APPENDIX

Table of contents:

Complete list of questions proposed by the panel

Question(s)
In men presenting with erectile dysfunction, does X compared to sham/placebo improve important and critical outcomes? X being: 1) PDE5, 2) VED, 3) IU alprostadil, 4) ICI, 5) Penile prosthesis, 6) Vascular reconstruction, 7) Extracorporeal shock wave therapy (ESWT), 8) Platelet-rich-plasma (PRP), 9) Referral to a mental health professional, 10) Stem cell therapy, 11) Testosterone replacement therapy
In patients with ED receiving PDE-5i who are non-responsive after 3 treatment trials, does performing a 4th PDE-5i trial before proceeding to the next line of treatment result in improvement in important and critical outcomes when compared with directly proceeding to next line of treatment?
In patients presenting with ED, does referring patients over 45 years of age with a family history of CVD to a cardiologist result in fewer cardiovascular events over 1 year when compared with referring any patient over 45 years of age?
In men presenting with ED, does lifestyle modification result in improvement in important and critical outcomes when compared to no lifestyle modification? Life style modifications: 1)Increased physical activity 2)Smoking cessation 3)Healthy diet
Is assessing testosterone levels performed on men presenting with ED more effective than not assessing testosterone levels in improving patient-important outcomes?
In men with ED decided to receive PDE-5i, does daily administration of a PDE-5i result in improvement in important and critical outcomes when compared with on-demand administration of a PDE-5i?
In men presenting with ED, does administration of penile duplex ultrasound result in improvement in important and critical outcomes when compared with sham procedure?
In men who had RP or radiation therapy for prostate cancer, does penile rehabilitation result in improvement in important and critical outcomes when compared with no rehabilitation?
In men with ED who watch pornography, does pornography watching cessation result in improvement in important and critical outcomes compared to no cessation?

Analysis of Efficacy and Harms of Phosphodiesterase 5 Inhibitors

TABLE 1. SUMMARY OF FINDINGS:

PDE5Is compared to placebo for erectile dysfunction

Patient or population: erectile dysfunction
Setting:
Intervention: PDE5Is
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with PDE5Is**				
Erectile function (tadalafil) assessed with: International Index of Erectile Function- Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED)	The mean erectile function (tadalafil) was **0.7**	MD **8.07 higher** (7.18 higher to 8.96 higher)	-	1877 (8 RCTs)	⨁⨁⨁⨁ HIGH	As the evidence demonstrates, tadalafil can lead to an IIEF-EF score increase of 8.07 points compared to the placebo (from 7.18 to 8.96). Since the panel decided the threshold for a large effect on erectile function in this domain is 6, we believe that tadalafil results in a large increase in erectile function.
Erectile function (Sildenafil) assessed with: International Index of Erectile Function- Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED)	The mean erectile function (Sildenafil) was **2.5**	MD **6.03 higher** (5.38 higher to 6.68 higher)	-	3404 (12 RCTs)	⨁⨁⨁⨁ HIGH	Similar to tadalafil, based on the determination of 5 units as moderate and 6 units as large effect, we believe that sildenafil results in a large increase in erectile function. Patients receiving sildenafil experienced 6.03 units larger increase in their erectile function scores compared to placebo (from 5.38 to 6.68 units higher).
Adverse events (tadalafil) assessed with: Number of participants with at least one adverse event	387 per 1,000	**527 per 1,000** (379 to 736)	**RR 1.36** (0.98 to 1.90)	760 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	The evidence suggests that on average 140 more people out of every 1000 will experience any adverse event when receiving tadalafil compared to placebo (confidence interval from 8 fewer to 349 more). We believe that this effect estimate for this outcome falls in the small category. Therefore, tadalafil probably increases adverse events slightly.
Adverse events (sildenafil) assessed with: Number of participants with at least one adverse event	303 per 1,000	**476 per 1,000** (409 to 555)	**RR 1.57** (1.35 to 1.83)	3390 (18 RCTs)	⨁⨁⨁⨁ HIGH	The evidence suggests that on average 173 more people out of every 1000 will experience any adverse event when receiving sildenafil compared to placebo (confidence interval from 106 more to 252 more). We believe that this effect estimate for this outcome falls in the small category. Therefore, sildenafil probably increases adverse events slightly.

TABLE 1. SUMMARY OF FINDINGS:

PDE5Is compared to placebo for erectile dysfunction

Patient or population: erectile dysfunction
Setting:
Intervention: PDE5Is
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PDE5Is				
Serious or severe adverse events (tadalafil)	16 per 1,000	**23 per 1,000** (10 to 54)	**RR 1.46** (0.63 to 3.37)	1967 (8 RCTs)	⨁⨁⨁⨁ HIGH	The evidence suggests that on average 7 more people out of every 1000 will experience a serious adverse event when receiving tadalafil compared to placebo (confidence interval from 6 fewer to 38 more). We believe that this effect estimate for this outcome falls in the trivial category. Therefore, tadalafil probably does not increases adverse events.
Serious or severe adverse events (sildenafil)	20 per 1,000	**28 per 1,000** (14 to 58)	**RR 1.38** (0.67 to 2.83)	2431 (10 RCTs)	⨁⨁⨁⨁ HIGH	The evidence suggests that on average 8 more people out of every 1000 will experience a serious adverse event when receiving tadalafil compared to placebo (confidence interval from 6 fewer to 38 more). We believe that this effect estimate for this outcome falls in the trivial category. Therefore, sildenafil probably does not increase adverse events.
Treatment discontinuation due to adverse events (sildenafil)	14 per 1,000	**22 per 1,000** (13 to 36)	**RR 1.51** (0.90 to 2.52)	3479 (13 RCTs)	⨁⨁⨁⨁ HIGH	The evidence suggests that on average 8 more people out of every 1000 will discontinue treatment due to adverse events when receiving sildenafil compared to placebo (confidence interval from 1 fewer to 22 more). We believe that this effect estimate for this outcome falls in the trivial category. Therefore, sildenafil probably does not increase treatment discontinuation.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Due to the limited number of events observed and wide confidence interval, we decided to rate down by one level for imprecision.

TABLE 2. EVIDENCE TO DECISION FRAMEWORK:

QUESTION

Should PDE5Is vs. placebo be used for erectile dysfunction?	
POPULATION:	erectile dysfunction
INTERVENTION:	PDE5Is
COMPARISON:	placebo
MAIN OUTCOMES:	Erectile function (tadalafil); Erectile function (Sildenafil); Adverse events (tadalafil); Adverse events (sildenafil); Serious or severe adverse events (tadalafil); Serious or severe adverse events (sildenafil); Treatment discontinuation due to adverse events (sildenafil);
SETTING:	Urology clinics
PERSPECTIVE:	Patients
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	Please refer to the methods section of the main guideline text on the selection of the questions. All the chosen questions were considered of priority.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Summary of Findings (SoF) table for PDE5Is versus placebo for erectile dysfunction	None

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Summary of Findings (SoF) table for PDE5Is versus placebo for erectile dysfunction	None

