Decision Support Unit Project Specification Form	
Project Number	
Appraisal title	**TA160/1 - Strontium Ranelate part only** TA160: Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. TA161: Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women
Synopsis of the technical issue	The technical issue to addressed in this project is a reconsideration of the relative effectiveness of strontium ranelate in preventing hip fractures, in the population covered by the marketing authorisation Servier, the manufacturer of strontium ranelate, one of the drugs appraised in TA160 and 161, applied for a judicial review following publication of the guidance. One of the points raised was related to the approach that the Appraisal Committee took to a particular subgroup analysis; this point was not upheld at the Judicial Review stage. Servier applied to the Court of Appeal to challenge the ruling on the subgroup analyses point and a hearing was held in December 2009. The substance of this point is that in developing the recommendations for TA160/1 the Appraisal Committee used clinical hip fracture efficacy data for strontium ranelate from the overall study population in the clinical trial presented by Servier; this was a relative risk (RR) of 0.85 with a 95% confidence interval of 0.61 to 1.19. Servier contends that NICE should have used a RR for hip fracture from a post hoc study in women over the age of 74 years, which was accepted by the European Medicines Agency in support of the grant of the marketing authorisation for strontium ranelate in reducing the risk of hip fracture; this RR was 0.64 (confidence interval of 0.412 to 0.997). Servier claimed that • NICE had not adequately explained its reasons for rejecting the post hoc subgroup data,

	particularly in the light of the fact that the same data had been accepted by the EMA (the 'reasons' ground). • the Appraisal Committee's decision to reject the post hoc subgroup data was not rational (the 'rationality' ground). Servier's arguments are closely linked to the European Public Assessment Report (EPAR), which states that because the overall hip fracture efficacy for the drug was not demonstrated, that is, it did not show a statistically significant effect (RR = 0.85 [0.61:1.19]), the EMA requested a specific subgroup analysis; Servier provided an alternative subgroup analysis (RR = 0.64, [0.412;0.997]), and this was used by the EMA to determine that strontium ranelate had a positive benefit-risk profile. Because of the EMA's acceptance of the subgroup analysis, Servier argues that NICE should use the RR from the subgroup as a basis for the decision making on cost effectiveness, for the entire population. The Court of Appeal has ruled in favour of Servier on the reasons ground, and the judges ordered NICE to reach a fresh decision and issue fresh guidance in respect of strontium ranelate. The Appraisal Committee will therefore reconsider the relative effectiveness of strontium ranelate and, if they consider appropriate, review their consideration of its cost effectiveness. In line with the Court order, NICE is proceeding with the reconsideration following the process outlined below, agreed between NICE and Servier: 1. NICE has sent Servier a document summarising the issues related to the Appraisal Committee reasoning behind their decision to base its recommendations on the RR for the entire TROPOS clinical trial population and not on the subgroup analysis, and the request for specific information (see attached 'Statement of Reasons), 2. Servier will make a submission of evidence and NICE will provide an opportunity for a clarification step with NICE, if necessary; 3. An independent academic group will be commissioned to review the submission, focussing on the validity of statistical analyses of the TROPOS clinical trial including the subgroup analysis; a period of 4 weeks is scheduled for this review. 4. Servier will be given an opportunity to comment on the independent review of their submission and these comments will be forwarded to the Appraisal Committee; 5. Servier representatives will be invited to attend the Appraisal Committee meeting (as

	per standard process) and they can include an expert in the clinical area as part of their representation. 6. NICE will issue a Final Appraisal Determination after the committee meeting. However, if the Appraisal Committee requests a consultation, then we will issue an Appraisal Consultation Document.
Question(s) to be answered by DSU	The DSU is requested to make arrangements to undertake an independent review (step 3 above) of Servier's submission (step 2). The questions to be answered by the DSU are 1. How scientifically valid is the proposition put forward by Servier related to the use of data derived from the TROPOS study subgroup analysis. 2. From a statistical viewpoint, what is the most appropriate approach to the use of data from the whole data set of the TROPOS study and the subgroup data set in relation to determining the relative effectiveness of strontium ranelate? 3. Given the data reviewed what, in their expert view, is the most plausible relative risk for strontium ranelate to use in making recommendations for the population covered by the marketing authorisation for strontium ranelate?
Why are these questions important	To provide an independent expert review of data submitted by Servier from the TROPOS study in relation to the relative effectiveness of Strontium Ranelate in the population covered by its marketing authorisation
In what way does this project extend the content of the TAR	n/a
How will the DSU address these questions	The DSU will identify appropriate expertise in biostatistics and clinical trial analyses to review the Serviers submission.
Relevant existing evidence	○ NICE statement of reasons document ○ Submission provided by Servier in response to the Statement of Reasons document.

	○ The Court of Appeal ruling as publicly available at: http://www.bailii.org/ew/cases/EWCA/Civ/2010/346.html ○ The original submission from Servier from 2005 ○ The EPAR and SmPC for Strontium Ranelate
Relevant new evidence requested by DSU	

Decision Support Unit Project Administration Form	
Project Number	
DSU Project Leader	
Date form sent to DSU	
NICE contacts[1] • Technical Lead • Technical Advisor • Project manager	
DSU contacts[1] • Project Leader • Lead analyst	[redacted], ScHARR. [redacted] [redacted]

Assessment Group • Lead reviewer[1]	
Details of Assessment Group involvement in the project	
Appraisal committee members involved in the project	
Experts nominated by consultees involved in the project	-
Other experts involved in the project	
Documentation sent to DSU	
Timelines:	
• Start date	25 August 2010
• Date for delivery of draft report	17 September 2010
• Date for delivery of report to Institute	24 September 2010
• Date for distribution of report to Servier	27 September 2010
• Date of Appraisal Committee meeting for presentation of report	20 October 2010
• Date for publication on website	

Overview of tasks – for full details see task form	
Total anticipated DSU person hours - for full details see task form	
Project approved [2]	[redacted] for DSU on / Elisabeth George for NICE on
Date[2]	
Post-project	
Output conforms to specification[3]	
Total actual DSU person hours	
Change to budget approved[2]	

[1] Include contact details (phone number and email)
[2] Approved by both the CHTE and DSU Director
[3] Did the project achieve its objective(s)