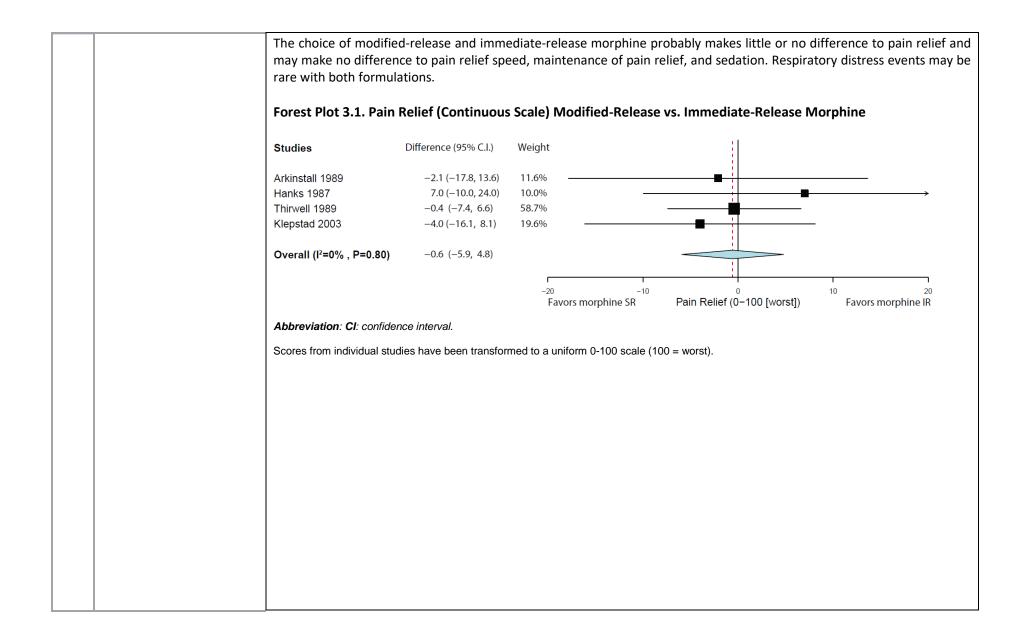
## Evidence-to-Decision table 3.1

In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of administering modified release morphine regularly as compared to immediate release morphine on a 4-hourly or as required basis, in order to maintain effective and safe pain control?

POPULATION:	Adults (including older persons) and adolescents with cancer- related pain	<ul> <li>Background:</li> <li>Clinical staff and patients are often faced with the options of administering modified-release morphine regularly or immediate-release morphine on a 4-hourly basis. There is some debate as to the importance of the differences between the medications<sup>64,65</sup></li> <li>Current WHO recommendation:</li> <li>The 1996 WHO Guidelines discuss the options of a 4-hourly regimen of morphine or slow-release morphine tablets every 12 hours. "The correct dose is the dose that works", though it states that in most patients, pain is controlled with 10-30mg every four hours. Slow release morphine tablets vary in strength between 10mg to 200mg. The analgesic should be given at regular time intervals, not merely when the patient complains of pain. The use of morphine should be dictated by intensity of pain, not by life expectancy.</li> </ul>				
INTERVENTION:	Modified release morphine					
COMPARISON:	Immediate release morphine					
MAIN OUTCOMES:	<ul> <li>Pain relief</li> <li>Pain relief speed</li> <li>Pain relief maintenance</li> <li>Quality of life (QoL)</li> <li>Functional outcomes</li> <li>Sedation (adverse event)</li> <li>Respiratory depression (adverse event)</li> </ul>					
STRATIFICATIONS:	<ul> <li>Age (adults, older persons, adolescents, children)</li> <li>History of substance abuse</li> <li>Refractory pain</li> </ul>					
SETTING: All						
PERSPECTIVE:	Population					

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	Research Evidence         Global consumption of morphine in 2015 was 39.6 tonnes <sup>66</sup> . Both immediate release and modified/extended/slow-release formulations are commonly used in clinical practice. Yet there is some debate as to the importance of the differences between the medications <sup>64,65</sup> .         Additional considerations         WHO should, if possible, provide evidence based guidance on the matter.