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Summary of Findings (SoF) table for PDE5Is versus placebo for erectile dysfunction	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Unfortunately, to the best of our knowledge, studies that investigate how erectile dysfunction patients value the main outcomes of our guideline are currently unavailable.	The panel relied on its extensive shared decision-making experience to discuss how the patients value the outcomes in question. After much deliberation, the panel unanimously concluded that there probably is no important uncertainty or variability among the patients on how they value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	Summary of Findings (SoF) table for PDE5Is versus placebo for erectile dysfunction	Considering the magnitudes of effect estimates and the certainty in the evidence, the panel believes that the balance of effects favors the intervention. Eight members voted for favors the intervention and one voted for probably favors the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost of on-demand tadalafil can be prohibitive as such, daily consumption can be further prohibitive to many Canadians (https://www.canadadrugsdirect.com/products/cialis/5mg).	PDE 5 inhibitors are often not covered by government and private drug plans, resulting in a direct cost to the patient. At a cost of over $20 per use, these medications can be prohibitively expensive for patients with limited finances. The panel members voted for moderate costs and negligible costs and savings eight and one times respectively.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	None	Considering the source of evidence, the panel believes that the current certainty of the required resources evidence is low.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	A 2019 review study identified 12 studies in the last ten years that evaluated the economic outcomes associated with the use of sildenafil for erectile dysfunction (PMID: **23347555**). The study indicates that no cost-effectiveness models have been published on the general ED population, however, the cost effectiveness models in populations with comorbidities and the incremental cost effectiveness ratios compared to other interventions such as cavernosal injections, vacuum devices, surgery, and other oral medications proved the superiority of sildenafil. Specifically, the Canadian study evaluated a model among erectile dysfunction patients with spinal cord injury which found the medication to be cost-effective (PMID: **16287667**).	Since the data from the acquired review was not directly addressing a general erectile dysfunction, the panel voted for probably favors the intervention.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	None	The panel considered the costs associated with the use of PDE5Is currently in the country and unanimously concluded that this intervention probably reduces the equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	The panel unanimously considers the intervention in question to be acceptable to all the stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	The panel unanimously considers the intervention in question to be feasible to be implemented, as already has been.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Recommendation 1: Daily vs. On-demand Tadalafil

TABLE 3. SUMMARY OF FINDINGS:

Daily tadalafil compared to on-demand tadalafil for erectile dysfunction

Patient or population: erectile dysfunction
Setting:
Intervention: daily tadalafil
Comparison: on-demand tadalafil

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with on-demand tadalafil	Risk with daily tadalafil				
Erectile function assessed with: International Index of Erectile Function-Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED) follow up: range 8 weeks to 12 weeks	The mean erectile function was **20.8**	MD **0.8 higher** (0.32 lower to 1.93 higher)	-	1498 (8 RCTs)	⨁⨁⨁◯ MODERATE [a]	Our results suggest that patients on daily tadalafil might have 0.8 units higher erectile function scores compared to those receiving on-demand doses. However, the confidence intervals indicate that this change can be as bad as 0.32 units lower to 1.93 higher. Also, as the established minimal important difference (MID) for the questionnaire used is 4 units, our confidence interval width excludes the MID. Therefore, daily tadalafil likely results in little to no difference in erectile function.
Adverse events assessed with: Number of participants with at least one adverse event follow up: range 8 weeks to 12 weeks	196 per 1,000	**194 per 1,000** (151 to 249)	**RR 0.99** (0.77 to 1.27)	1377 (5 RCTs)	⨁⨁⨁◯ MODERATE [b]	According to the findings of our meta-analysis, in every 1000 patients receiving daily tadalafil, 2 fewer people experience adverse events compared to on-demand dose (confidence interval from 53 more people to 45 fewer). As this difference is trivial and the confidence interval covers no effect, the evidence suggests that daily tadalafil does not reduce adverse events. However, since the certainty in the evidence is low, it is likely that the true effect size is considerably different.
Discontinuation due to adverse events follow up: range 8 weeks to 12 weeks	26 per 1,000	**36 per 1,000** (18 to 76)	**RR 1.41** (0.68 to 2.95)	935 (3 RCTs)	⨁◯◯◯ VERY LOW [c,d]	The evidence is very uncertain about the effect of daily tadalafil on discontinuation due to adverse events. A small number of discontinuations were observed due to lack of sufficient sample size and our confidence interval ranges from significant harm to considerable benefit.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

TABLE 3. SUMMARY OF FINDINGS:

Daily tadalafil compared to on-demand tadalafil for erectile dysfunction

Patient or population: erectile dysfunction
Setting:
Intervention: daily tadalafil
Comparison: on-demand tadalafil

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with on-demand tadalafil	**Risk with daily tadalafil**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Most of the included trials were at a high or unclear risk of bias in more than one domain. Only one study with 15 % of the weight was at low risk of bias. Therefore, we decided to rate down by one level for risk of bias.
b. All of the included studies, except one, are at a high risk of bias. The only study at a low risk of bias only builds up less than 40% of analysis weight. However, the pooled effect estimate overlaps this study confidence interval. Therefore, we decided to rate down certainty by one level for the risk of bias.
c. Since more than 50% of the analysis weight comes from one study that included prostate cancer patients, we decided to rate down our certainty by one level for indirectness.
d. Only 29 events were observed across the studies and the confidence interval includes serious harm to significant benefit. Therefore, we decided to rate down our certainty by two levels for imprecision.

TABLE 4. EVIDENCE TO DECISION FRAMEWORK:

Should daily tadalafil vs. on-demand tadalafil be used for erectile dysfunction?	
POPULATION:	erectile dysfunction
INTERVENTION:	daily tadalafil
COMPARISON:	on-demand tadalafil
MAIN OUTCOMES:	Erectile function; Adverse events; Discontinuation due to adverse events;
SETTING:	Urology clinics
PERSPECTIVE:	Patients
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	Please refer to the methods section of the main guideline text on the selection of the questions. All the chosen questions were considered of priority.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Summary of Findings (SoF) table: Daily tadalafil versus on-demand tadalafil for erectile dysfunction.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Summary of Findings (SoF) table: Daily tadalafil versus on-demand tadalafil for erectile dysfunction.	None

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Summary of Findings (SoF) table: Daily tadalafil versus on-demand tadalafil for erectile dysfunction.	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Unfortunately, our panel was unable to find any studies addressing this area. A panel member was tasked with searching the literature for pertinent evidence in each domain.	Our panel believes, based on their shared decision-making experience, that possibly important uncertainty or variability exists among patients regarding how they would value the outcomes in consideration. Six members voted possibly important uncertainty and three members voted important uncertainty or variability.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	See the SoF table and Values above.	Considering the desirable and undesirable effects alongside the judgment of the panel on values and preferences, 5 members believed that the effects do not favor either of the options while 4 other members stated that

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost of on-demand tadalafil can be prohibitive as such, daily consumption can be further prohibitive to many Canadians (https://www.canadadrugsdirect.com/products/cialis/5mg).	Considering the anecdotal evidence, the panel believes that the choice of daily tadalafil will pose a moderate cost to the patients from their view compared to on-demand tadalafil. Seven members agreed to moderate costs while the other two considered the costs and savings negligible.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	None	Since the evidence on the required resources is anecdotal, panel unanimously agreed on a very low quality of evidence for this domain.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Unfortunately, our search did not yield any cost effectiveness studies addressing this particular question.	Considering the costs and the balance of desirable and undesirable effects, eight members voted for probably favours comparison while the remaining member chose does not favor either the intervention or the comparison.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	To the best of our knowledge, studies addressing equity in ED are lacking.	Our panel, considering their patients, concluded that this intervention probably reduces equity since the costs needed to implement this intervention for the patients probably will not increase their utility. Six members voted for probably reduced and the rest for probably no impact.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Unfortunately, our search did not yield any acceptability studies addressing the use of PDE5Is.	The panel considers that daily dosing of tadalafil is probably acceptable to all of the key stakeholders compared to on-demand dosing. Only one member voted for yes compared to probably yes.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Unfortunately, our search did not yield any feasibility studies addressing the use of PDE5Is.	The panel considers that the implementation of daily dosing of tadalafil is probably feasible compared to on-demand dosing. Only one member voted for yes compared to probably yes.

