

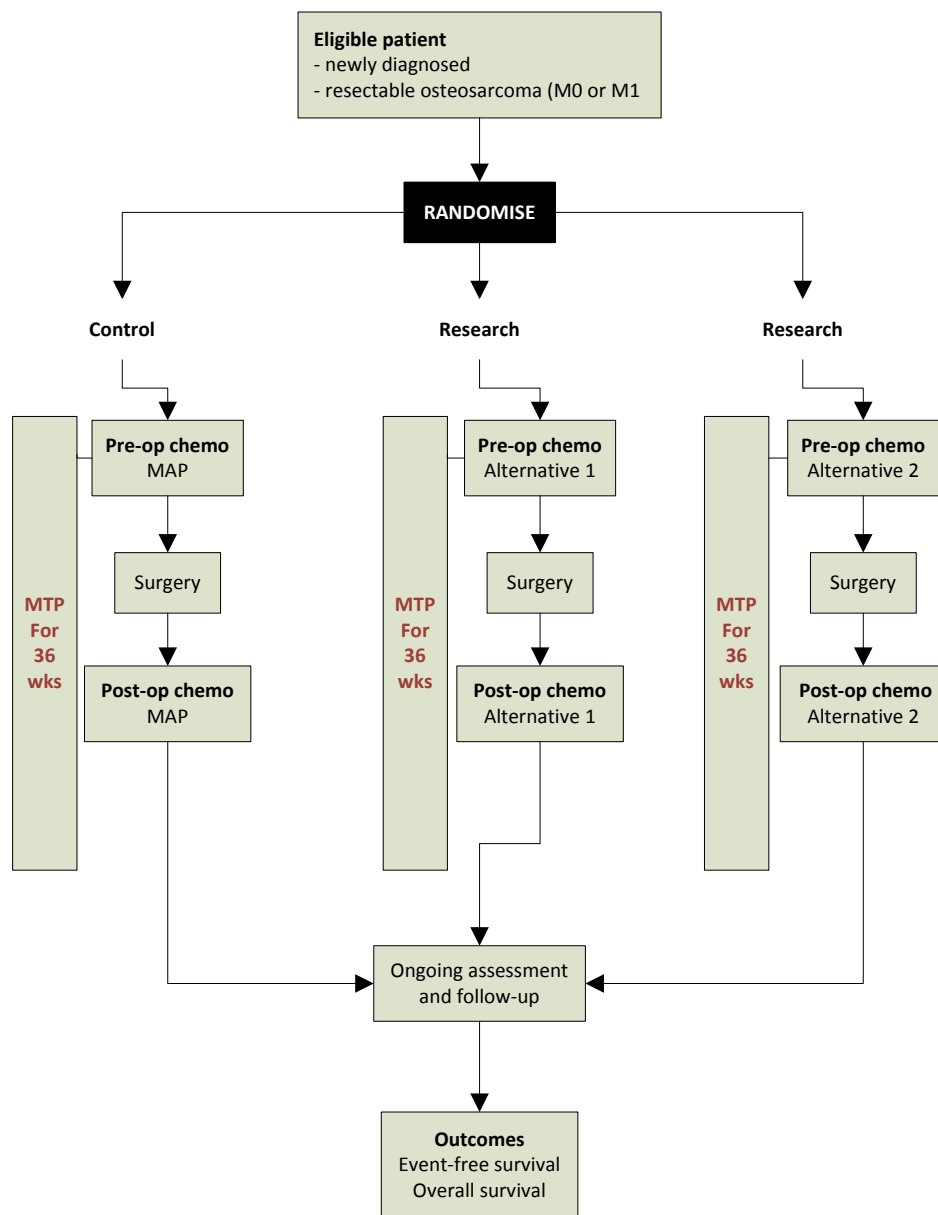
CONCEPT A: Concept Sheet for a Potential Trial Addressing an Unresolved Issue in Osteosarcoma

Proposers' names	Whelan, Bielack, Smeland, Sydes
Short title	[A] Randomised controlled trial comparing standard of chemotherapy regimens (with mifamurtide) for osteosarcoma
Summary diagram	(See end of document)
Patient group (Summary only)	High grade osteosarcoma of the extremity or axial skeleton
Main eligibility criteria (Summary only)	<p><i>As per EURAMOS-1</i></p> <ol style="list-style-type: none"> 1. Histologically proven high grade osteosarcoma of the extremity or axial skeleton (including from second malignancies) 2. Resectable disease 3. Age up to 40 years 4. Registration within 30 days of diagnostic biopsy 5. Start chemotherapy within 30 days of diagnostic biopsy 6. Adequate neutrophils, platelets, GFR, bilirubin and cardiac function 7. Adequate performance status
Control treatment (Name, administration route, duration)	1. Neo-adjuvant 3-drug MAP (doxorubicin, cisplatin and high dose methotrexate) chemotherapy (as per AOST-0133 and EURAMOS-1). Plus mifamurtide (for 36 weeks) from the start of chemotherapy.
Research treatment(s) (Name, administration route, duration)	<ol style="list-style-type: none"> 2. 4-drug ifosfamide-containing chemotherapy (eg COSS-96) doxorubicin, cisplatin, high-dose methotrexate and ifosfamide). Plus mifamurtide (for 36 weeks) from the start of chemotherapy. 3. 3-drug non-methotrexate chemotherapy (eg API-AI: doxorubicin, cisplatin and ifosfamide). Plus mifamurtide (for 36 weeks) from the start of chemotherapy.
Current knowledge (Known safety data and known activity data)	<p>Mifamurtide is the only licensed drug for use in osteosarcoma and may become part of standard practice. The safety data are well-reported.</p> <p>There are many potential regimens for chemotherapy. These have been used in individual trials but have not been compared directly, nor widely used in the context of mifamurtide. The activity and safety of these regimens (without mifamurtide) has been published.</p>
Rationale (250 words max)	There are many chemotherapy regimens considered standard around the world but the best regimen is not widely agreed. A standard of care in EURAMOS-1 is MAP (methotrexate, doxorubicin

