the protocol by the  
30  
31 373 coordinating investigator must be sent to the sponsor for approval. After approval is given, the  
32  
33 374 sponsor must obtain, before starting the research, a favourable opinion from the CPP and  
34  
35 375 authorisation from the ANSM within the scope of their respective authorities. The information  
36  
37 376 sheet and the consent form can be revised if necessary, particularly with substantial  
38  
39 377 modification to the research or if adverse reactions occur.  
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43 378 **Safety considerations**. The investigator will record all serious AEs (SAEs) and non-  
44  
45 379 SAEs since the last contact by asking an open-ended question ("Did you have any adverse  
46  
47 380 events since last contact?") during face-to-face visits at 3 and 6 months. In the event that the  
48  
49 381 participant missed the appointment, AEs will be requested by mail, email or phone by a  
50  
51 382 biomedical research technician and recorded. All SAEs and non-SAEs will be recorded in the  
52  
53 383 "Adverse events" section of the eCRF by the investigator.  
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3 384 Notification of an SAE. The investigator will notify the sponsor, immediately on the  
4  
5 385 day when he/she becomes aware, of any serious SAE, except those that are prespecified (see  
6  
7 386 below). The investigator must report all SAEs that occur in research participants on the date  
8  
9 387 of the first administration of an investigational product and throughout the period when the  
10  
11 388 participant is monitored. SAEs that do not require immediate notification to the sponsor are  
12  
13 389 recorded in the "Adverse events" section of the eCRF. They include events associated with 1)  
14  
15 390 the normal and natural evolution of the pathology including scheduled medical visits for the  
16  
17 391 follow-up of knee OA, scheduled hospitalisations for the routine treatment of knee OA (joint  
18  
19 392 injection, rehabilitation), and not related to a worsening of the condition, and expected  
20  
21 393 symptoms secondary to knee OA worsening such as joint pain, joint effusion, OA flare,  
22  
23 394 walking difficulties, or surgical knee joint replacement for OA; 2) special circumstances  
24  
25 395 including hospitalisations for pre-existing conditions, surgery scheduled prior to the research,  
26  
27 396 social or administrative purposes or admission to the emergency room less than 12 hr; and 3)  
28  
29 397 AEs likely to be associated with the treatments prescribed as part of the patient's care during  
30  
31 398 the monitoring of the research, including AEs related to rescue medications (analgesics and  
32  
33 399 NSAIDs) or joint injections (hyaluronic and corticosteroids) that include increased pain, joint  
34  
35 400 swelling, mild joint effusion that can last a few days, skin flush following corticosteroid  
36  
37 401 injections that can last a few hours, and exceptionally, septic arthritis or allergic reaction.  
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42 Investigation of an SAE. The investigator will document the SAE as thoroughly as  
43  
44 403 possible and provide the medical diagnosis by using a specific SAE form. The investigator  
45  
46 404 will assess the severity of the SAE: 1) mild, tolerated by the participant, does not interfere  
47  
48 405 with daily activities; 2) moderate, sufficiently uncomfortable to affect daily activities; and 3)  
49  
50 406 serious, preventing daily activities. The investigator will assess the causality relation between  
51  
52 407 the SAE and the clinical trial. The method the investigator uses will be based on the World  
53  
54 408 Health Organisation–Uppsala Monitoring Centre (WHO-UMC) method and will include the  
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3 409 following 4 causality terms: 1) certain, 2) probable/likely, 3) possible, and 4) unlikely (not  
4  
5 410 excluded). Their comprehensive definition is provided in **Appendix 3**. The sponsor  
6  
7 411 represented by the Vigilance department will continuously assess the safety of the clinical  
8  
9 412 trial throughout the trial. The sponsor is responsible for assessing 1) the seriousness of all AEs  
10  
11 413 reported and 2) the causality relation between the SAE and the acts/procedures/tests added by  
12  
13 414 the clinical trial.

14  
15  
16 415 Investigation of an AE. All SAEs considered by the investigator and/or the sponsor to  
17  
18 416 be possibly related to the act/procedures/tests/products administered, specific to the clinical  
19  
20 417 trial, can be reasonably considered suspected adverse reactions (SARs). Any SAR whose  
21  
22 418 nature, severity or outcome is not consistent with the information related to the  
23  
24 419 acts/procedures/and or products administered during the clinical study is considered  
25  
26 420 unexpected. The sponsor represented by the Vigilance department will assess the  
27  
28 421 expected/unexpected nature of an SAR according to the information described in **Appendix 4**  
29  
30 422 <sup>26</sup>. The sponsor reports any suspected unexpected serious adverse reaction (SUSAR), within  
31  
32 423 the legal deadline, to the ANSM and CPP.