SUMMARY OF JUDGEMENTS

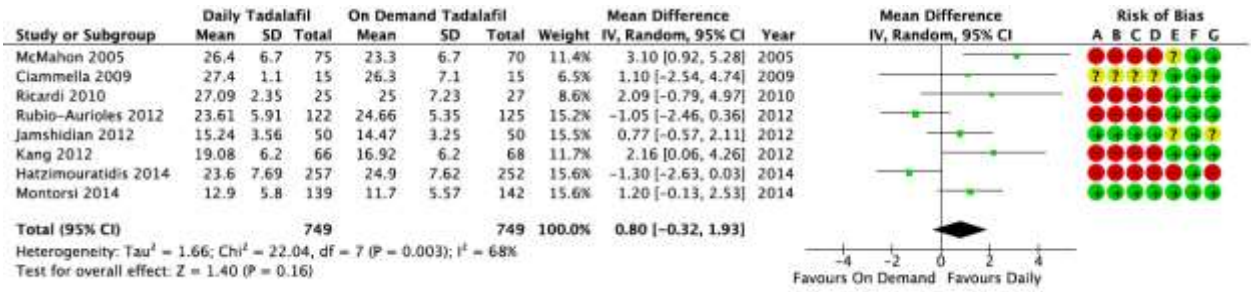
	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies

	JUDGEMENT						
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

FIGURE 1. FOREST PLOT:
DAILY TADALAFIL VS. ON-DEMAND TADALAFIL, OUTCOME: ERECTILE FUNCTION

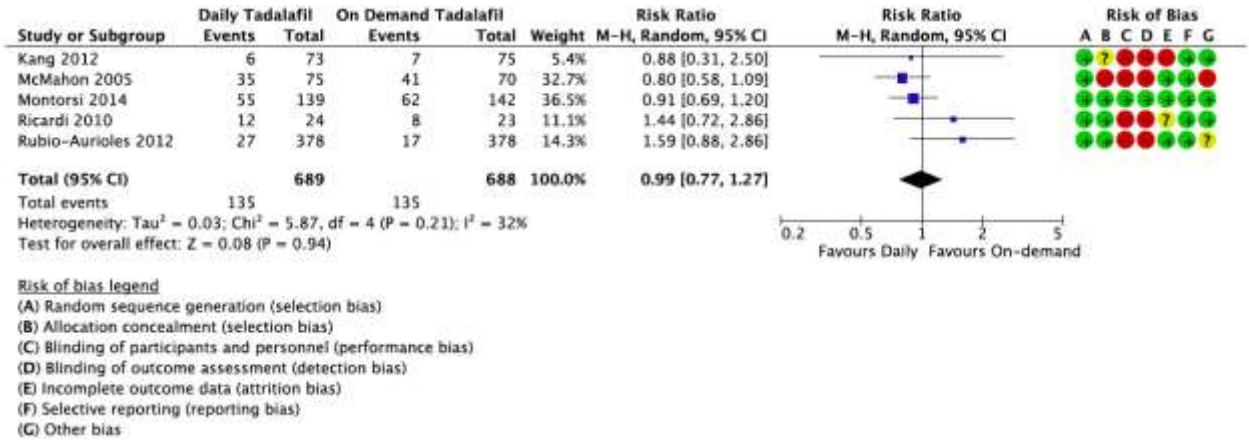


Study or Subgroup	Daily Tadalafil Mean	SD	Total	On Demand Tadalafil Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
McMahon 2005	26.4	6.7	75	23.3	6.7	70	11.4%	3.10 [0.92, 5.28]	2005
Ciammella 2009	27.4	1.1	15	26.3	7.1	15	6.5%	1.10 [-2.54, 4.74]	2009
Ricardi 2010	27.09	2.35	25	25	7.23	27	8.6%	2.09 [-0.79, 4.97]	2010
Rubio-Aurioles 2012	23.61	5.91	122	24.66	5.35	125	15.2%	-1.05 [-2.46, 0.36]	2012
Jamshidian 2012	15.24	3.56	50	14.47	3.25	50	15.5%	0.77 [-0.57, 2.11]	2012
Kang 2012	19.08	6.2	66	16.92	6.2	68	11.7%	2.16 [0.06, 4.26]	2012
Hatzimouratidis 2014	23.6	7.69	257	24.9	7.62	252	15.6%	-1.30 [-2.63, 0.03]	2014
Montorsi 2014	12.9	5.8	139	11.7	5.57	142	15.6%	1.20 [-0.13, 2.53]	2014
Total (95% CI)			**749**			**749**	**100.0%**	**0.80 [-0.32, 1.93]**	

Heterogeneity: $Tau^2 = 1.66$; $Chi^2 = 22.04$, df = 7 (P = 0.003); $I^2 = 68\%$
Test for overall effect: Z = 1.40 (P = 0.16)

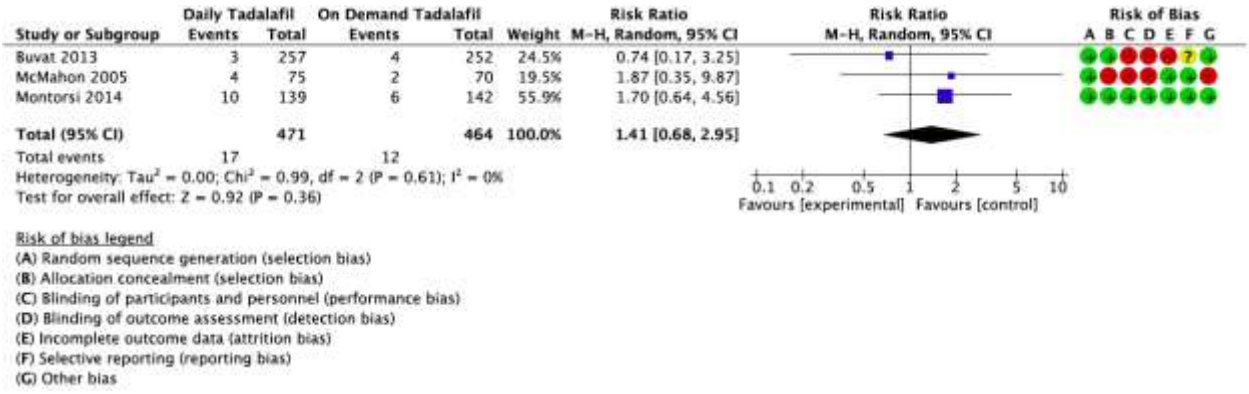
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE 2. FOREST PLOT:
DAILY TADALAFIL VS. ON-DEMAND TADALAFIL, OUTCOME: ADVERSE EVENTS



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE 3. FOREST PLOT:
DAILY TADALAFIL VS. ON-DEMAND TADALAFIL, OUTCOME: DISCONTINUATION



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Recommendation 2: Extracorporeal Shockwave Therapy (ESWT)

TABLE 5. SUMMARY OF FINDINGS:

ESWT compared to Sham for Erectile Dysfunction

Patient or population: Erectile Dysfunction
Setting:
Intervention: ESWT
Comparison: Sham