	<p>and cisplatin). Several regimens have published encouraging results and may warrant further investigation. These regimens should be compared in a definitive trial to assess which regimen has the greater activity, particularly in the context of consistent use of mifamurtide, and short-term and long-term safety data can be prospectively collected (eg cardiac function, hearing loss, nephrotoxicity, fertility). Only a direct randomised comparison of these agents will the best approach be decided for the future.</p> <p>Given that MAP is the only regimen with known data in the context of mifamurtide and if mifamurtide is considered part of the new standard practice, then the combination of MAP+MTP should be considered the control arm here. The trial addresses whether the other combinations of chemotherapy with MTP are more effective. A hazard ratio of 0.80 is considered evidence required for all groups to consider a change to standard chemotherapy.</p>								
Hypothesis (50 words max)	One of the chemotherapy regimens will be shown better than the others given the totality of long-term efficacy and safety data.								
Trial design	<table border="1"> <tr> <td><input type="checkbox"/></td> <td>Phase I</td> </tr> <tr> <td><input type="checkbox"/></td> <td>non-randomised Phase II, specify: _____</td> </tr> <tr> <td><input type="checkbox"/> (?)</td> <td>randomised phase II, specify: (Pick the winner) _____</td> </tr> <tr> <td><input checked="" type="checkbox"/> X</td> <td>Phase III</td> </tr> </table>	<input type="checkbox"/>	Phase I	<input type="checkbox"/>	non-randomised Phase II, specify: _____	<input type="checkbox"/> (?)	randomised phase II, specify: (Pick the winner) _____	<input checked="" type="checkbox"/> X	Phase III
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Blinding	<table border="1"> <tr> <td><input type="checkbox"/></td> <td>Single blinding possible</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Double blinding possible</td> </tr> <tr> <td><input checked="" type="checkbox"/> X</td> <td>No blinding possible</td> </tr> </table>	<input type="checkbox"/>	Single blinding possible	<input type="checkbox"/>	Double blinding possible	<input checked="" type="checkbox"/> X	No blinding possible		
<input type="checkbox"/>	Single blinding possible								
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Primary outcome measure	Event-free survival (disease progression or death from any cause)								
Secondary outcome measures	<p>Overall survival</p> <p>Toxicity</p> <p>Quality of life</p> <p>Acceptance of randomisation</p>								
Control arm event rate	<p>67 % EFS at 3 years</p> <p><i>(AOST-0133 showed 71% PFS in non-metastatic patients at 3 years)</i></p>								
Target difference	HR=0.80 is used for sample size calculations								
Accrual duration	5.0 years								
Accrual rate / year	400 patients per year								

Accrual total target	2084 patients	
Total trial duration	7 years	
Need for international collaboration	Defining an internationally agreed standard chemotherapy for patients with osteosarcoma requires broad global input in order to have generalisable and widely acceptable results. Furthermore, high recruitment rates are required.	
Potential sub-studies	X	Biology / translation
	X	Quality of life
		Other, specify:
Strengths	<ul style="list-style-type: none"> • Defines the standard of care for future internationally collaborative trials • Randomisation performed before treatment starts • Arms diverge quickly after randomisation • Provides trials groups standard regimen to exposure by other groups • Broad accrual leads to internally acceptable results • More than 3 regimens could be considered 	
Limitations	<ul style="list-style-type: none"> • Requires agreement on which chemo regimens to use and which of those is considered "standard". This includes appropriate regimens to cover both paediatric and adult patients • Assumes that MTP is part of standard of care • Does not address other promising agents 	

Summary diagram



Scenario: HR=0.8 (EFS at 3 years 67% to 73%)

ART - ANALYSIS OF RESOURCES FOR TRIALS (version 1.0.7, 19 October 2009)

A sample size program by Abdel Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit, London NW1 2DA, UK.

Type of trial	Superiority - time-to-event outcome
Statistical test assumed	Unweighted logrank test (local)
Number of groups	3
Allocation ratio	Equal group sizes
Global test	
Total number of periods	7
Length of each period	One year
Survival probs per period (group 1)	0.875 0.766 0.670 0.586 0.513 0.449 0.393
Survival probs per period (group 2)	0.899 0.808 0.726 0.652 0.586 0.527 0.474
Survival probs per period (group 3)	0.899 0.808 0.726 0.652 0.586 0.527 0.474
Number of recruitment periods	5
Number of follow-up periods	2
Method of accrual	Uniform
Recruitment period-weights	1 1 1 1 1 0 0
Hazard ratios as entered (groups 1, 2, 3)	1, .8, .8
Hazard ratios per period (group 1)	1.000 1.000 1.000 1.000 1.000 1.000 1.000
Hazard ratios per period (group 2)	0.800 0.800 0.800 0.800 0.800 0.800 0.800
Hazard ratios per period (group 3)	0.800 0.800 0.800 0.800 0.800 0.800 0.800
Alpha	0.050 (two-sided)
Power (designed)	0.800
Total sample size (calculated)	2084
Expected total number of events	827