	Do the desirable effects outweigh the undesirable effects? Yes No Uncertain Yes	• Ten randomized controlled trials compared modified-release versus immediate-release morphine. The trials generally included all patients with cancer pain. Within trials, participants had either a variety of types of cancer (e.g., breast, prostate, colon, lung, lymphatic, gastric, liver) or the trials did not report cancer types (implying a variety of cancers). Among trials that reported participant ages, trial participants were generally middle-age to older adults (mostly about 40 or 50 to 70 or 90 years old). In all trials, patients being given modified-release morphine were also being offered immediate release morphine as a rescue medication. Therefore, strictly speaking, the comparison is between modified-release morphine with immediate release morphine as rescue medication.
		BENEFITS and HARMS
		<ul> <li>Four trials provided moderate strength of evidence of no difference in pain relief between modified- and immediate-release morphine. Four trials mostly found 100% pain-relief regardless of which modality was used (moderate strength of evidence), yielding a summary RR = 0.99 (95% CI 0.95, 1.03).</li> </ul>
ARMS		<b>Four trials</b> provided <b>moderate strength of evidence</b> of no difference in pain scores. Summary difference in pain scores (transformed to a 0 to 100 [worst]) scale) was -0.6 (95% CI -5.9, 4.8).
S & H/		• One trial provided low strength of evidence of no difference in pain relief speed (difference between arms -0.4 days; 95% Cl -1.1, 0.3).
BENEFITS & HARMS		• One trial provided very low strength of evidence regarding modified-release morphine for improved QoL, with a difference between arms of 9 points (on a transformed scale of 1 to 100 [best]) with 95% CI -6 to 24. We are uncertain of any difference.
		No trial reported on functional outcomes.
		• <b>Two trials</b> provided <b>low strength of evidence</b> of <b>no difference in sedation</b> . Neither trial evaluated the outcome as an adverse event, but rather on a scale. The difference in sedation scores (on a 0 to 100 [worst] was 2.9 (95% CI -14.2, 8.5).
		• Two trials provided low strength of evidence with no respiratory distress events in a small sample of patients.
		STRATIFICATIONS
		<ul> <li>Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons.</li> </ul>
		<ul> <li>Studies provide no data regarding history of substance abuse.</li> </ul>
		Studies provide no data regarading refractory pain.
		SUMMARY



	Is there important	Research Evidence
	uncertainty or variability	None
	about how much people	
10	value the options?	Additional considerations
CES	Major variability	The GDG identified reasons for variability in patient preferences from clinical experience. Some patients prefer modified
PREFERENCES	Yes	release morphine because of the lower pill burden, more even analgesia, and less waking at night. Other patients, however, may prefer a higher pill burden for psychological reasons. In other patients still there may be stigma against certain
_	Minor variability	formulations. This indicates major variability.
ACCEPTABILITY &	Uncertain	The GDG deemed variability in clinicians preferences between the two formulations to be minor, considering there to be no strong reasons for a clinician or other key stakeholder to prefer one over the other.
ACC	Is the option acceptable to key stakeholders?	
	Yes No Uncertair Yes	