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Sham	**Risk with ESWT**				
Erectile Function assessed with: International Index of Erectile Function- Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED) follow up: mean 1 months	The mean erectile Function was **13.4**	MD **2.07 higher** (0.19 higher to 3.96 higher)	-	277 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	Currently, the established minimal clinically important difference on the IIEF-ED scale is believed to be 4 units for erectile dysfunction. Our findings suggest that ESWT leads to 2.07 units improvement in erectile function score compared to sham. However, the confidence interval indicates that this improvement can be as low as 0.19 units to as high as 3.96. Therefore, considering our certainty in the evidence, ESWT probably results in little to no difference in erectile function.
Sexual Quality of Life assessed with: SQoL-M	The mean sexual Quality of Life was **43.3**	MD **2.1 higher** (7.9 lower to 12.1 higher)	-	118 (1 RCT)	⨁◯◯◯ VERY LOW [b]	The evidence is very uncertain about the effect of ESWT on sexual quality of life. Our effect estimate originates from only one study with limited sample size and at a high risk of bias. Therefore, any conclusion regarding this outcome is very uncertain.
Adverse Events	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 1** (1 to 1)	(4 RCTs)	⨁◯◯◯ VERY LOW [c]	None of the trials investigating the effects of ESWT on erectile dysfunction reported any adverse events other than mild penile burning sensation. However, more robust methods of capturing adverse events are required to inform our effect estimate.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. In this effect size estimate calculation, we included 4 studies that were not at a high risk of bias. Individual study effect sizes were slightly inconsistent ranging from small harm to small but important benefit according to the established minimal clinically important difference of 4 units on the IIEF-ED domain. We also observed an I

squared pf 58%. Finally, a total of fewer than 300 participants included poses a concern in the imprecision domain, however, the confidence interval lies totally in the small but not important effect area. Therefore, we decided to rate down only by one level combined for inconsistency and imprecision.
b. The results are from a single study where the sham group participants received 4 weeks of the sham procedure and 4 weeks of ESWT, while the active treatment group participants received 8 weeks of ESWT. The results are imprecise and at risk of bias, especially for selective reporting of outcomes and allocation concealment. Moreover, since a systematic review for this outcome is lacking publication bias cannot be ruled out. Therefore, we decided to rate down the certainty of the evidence for imprecision, risk of bias, and publication bias.
c. No well-conducted, comparative study with reliable methods to capture this outcome was found.

TABLE 6. EVIDENCE TO DECISION FRAMEWORK:

Should ESWT vs. Sham be used for Erectile Dysfunction?	
POPULATION:	Erectile Dysfunction
INTERVENTION:	ESWT
COMPARISON:	Sham
MAIN OUTCOMES:	Erectile Function; Sexual Quality of Life; Adverse Events;
SETTING:	Urology clinics
PERSPECTIVE:	Patients
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	Please refer to the methods section of the main guideline text on the selection of the questions. All the chosen questions were considered of priority.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Summary of Findings (SoF) table: ESWT vs. Sham for erectile dysfunction question	The minimal clinically significant change in IIEF score ranges depending on the baseline IIEF score. The range of change in IIEF in our evaluation can be as high as 3.96, which for patients with mild to moderate ED, would be clinically significant and therefore these patients may perceive this outcome to be positive

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Summary of Findings (SoF) table: ESWT vs. Sham for erectile dysfunction question	The trials investigating LiESWT for erectile dysfunction did not use rigorous methods to evaluate adverse events associated with this intervention.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Summary of Findings (SoF) table: ESWT vs. Sham for erectile dysfunction question	**When excluding the studies with a high risk of bias, the mean difference in IIEF between LiESWT and placebo is 2.07, which is not considered clinically significant.** **While analyzing the data, the panel noticed that sufficient data was available to include studies, not at a high risk of bias, as a separate analysis. After extended debate as to which analysis to be considered the main reference, the panel decided, since the exclusion of studies at a high risk of bias provides higher certainty of the evidence, to use this effect estimate. It is noteworthy that the inclusion of all studies yielded a slightly higher effect estimate that would overlap the clinically small but important range in erectile function improvement with low certainty of the evince.**

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Unfortunately, we were unable to locate any study addressing the values and preferences of patients with erectile function relevant to this question. Panel members were tasked to search the literature for pertinent studies.	Considering their extensive shared decision-making with patients, the panel members believe that possibly important uncertainty or variability exists regarding how patients value the outcomes. The panel was unanimous.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Summary of Findings (SoF) table: ESWT vs. Sham for erectile dysfunction question	Five members voted for does not favor either while the other four voted for probably favors the comparison.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	device: 50'000 to There is no scientific evidence available that formally analyzes or discusses the cost associated with LiESWT from a patient or provider standpoint. Upon discussion with providers currently offering this service within Canada, the LiESWT machine and maintenance costs can range from 50,000 – 75,000 per 3-year contract. In addition, the estimated cost for a patient to receive a full treatment can range from $3000-$5000. This data is based on a non-systematic review from a select group of providers and therefore this range could be much larger in the general population.	Considering the anecdotal evidence, the panel was unanimous that this cost is considered large.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	We have a very limited available of resources available to determine resource cost. The data gathered for the purpose of discussion for this guideline was based on a non-systematic review of provider practices. There is no available data exploring cost to Canadian health care system or to patients regarding LiESWT for ED.	None.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	LIESWT is currently not a covered procedure and therefore patients pursuing this treatment, outside of a clinical study, would need to pay for this technology out of pocket. There is no available cost-effectiveness data available for this technology.	Although cost-effectiveness evidence from the literature is absent for LiESWT, considering the trivial benefits and the high probable cost for both providers and patients, the panel unanimously voted for favors the comparison.

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	None	At this time LiESWT is not an intervention covered by the government or insurance companies. Patients unable to pay for this intervention would not have equal access. Also, there are a limited number of clinics in Canada, and therefore unless patients live in relative proximity to these centers, they would not have access to this technology. All panel members voted for reduced except two who voted for probably reduced.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	There is no systematic research exploring patient acceptability.	Based on group discussion from the panel of experts, it is felt that this technology is considered to be acceptable when performed under the supervision of a clinical trial. However, in a clinical setting, the panel felt that, at this time, implementation of this intervention is probably not acceptable by either providers or patients in general. The vote was unanimous.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	here is no systematic research exploring the feasibility of using LiESWT for erectile dysfunction.	This technology is not currently widely available in Canada. The panel of experts felt that implementing this technology in routine patient care is not currently feasible due to the lack of evidence and patient perspective of treatment outcomes alongside the implementation and maintenance costs. Seven members voted for probably no and two for no in this domain.

SUMMARY OF JUDGEMENTS

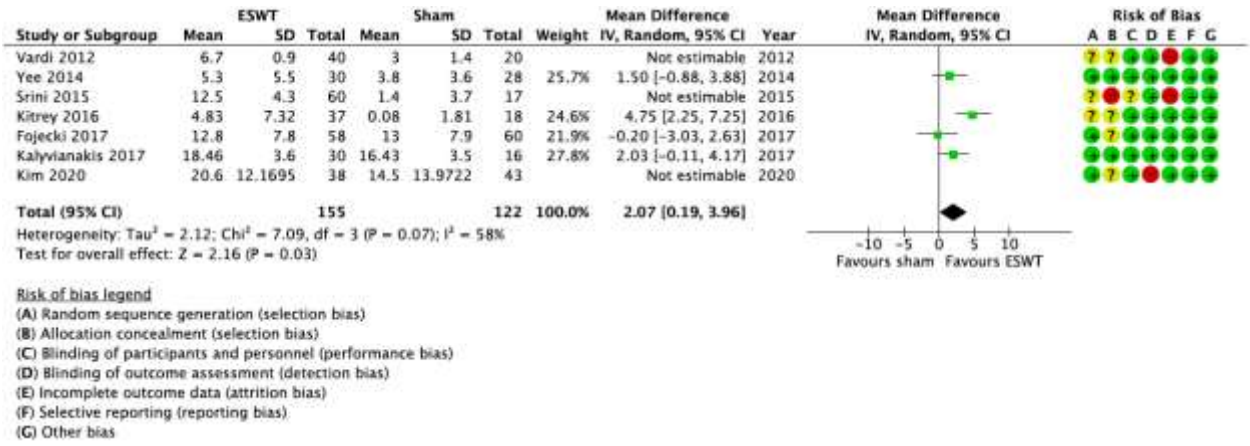
	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