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36 424 **Dissemination plan.** We aim to publish the results of ARTHROL trial in a peer-  
37  
38 425 review journal and present the findings to physicians who manage knee OA at national and  
39  
40 426 international conferences. The investigators will be involved in drafting manuscripts,  
41  
42 427 abstracts, press releases and any other publications arising from the trial. Authorship will be  
43  
44 428 determined in accordance with the International Committee of Medical Journal Editors  
45  
46 429 guidelines. There will be no intended use of professional writers. AP-HP is the owner of the  
47  
48 430 data, which cannot be used or disclosed to a third party without prior approval from the AP-  
49  
50 431 HP. The full original protocol in English and the full dataset will be available by contacting  
51  
52 432 the coordinating investigator, Prof François Rannou (francois.rannou@aphp.fr). Statistical  
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3 433 codes will be available by contacting the biostatistician of the study, Dr Gabriel Baron  
4  
5 434 (gabriel.baron@aphp.fr).  
6

7 435 The ARTHROL study will be the first to assess the clinical effects of oral resveratrol  
8  
9 436 in knee OA. If the results are positive, resveratrol will represent an interesting and safe  
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11 437 alternative for treating painful knee OA.  
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520 Table 1. Schedule of enrolment, interventions, and assessments.

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

<i>Non-pharmacological co-interventions</i>	X	X	X
<i>Adverse events</i>	-	X	X
<i>Adherence</i>	-	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.

For peer review only

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3 521 **Author's contributions**  
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5  
6 522 Conception and design of the study. CN, IB, GB, EC, FB, SP, FR.  
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8 523 Drafting of the original protocol. CN, IB, GB, SP, FR.  
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10 524 Coordination of the study. CN, FR.  
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12 525 Design of the statistical analysis plan. IB, GB.  
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14 526 Drafting of the present manuscript. CN, IB.  
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16 527 Final approval. CN, IB, GB, EC, FB, FR.  
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22 529 **Data sharing statement**  
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25 530 The full original protocol in English and the full dataset will be available by contacting the  
26

27 531 coordinating investigator, Prof François Rannou (francois.rannou@aphp.fr). Statistical codes  
28

29 532 will be available by contacting the biostatistician of the study, Dr Gabriel Baron  
30

31 533 (gabriel.baron@aphp.fr).  
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47 539 **Competing interests statement**  
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50 540 None to declare.  
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55 542 **Checklist compliance statement**  
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3 543 The authors confirm that their manuscript fully adheres with the SPIRIT Checklist.  
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**Appendix 1. Additional inclusion and non-inclusion criteria.**

<b>Inclusion criteria</b>
Age $\geq$ 40 years-old
Written consent obtained
Health insurance coverage
<b>Non-inclusion criteria</b>
History of symptomatic crystal or inflammatory arthritis
Knee surgery $\leq$ 1 year
Knee intra-articular injection of corticosteroids and/or hyaluronic acid $\leq$ 2 months
Current use of intramuscular, intravenous or oral corticosteroids
Uncontrolled diseases that may require intramuscular, intravenous or oral corticosteroids
Knee trauma $\leq$ 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)  $\geq 50\%$  and absolute change  $\geq 20$ , or improvement in at least 2 of the 3 following: 1) pain  $\geq 20\%$  and absolute change  $\geq 10$ , 2) function  $\geq 20\%$  and absolute change  $\geq 10$ , 3) patient global assessment (assessed by an 11-point global assessment NRS)  $\geq 20\%$  and absolute change  $\geq 10$ .

**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*
<b>Certain</b>	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
<b>Probable/likely</b>	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
<b>Possible</b>	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
<b>Unlikely (not excluded)</b>	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 <i>in vivo</i> animal studies
Rash
Somnolence


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

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Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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

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2  
3 **Introduction**  
4

5	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	6 and 7
6	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
7				
8		6b	Explanation for choice of comparators	8
9				
10	Objectives	7	Specific objectives or hypotheses	8 and 9
11				
12	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	7 and 9
13			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
14				

15  
16 **Methods: Participants, interventions, and outcomes**  
17

18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	8
19			be collected. Reference to where list of study sites can be obtained	
20				
21	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	7, 8 and appendix
22			individuals who will perform the interventions (eg, surgeons, psychotherapists)	1
23				
24	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	8
25			administered	
26				
27		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	N/A
28			change in response to harms, participant request, or improving/worsening disease)	
29				
30		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	8
31			(eg, drug tablet return, laboratory tests)	
32				
33		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
34				
35	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	8, 9 and appendix
36			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	2
37			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
38			efficacy and harm outcomes is strongly recommended	
39				
40	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	11, 12 and figure 1
41			participants. A schematic diagram is highly recommended (see Figure)	
42				
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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



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2				
3	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
4				
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7	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
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
11				
12		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
13				
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15				
16	<b>Methods: Monitoring</b>			
17				
18	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
19				
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23		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
24				
25				
26	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
27				
28				
29	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
30				
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33	<b>Ethics and dissemination</b>			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
36				
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38	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
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3	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
4				
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
7				
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9	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
10				
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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15	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
16				
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18	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
19				
20				
21	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
22				
23				
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25				
26		31b	Authorship eligibility guidelines and any intended use of professional writers	19
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18 and 19
29				
30	<b>Appendices</b>			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendices
33				
34				
35	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
36				
37				

\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.