	How large are the resource	Research Evidence		r	r			
	requirements?							
	Major Minor Uncertai							
	Yes						0	
			Number of		Price of one 30-Day Opioid Treatment			
	Is the option feasible to implement?		Number of Countries Where	Number of Countries				
			Available	Where				
	Yes No Uncertair	Source: <sup>12</sup>	for Free	Available	Median	IQR	Mean	SD
ш	Yes	Morphine oral immediate release						
ISI		(tablet, capsule)	11	35	\$ 49.70	\$ 80.50	\$ 78.50	\$ 92.00
RCE		Morphine oral slow release			+ = = = = =	A 4 4 9 5 9	+	4 00 70
no O		(tablet, capsule)	15	44	\$ 56.80	\$ 110.50	\$ 83.80	\$ 90.70
SES		Morphine oral (liquid)	9	26	\$ 41.90	\$ 96.50	\$ 67.58	\$ 63.60
FEASIBILITY ./ RESOURCE USE		Morphine injectable (ampoule)	19	49	\$ 88.50	\$ 167.30	\$ 167.20	\$ 225.30
		Fentanyl (transdermal patch)	15	47	\$ 81.20	\$ 263.40	\$ 144.60	\$ 154.10
BL		Methadone oral solid (tablet,					4	
B		capsule)	9	22	\$ 26.50	\$ 38.30	\$ 40.50	\$ 29.10
Ë		Methadone oral (liquid)	9	26	\$ 13.10	\$ 70.90	\$ 58.80	\$ 103.40
		Oxycodone oral immediate release (tablet, capsule)	6	19	\$ 202.90	\$ 156.80	\$ 198.10	\$ 125.20
		Oxycodone oral slow release	0	19	\$ 202.90	\$ 100.00	\$ 198.10	Ş 125.20
		(tablet, capsule)	6	21	\$ 237.20	\$ 473.70	\$ 312.40	\$ 252.10
		Hydromorphone oral immediate			7	Ţ	7	+
		release (tablet, capsule)	2	7	\$ 103.45	\$ 115.60	\$ 78.30	\$ 61.50
		Hydromorphone oral slow release						
		(tablet, capsule)	3	10	\$ 14.97	\$ 89.10	\$ 51.60	\$ 54.90
		Hydromorphone oral (liquid)	0	2	\$ 146.20	NA	\$ 150.30	\$ 146.20
		Hydromorphone injectable	2		ć 101 10		ć 72.20	¢ 101 10
		(ampoule)	2	4	\$ 101.10	NA	\$ 73.20	\$ 101.10

	Additional considerations Typically, modified release formulations are more expensive per dose. It is not clear which formulation is more cost effective.
Would the option improve equity in health?	Research Evidence None
Yes No Uncertai	

Recommendation	<ul> <li>Current recommendation:</li> <li>The 1996 WHO Guidelines discuss the options of a 4-hourly regimen of morphine or slow-release morphine tablets every 12 hours. "The correct dose is the dose that works", though it states that in most patients, pain is controlled with 10-30mg every four hours. Slow release morphine tablets vary in strength between 10mg to 200mg. The analgesic should be given at regular time intervals, not merely when the patient complains of pain. The use of morphine should be dictated by intensity of pain, not by life expectancy.</li> <li>New (draft) recommendation:</li> <li>Regularly-dosed immediate-release oral morphine, or regularly-dosed slow-release morphine should be used for pain relief. With either formulation, immediate-release oral morphine should be used as rescue medication.</li> </ul>			
Strength of Recommendation	Strong			
Quality of Evidence	<ul> <li>MODERATE         [Pain (critical) = moderate (pain relief), low (pain score)         Pain relief speed (important) = low         Pain reduction maintenance (critical) = low         Sedation (adverse event) (important) = low         Other outcomes omitted for no data or inconclusive findings]     </li> </ul>			
Justification	Modified release morphine is typically more expensive and its use probably makes little to no difference to pain relief, pain relief speed, maintenance of pain relief, and sedation. Yet patients sometimes place high option value on the availability of both formulations. The GDG therefore felt that having both modified- and immediate-release morphine available in an oral formulation would be preferred, and either regimen (modified-release for pain relief maintenance with immediate release as rescue medication or immediate-release used for both) could be used. They noted that if a health system must choose between one or the other formulation, immediate-release oral morphine should be chosen as it can be used as both maintenance and rescue medication whereas modified release morphine cannot. The GDG complained that in many settings, especially some low- and middle-income ones, only modified release morphine is available, where a faster release morphine is necessary for breakthrough pain relief. They reported that in some settings, clinical staff are forced to crush up modified release medication in order to make it release more quickly, since immediate release morphine is not available. On occasion, injectable immediate release morphine is available, but this is less appropriate for outpatients.			

The text of the guidelines explains that the regularity of dosing should depend on clinical assessment and the recommendation applies only if the decision to use morphine has been made.

Subgroup considerations

Implementation considerations [incl. M&E]

**Research priorities**