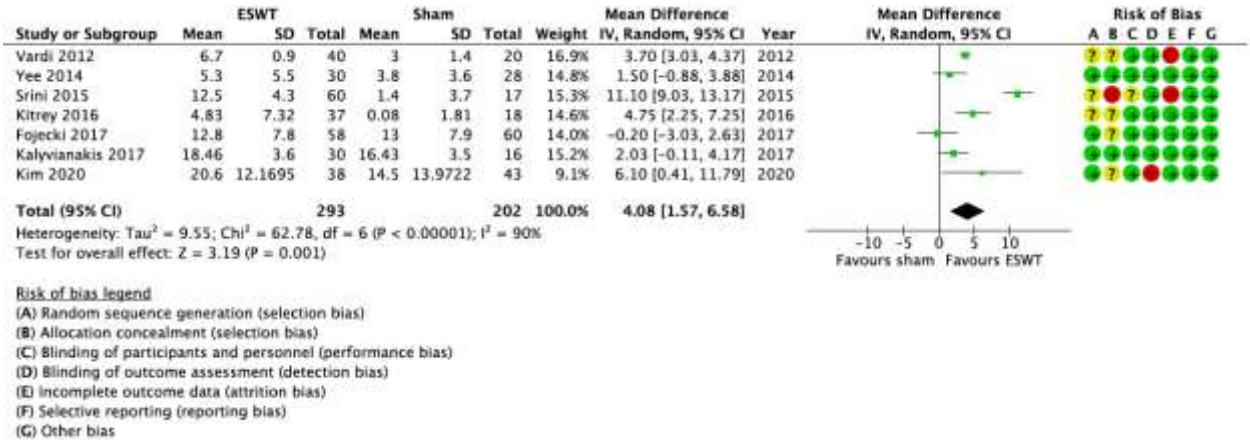
Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

FIGURE 4. FOREST PLOT:
ESWT VS. SHAM, OUTCOME: ERECTILE FUNCTION, STUDIES NOT A HIGH RISK OF BIAS



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE 5. FOREST PLOT:
ESWT VS. SHAM, OUTCOME: ERECTILE FUNCTION, ALL STUDIES



Study or Subgroup	ESWT Mean	ESWT SD	ESWT Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Random, 95% CI	Year
Vardi 2012	6.7	0.9	40	3	1.4	20	16.9%	3.70 [3.03, 4.37]	2012
Yee 2014	5.3	5.5	30	3.8	3.6	28	14.8%	1.50 [-0.88, 3.88]	2014
Srini 2015	12.5	4.3	60	1.4	3.7	17	15.3%	11.10 [9.03, 13.17]	2015
Kitrey 2016	4.83	7.32	37	0.08	1.81	18	14.6%	4.75 [2.25, 7.25]	2016
Fojecki 2017	12.8	7.8	58	13	7.9	60	14.0%	-0.20 [-3.03, 2.63]	2017
Kalyvianakis 2017	18.46	3.6	30	16.43	3.5	16	15.2%	2.03 [-0.11, 4.17]	2017
Kim 2020	20.6	12.1695	38	14.5	13.9722	43	9.1%	6.10 [0.41, 11.79]	2020
Total (95% CI)			**293**			**202**	**100.0%**	**4.08 [1.57, 6.58]**	

Heterogeneity: $Tau^2 = 9.55$; $Chi^2 = 62.78$, df = 6 ($P < 0.00001$); $I^2 = 90\%$
Test for overall effect: Z = 3.19 (P = 0.001)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Recommendation 3: Testosterone Replacement Therapy (TRT)

TABLE 7. SUMMARY OF FINDINGS:

Testosterone therapy compared to placebo for hypogonadal men

Patient or population: hypogonadal men
Setting:
Intervention: testosterone therapy
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with testosterone therapy**				
IIEF-EF assessed with: International Index of Erectile Function- Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED) follow up: range 3 months to 12 months	The mean IIEF-EF was **10.3**	MD **2.65 higher** (0.81 higher to 4.48 higher)	-	916 (6 RCTs)	⨁⨁⨁◯ MODERATE [a]	Our analysis suggests that hypogonadal men receiving testosterone therapy have 2.65 units higher average compared to placebo on the erectile function domain of the IIEF questionnaire. This difference can be from 0.81 units higher to 4.48 units higher. As the established minimum important difference (MID) for this scale is 4, we can consider 2.56 a clinically unimportant improvement. Therefore, testosterone therapy likely results in little to no difference in erectile function.
Quality of life assessed with: AMS, SF36, and self assessment (Lower numbers represent improvement in QoL) follow up: range 12 weeks to 36 months	-	SMD **0.26 SD lower** (0.41 lower to 0.11 lower)	-	2834 (21 RCTs)	⨁⨁◯◯ LOW [b,c]	As an established MID for all the various measures is not currently in hand, we decided to use the standardized mean difference to calculate the pooled effect estimate. We then used the standard deviation from the most relevant trial to recalculate the estimate on the AMS scale. Testosterone therapy can improve AMS score 2.7 units (from 1.1 better to 4.3 better) compared to placebo.
Serious adverse events follow up: range 12 weeks to 3 years	88 per 1,000	**79 per 1,000** (64 to 97)	**OR 0.88** (0.70 to 1.11)	4040 (18 RCTs)	⨁⨁⨁◯ MODERATE [d]	Our findings suggest that out of every 1000 patients who receive testosterone, 9 fewer people (from 24 fewer to 9 more) experience serious adverse events compared to placebo. Therefore, testosterone therapy likely results in little to no difference in serious adverse events.

TABLE 7. SUMMARY OF FINDINGS:

Testosterone therapy compared to placebo for hypogonadal men

Patient or population: hypogonadal men
Setting:
Intervention: testosterone therapy
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with testosterone therapy**				
Discontinuation due to adverse events follow up: range 4 months to 36 months	59 per 1,000	**70 per 1,000** (58 to 98)	**OR 1.21** (0.98 to 1.73)	5391 (48 RCTs)	⨁⨁◯◯ LOW [d,e]	Our findings suggest that out of every 1000 patients who receive testosterone, 11 more people (from 1 fewer to 39 more) will discontinue treatment due to adverse events compared to placebo. Therefore, testosterone therapy may increase discontinuation due to adverse events slightly.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The effect estimates from various studies showed values that represented both greater than and below MID, also the CI interval of the pooled effect estimate passes the MID. Therefore, we decided to rate down by one level for inconsistency and imprecision.
b. Evaluation of the heterogeneity of effect estimates through visual inspection and statistical indices revealed a substantial heterogeneity. One of the studies at low risk of bias demonstrated a harmful effect for testosterone replacement. Therefore, we decided to rate down by one level for inconsistency.
c. As the upper and lower limits of the confidence interval warrants different recommendations, we decided to rate down by one level for imprecision.
d. As the extremes of the pooled effect estimate warranted different recommendations, we decided to rate down by one level for imprecision.
e. Only a few of the included studies were at low risk of bias. Therefore, we decided to rate down by one level for the risk of bias.

TABLE 8. EVIDENCE TO DECISION FRAMEWORK:

Should testosterone therapy vs. placebo be used for hypogonadal men with erectile dysfunction?	
POPULATION:	hypogonadal men
INTERVENTION:	testosterone therapy
COMPARISON:	placebo
MAIN OUTCOMES:	IIEF-EF; Quality of life; Serious adverse events; Discontinuation due to adverse events;
SETTING:	Urology clinics
PERSPECTIVE:	Patients
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	Please refer to the methods section of the main guideline text on the selection of the questions. All the chosen questions were considered of priority.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Summary of Findings (SoF) table for testosterone replacement therapy for erectile dysfunction While current evidence does not support the use of testosterone as monotherapy for erectile dysfunction, there is evidence to support its use as combination therapy to "salvage" patients who have failed phosphodiesterase inhibitors. Therefore, we also undertook a meta-analysis of three randomized trials investigating the addition of testosterone to PDE5Is in patients who did not respond to PDE5Is alone. This, similarly, resulted in an MD effect estimate for improvement in IIEF-EF	Furthermore, while not substantiated as a significant treatment for erectile dysfunction, testosterone therapy has been shown in robust randomized control trials to effectively treat other symptoms of Testosterone Deficiency Syndrome including low libido Considering the data, 6 panel-members voted for trivial and 3 for small.

