Evidence-to-Decision table 3.2		
In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of using the subcutaneous, transdermal, or transmucosal route as compared to the intramuscular and intravenous routes when the oral route for opioids is inappropriate (e.g. adults (including older persons) and adolescents with diminished consciousness, ineffective swallowing or vomiting) in order to maintain effective and safe pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:** While the default preferred route for administration of opioid medications is the oral route, in some patients, this route may be inappropriate due to dysphagia or vomiting[67]. WHO has not issued evidence-based guidance on which alternative routes are preferred between subcutaneous, transdermal, or transmucosal routes compared with the intramuscular and intravenous routes. Yet these routes are commonly used in clinical practice. **Current WHO recommendation**: The 1996 WHO guidelines suggest that rectal, subcutaneous, intramuscular, spinal, or transdermal administration can be considered when the oral route is inappropriate, such as with dysphagia, common toward the end of life. The subcutaneous route should be considered if the patient is unable to take oral and rectal morphine. Repeated injections should be avoided, and continuous subcutaneous infusion is preferred. If injected, pethidine should be given intramuscularly because it causes tissue irritation. Intravenous injection of morphine can be either bolus injection or continuous infusion. The dose of morphine or other opioid is the same whether given subcutaneously, intramuscularly, or intravenously. In settings with the capacity for spinal administration, the epidural or intrathecal routes can be considered in patients who experience severe adverse effects or whose pain is poorly responsive to opioids. Transdermal fentanyl citrate is a proposed route of administration and it may have good patient compliance. But cost and availability might restrict its use in many settings.
INTERVENTION:	Subcutaneous, transdermal, or transmucosal opioid	
COMPARISON:	Intramuscular and intravenous opioid	
MAIN OUTCOMES:	• Effective cessation of opioid • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Toxicity (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research Evidence** While the default preferred route for administration of opioid medications is the oral route, in some patients, this route may be inappropriate in some patients due to diminished consciousness, ineffective swallowing, or vomiting[67]. **Additional considerations** WHO has not issued evidence-based guidance on which alternative routes are preferred between subcutaneous, transdermal, or transmucosal routes compared with the intramuscular and intravenous routes. Yet these routes are commonly used in clinical practice.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: [ ] No: [ ] Uncertain: [Yes]	• **One randomized controlled trial** compared **subcutaneous vs. intravenous hydromorphone**. The study was conducted in adults with multiple types of cancer who could not tolerate oral or rectal opioids. **BENEFITS and HARMS** • **One trial** provided **very low strength of evidence** of **no difference in pain relief** between subcutaneous and intravenous hydromorphone.[68] • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **sedation**. (One trial found improved sedation with opioid treatments.) • **No trial** reported on **toxicity**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** We are uncertain whether about relative effects between subcutaneous and intravenous hydromorphone.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major ☐ Minor ☐ Uncertain ☒ Yes **Is the option feasible to implement?** Yes ☐ No ☐ Uncertain ☒ Yes	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None
	Would the option improve equity in health? Yes ☐ No ☐ Uncertain ☒ Yes	**<u>Research Evidence</u>** None **<u>Additional considerations</u>** None

Recommendation	**Current recommendation:** • The 1996 WHO guidelines suggest that rectal, subcutaneous, intramuscular, spinal, or transdermal administration can be considered when the oral route is inappropriate, such as with dysphagia, common toward the end of life. • The subcutaneous route should be considered if the patient is unable to take oral and rectal morphine. Repeated injections should be avoided, and continuous subcutaneous infusion is preferred. • If injected, pethidine should be given intramuscularly because it causes tissue irritation. • Intravenous injection of morphine can be either bolus injection or continuous infusion. • The dose of morphine or other opioid is the same whether given subcutaneously, intramuscularly, or intravenously. • In settings with the capacity for spinal administration, the epidural or intrathecal routes can be considered in patients who experience severe adverse effects or whose pain is poorly responsive to opioids. • Transdermal fentanyl citrate is a proposed route of administration and it may have good patient compliance. But cost and availability might restrict its use in many settings. **New (draft) recommendation:** None
Strength of Recommendation	**None**
Quality of Evidence	➢ Very Low [Pain relief (critical) = very low Other outcomes omitted for no data]
Justification	The GDG could not make a new recommendation on the basis of the low quality and amount of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	