	score of 1.68[0.30, 3.07] which also falls into the statistically significant bud clinically insignificant. Our certainty in this effect estimate is low.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Summary of Findings (SoF) table for testosterone replacement therapy for erectile dysfunction	There is ongoing controversy regarding the risk of cardiovascular events occurring in men taking testosterone therapy. Four studies of varying quality have demonstrated an increased risk of cardiovascular events. Furthermore, the use of testosterone is associated with additional treatment burdens including routine surveillance of PSA levels and digital rectal exams to evaluate for prostate cancer since the possibility of a relationship is not ruled out. Ongoing prostate cancer screening in populations that would not normally undergo screening may lead to unnecessary anxiety and further investigations such as prostate biopsy (with its own inherent risks). Also, Testosterone therapy is contraindicated in men with a history of prostate or breast cancer, and those desiring future fertility. Finally, considering the evidence and the additional considerations, the panel felt that testosterone therapy has small undesirable effects. The vote was six to three between small and trivial.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Summary of Findings (SoF) table for testosterone replacement therapy for erectile dysfunction	Seven members voted for low while two voted for moderate.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Unfortunately, although some evidence suggests that treatment of erectile dysfunction improves utility measures, we were unable to locate any studies addressing how the patients would value the outcomes in question.	The panel unanimously considered a possibly important uncertainty or variability among the patients on how they would value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Summary of Findings (SoF) table for testosterone replacement therapy for erectile dysfunction	Relying on their extensive shared decision-making experience, 7 members believed that the balance of effects probably favors the comparison while the remaining 2 felt that it does not favor either. Additional considerations should be made for patients who have failed phosphodiesterase inhibitors and for men with symptomatic hypogonadism that are seeking testosterone therapy for symptoms related to low testosterone such as patients with low libido that have concomitant erectile dysfunction.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	None	Testosterone therapy can be delivered in various methods with significant differences in costs. There is no current Canadian evidence that has explored the specific patient and system costs of testosterone treatment. We feel the costs associated with testosterone therapy are significant and include the cost of treatment itself, ongoing laboratory testing (testosterone, PSA, and hemoglobin), and the costs associated with investigations and treatment related to monitoring (for example, prostate biopsy and phlebotomy). Testosterone therapy, if it is effective in relieving symptoms, is often a long-term or life-long therapy, and therefore the costs of treatment will be additive over many years. Therefore, the panel unanimously considers this intervention to have moderate costs for the patients.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	None.	Since the evidence is mostly anecdotal and unsystematic, the panel unanimously suggests a very low certainty for the relevant evidence.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We were unable to find studies that assess the cost-effectiveness of testosterone treatment for patients with erectile dysfunction. However, a Swedish study investigated life-long testosterone replacement among hypogonadal men due to Klinefelter (PMID: **23937088**).	Due to the lack of robust evidence favoring the use of testosterone therapy over placebo in addition to the significant cost of treatment and monitoring we feel the cost-effectiveness does not support the use of testosterone therapy. The panel unanimously voted for probably favors the comparison.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	None	Studies have not explored health equity in Canada with regards to testosterone therapy. However, the treatment and monitoring of testosterone therapy require routine medical appointments and proximity to physicians, laboratories, and pharmacies. It is known that regular physician appointments are associated with significant patient costs (73) and create an undue burden on many patient populations. The use of testosterone therapy and its safety monitoring have limitations from an equity perspective. Further, elevations in PSA would require patients to seek urology opinions that in some geographic areas are distant and inaccessible. Despite multiple published clinical practice guidelines concerning the management of men with Testosterone Deficiency Syndrome, many primary care physicians are reluctant to assess and treat men for this condition. Patients may therefore never be properly assessed and treated for TRT, or need to wait for a specialist referral that may not be available in their geographic location. The was unanimous in its choice.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	None	Our panel feels that testosterone therapy would be a feasible treatment if the evidence supported its use as a treatment for erectile dysfunction. Its ubiquity, lack of significant adverse effects, and relatively low cost influence its feasibility to implement if it demonstrated adequate efficacy. The was unanimous in its choice.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	None	The panel unanimously believes that this intervention is probably feasible to implement.

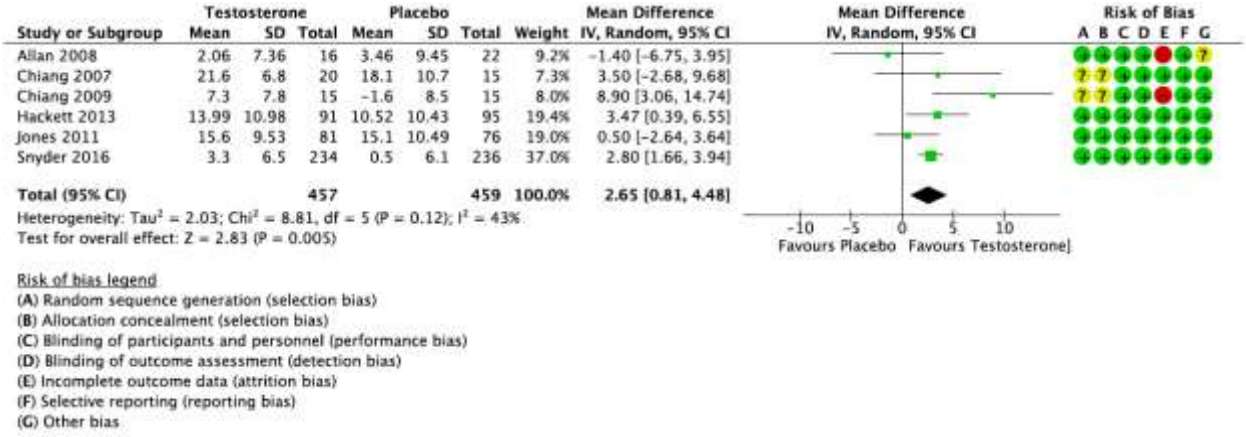
SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

FIGURE 6. FOREST PLOT:
TRT VS. PLACEBO, OUTCOME: ERECTILE FUNCTION



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Recommendation 4: Physical Activity

TABLE 9. SUMMARY OF FINDINGS:

Increased physical activity compared to normal activity for erectile dysfunction

Patient or population: erectile dysfunction
Setting:
Intervention: increased physical activity
Comparison: normal activity

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with normal activity	**Risk with increased physical activity**				
Erectile function assessed with: International Index of Erectile Function- Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED) follow up: range 2 months to 2 years	The mean erectile function was **14.8**	MD **3.77 higher** (2.04 higher to 5.5 higher)	-	366 (5 RCTs)	⨁⨁◯◯ LOW [a,b]	Although the certainty in the evidence is low, the pooled effect estimate is slightly below the accepted minimal clinical difference (MID) which is 4 units. Patients who had increased physical activity scored 3.77 points higher on the erectile function domain of the IIEF questionnaire compared to those who had normal physical activity (from 2.04 higher to 5.50 higher). Therefore, increased physical activity may result in a slight increase in erectile function.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. None of the included studies is at a low risk of bias. However, blinding is unattainable due to the intervention under study. As a majority of studies suffered the risk of bias in other domains as well, we decided to rate down by one level for risk of bias.
b. Visual inspection of the confidence intervals, I square index, and chi-square test for heterogeneity revealed significant heterogeneity of the results. Furthermore, the effect estimates were distributed at both sides of the MID.

TABLE 10. EVIDENCE TO DECISION FRAMEWORK

Should increased physical activity vs. normal activity be used for erectile dysfunction?	
POPULATION:	erectile dysfunction
INTERVENTION:	increased physical activity
COMPARISON:	normal activity
MAIN OUTCOMES:	Erectile function;
SETTING:	Urology clinics
PERSPECTIVE:	Patients
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	None	Please refer to the methods section of the main guideline text on the clinical question selection. All the questions selected were considered oh high priority.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Summary of Findings (SoF) table: Physical activity for erectile dysfunction	None

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Summary of Findings (SoF) table: Physical activity for erectile dysfunction	During our search for systematic reviews and trials assessing the effects of physical activity on erectile function, we were unable to find studies reporting on undesirable outcomes. Therefore, the panel felt that no reliable evidence for the adverse effects of physical activity is known at this time.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Summary of Findings (SoF) table: Physical activity for erectile dysfunction	As the only outcome for which evidence was available was erectile function, in general, lack of effect estimates for other outcomes compelled us to choose very low.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Although some studies regarding disutility of erectile function are in hand, the literature, to the best of our knowledge, fails to address how patients value outcomes related to erectile dysfunction.	In the absence of evidence through research, the panel members leaned on their extensive shared decision-making experience to approximate the values and preferences of patients. The panel was unanimous that possibly important uncertainty or variability exists.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Summary of Findings (SoF) table: Physical activity for erectile dysfunction	As no evidence for harm outcomes is in hand, the panel deliberated the plausibility of severe adverse events in this context through a panel discussion. Considering the possible bias, the panel unanimously voted that the balance of effects probably favors the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The time cost of exercise is estimated to be 15-30% of the net salary for employed individuals and less for unemployed individuals (PMID 32206041). Additionally, less experienced exercisers value a higher time cost to exercise (26% of net wages) compared to more experienced exercisers (7% of net wages) (PMID 20459761).	There is a broad spread of potential material resources required for physical activity to occur. Effective aerobic and resistance physical activity can be achieved at minimal material cost using one's natural environment and bodyweight or at significant cost through the use of various exercise programs/trainers, equipment, and/or facilities. However, the ability to accomplish physical activity at little-to-no material cost and the potential to produce substantial additional health benefits means that there could be large potential savings with this intervention. Eight panel members considered negligible costs and savings. While the other member chose moderate savings.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	None	While there is little evidence on the resources required for physical activity in the management of the erectile function, the evidence is more robust for chronic diseases such as coronary artery disease, diabetes, and stroke. Extrapolating the data from coronary artery disease to erectile dysfunction adds to the uncertainty while the wide range of physical activity also makes it difficult to accurately estimate required resources.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	None	It is the view of five of the panel members that increased physical activity is probably cost-effective due to the minimal material cost and the potential to avoid more expensive pharmaceutical/medical interventions for ED. However, others believe that alternatives are equal in terms of cost-effectiveness.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased	None	It is the view of all the panel members that effective physical activity is equally accessible for all populations and probably would not impact equity significantly.

○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	It is the panel's view that almost all stakeholders would consider physical activity to be an acceptable intervention. Some patients may object to the time cost of physical activity.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	Physical activity can be accessed by any patient of any socioeconomic level in nearly any setting.

SUMMARY OF JUDGEMENTS

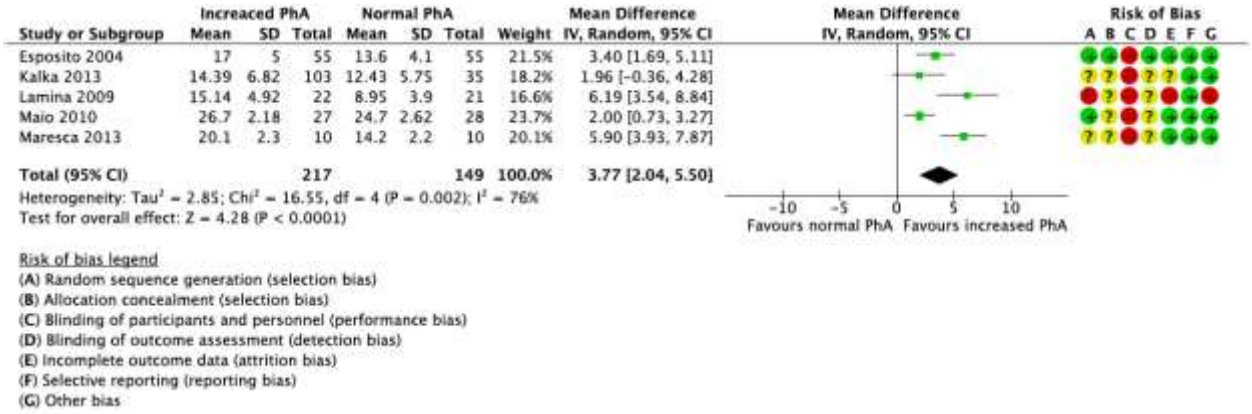
	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

FIGURE 7. FOREST PLOT:
INCREASED PHYSICAL ACTIVITY VS. NORMAL PHYSICAL ACTIVITY, OUTCOME: ERECTILE FUNCTION



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Recommendation 5: Penile Rehabilitation

TABLE 11. SUMMARY OF FINDINGS:

Scheduled PDE5Is compared to placebo or no treatment in post-prostatectomy erectile dysfunction

Patient or population: post-prostatectomy erectile dysfunction
Setting:
Intervention: scheduled PDE5Is
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	**Risk with scheduled PDE5Is**				
Erectile function restoration assessed with: Number or percentage of participants achieving potency after RP according to IIEF-EF and IIEF-5 scores. follow up: range 24 weeks to 48 weeks	250 per 1,000	**278 per 1,000** (200 to 388)	**RR 1.11** (0.80 to 1.55)	757 (5 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	The evidence is very uncertain about the effect of scheduled PDE5Is on erectile function restoration. The pooled effect estimate suggests that in every 1000 patients who receive the intervention, compared to placebo or no treatment, 28 more people have ED resolution. However, the confidence interval suggests this can be from 50 fewer patients to 138 more.
Erectile function assessed with: International Index of Erectile Function- Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED) follow up: mean 48 weeks	The mean erectile function was **6.4**	MD **2.09 higher** (1.85 lower to 6.03 higher)	-	356 (2 RCTs)	⨁⨁◯◯ LOW [a,d]	The evidence suggests that scheduled PDE5Is results in little to no difference in erectile function. As the established minimal clinically important difference for the IIEF erectile function domain is 4, the pooled effect estimate suggests that the additional benefit from scheduled PDE5Is administration among post-prostatectomy erectile dysfunction patients is not clinically significant. However, the fact that our certainty in the evidence is low implies that the true effect might be different.
Sexual quality of life assessed with: Expanded Prostate Cancer Index Composite (sexual domain) Scale from: 0 (worst) to 100 (best) follow up: mean 54 weeks	The mean sexual quality of life was **33.4**	MD **3.2 higher** (5.91 lower to 12.31 higher)	-	280 (1 RCT)	⨁⨁◯◯ LOW [a,d]	The evidence suggests that scheduled PDE5Is results in little to no difference in sexual quality of life.

TABLE 11. SUMMARY OF FINDINGS:

Scheduled PDE5Is compared to placebo or no treatment in post-prostatectomy erectile dysfunction

Patient or population: post-prostatectomy erectile dysfunction
Setting:
Intervention: scheduled PDE5Is
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	**Risk with scheduled PDE5Is**				
Serious adverse event assessed with: Rate of participants who experienced at least one serious adverse events using an erectile aid (using the NCI Common Terminology Criteria for Adverse Events (CTCAE) reporting; grades 3 to 5) follow up: range 24 weeks to 48 weeks	71 per 1,000	**23 per 1,000** (8 to 67)	**RR 0.32** (0.11 to 0.94)	403 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c]	The evidence is very uncertain about the effect of scheduled PDE5Is on serious adverse event.
Treatment discontinuation assessed with: Treatment discontinuation from any cause at any time. follow up: range 24 weeks to 48 weeks	273 per 1,000	**268 per 1,000** (197 to 366)	**RR 0.98** (0.72 to 1.34)	403 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c]	The evidence is very uncertain about the effect of scheduled PDE5Is on treatment discontinuation.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one level for study limitations: unclear or high risk of bias in one or more domains.

b. Downgraded by one level for indirectness: difference in the outcome measure.
c. Downgraded by two levels for imprecision: wide confidence interval crosses assumed threshold of clinically important difference.
d. Downgraded by one level for imprecision: confidence interval crosses the assumed threshold of clinically important difference.

TABLE 12. SUMMARY OF FINDINGS:

PDE5Is compared to placebo for erectile dysfunction after radiotherapy for prostate cancer

Patient or population: erectile dysfunction after radiotherapy for prostate cancer
Setting:
Intervention: PDE5Is
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with PDE5Is**				
IIEF-EF assessed with: International Index of Erectile Function- Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED) follow up: 6 weeks	The mean IIEF-EF was **9.0**	MD **6.1 higher** (4.69 higher to 7.52 higher)	-	362 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	Our findings suggest that those receiving a PDE5I for ED after undergoing radiotherapy for prostate cancer have 6.1 units higher IIEF-EF scores on average compared to those on placebo (from 4.69 higher to 7.51 higher). As the established minimal important difference (MID) on this scale is 4 units, we conclude that PDE5Is may result in an increase in iIEF-EF.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. All studies were at a high risk of bias for at least one domain. All of the studies were cross-over trials. One study did not recruit the pre-determined sample size and had a significant loss to follow-up rate. The two other studies did not use any wash-out period between at the cross over. Therefore, we decided to rate down by one level for risk of bias.
b. As the included studies chose to use on-demand dosing for a relatively short period of time, we believe that the intervention does not directly represent what the intended intervention in our research question is. Therefore, we decided to rate down by one level for the indirectness domain.

TABLE 13. EVIDENCE TO DECISION FRAMEWORK:

Should PDE5Is vs. placebo or no treatment be used for post-prostatectomy or post-radiotherapy erectile dysfunction?	
POPULATION:	post-prostatectomy erectile dysfunction
INTERVENTION:	scheduled PDE5Is
COMPARISON:	placebo or no treatment
MAIN OUTCOMES:	Erectile function restoration; Erectile function; Sexual quality of life; Serious adverse event; Treatment discontinuation;
SETTING:	Urology clinics
PERSPECTIVE:	Patients
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Prostate cancer is diagnosed among 1 in 7 men in Canada during their lifetime, and many of these men will go on to receive localized treatment in the form of surgical extirpation or radiotherapy (Canadian Cancer Society's Advisory Committee on Cancer Statistics. Toronto, ON: Canadian Cancer Society, 2017). Significant heterogeneity for reporting of erectile dysfunction exists in the literature following localized prostate cancer therapy; collectively, the literature suggests that a vast number of men will have a temporary or permanent reduction in erectile function following therapy (PMID 19515209; 12419432).	Please refer to the methods section on the selection of clinical questions. All of the selected questions are of high priority.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Summary of Findings (SoF) table: PDE5Is for post-prostatectomy erectile dysfunction and PDE5Is for post-radiotherapy erectile dysfunction.	None

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Summary of Findings (SoF) table: PDE5Is for post-prostatectomy erectile dysfunction and PDE5Is for post-radiotherapy erectile dysfunction.	None

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Summary of Findings (SoF) table: PDE5Is for post-prostatectomy erectile dysfunction and PDE5Is for post-radiotherapy erectile dysfunction.	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Unfortunately, our members' literature search for studies evaluating values and preferences regarding erectile dysfunction did not yield any results.	Optimizing erectile function after localized prostate cancer therapy is believed to be important for most patients. However, sexual satisfaction is not fully dependent upon erectile function, and thus some possible uncertainty exists. Based on their extensive shared decision-making experience, our panel considers the possibility of important uncertainty or variability in how patients value these outcomes in the given setting. Eight members voted for possibly important uncertainty while one voted for probably no important uncertainty.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Summary of Findings (SoF) table: PDE5Is for post-prostatectomy erectile dysfunction and PDE5Is for post-radiotherapy erectile dysfunction.	The panel was more split on this domain. After much deliberation and discussion, five members believed that the balance of effects probably favors the intervention while the remaining four were equally split on does not favor either and probably favors the comparison.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The cost of PDE5Is can be prohibitive as such, daily consumption can be further prohibitive to many Canadians (https://www.canadadrugsdirect.com/products/cialis/5mg).	The panel unanimously voted that the required resources have a moderate cost.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Unfortunately, we were unable to locate any directly relevant studies investigating the resources required for PDE5Is in this context. Panel members were tasked to search the literature for these studies.	Since the evidence is anecdotal, the panel considers it as very low for the certainty of evidence.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Just like the resource required, we were unable to locate studies addressing this domain due to the poor literature around erectile dysfunction.	Due to the lack of robust evidence favoring the use of regular PDE5i's over placebo in addition to the significant cost of treatment, we feel that the cost-effectiveness does not support the use of PDE5i's among men receiving localized prostate cancer therapy. Therefore, the panel unanimously voted for probably favors the comparison.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No relevant studies exist to the best of our knowledge.	Considering the costs of this intervention and lack of efficacy evidence, the panel believes that the costs with minimal benefits will probably reduce the equity. The vote was unanimous.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No relevant studies were found.	While the available research does not favor the use of regular PDE5i's for penile rehabilitation, it is probably acceptable for physicians to consider the use of PDE5i's in men who have received localized therapy for prostate cancer. Our panel believes that the use of PDE5i's for symptomatic relief of erectile dysfunction in responsive men is likely more acceptable. Eight members voted for probably yes and one for yes.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No relevant studies were found.	Since the implementation of this intervention does not require additional infrastructures, the panel unanimously believed that s intervention is probably feasible.

SUMMARY OF JUDGEMENTS

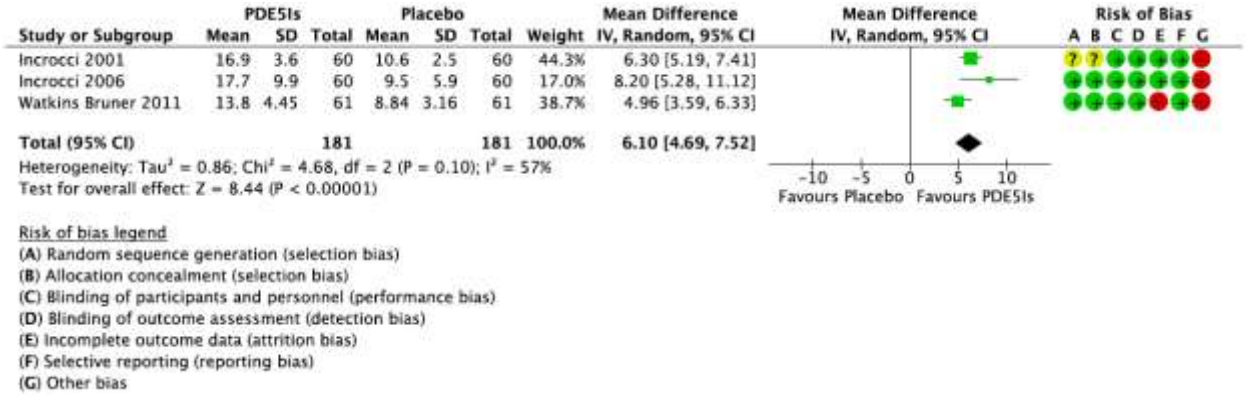
	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

FIGURE 9. FOREST PLOT:
PDE5 INHIBITORS VS. PLACEBO FOR ERECTILE DYSFUNCTION AFTER RADIOTHERAPY, OUTCOME: ERECTILE FUNCTION



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias