Supplementary material

A summary benefit-risk table was created to allow visualisation of the magnitude of each benefit and risk. Risk differences and corresponding 95% confidence intervals (CI) were calculated for each outcome where both numerator (number of events) and denominator (number of patients at risk) were available. Where spontaneous reporting data were used to examine an outcome, only the reporting odds ratio (ROR) could be calculated with 95% CI. For the ROR, a spontaneous reporting database is considered source data for a case-control study, therefore the ROR can be used to estimate relative risk[1].

1. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf 2004;13:519–23. doi:10.1002/pds.1001

Supplementary Table 1. Data for key benefits and risks identified for buprenorphine implant

Outcome name	Study	Study primary outcome	Total sample size	Implant BPN risk estimate	Implant BPN number of patients	Implant BPN number of events	S/L BPN risk estimate	S/L BPN number of patients	S/L BPN number of events	RD point estimate	RD lower 95% CI	RD upper 95% CI	ROR	ROR lower 95% CI	ROR upper 95% CI
Benefits															
Improved compliance and convenience	Carter et al	Cost-effectiveness of implant vs S/L BPN	n/a (modelled data)	0.78			0.58			0.20					
Reduced risk of illicit opioid use	PRO-814#	Evidence of of illicit opioid use	173*	0.96	84	81	0.88	89	78	0.09	0.01	0.17			
Quality of life measures	Carter et al	Cost-effectiveness of implant vs S/L BPN	n/a (modelled data)	0.83			0.80			0.03					
Risk of misuse and diversion	FAERS	None (database)	3924*		72	1		3852	375				0.13	0.02	0.94
Risks															
Migration/missing implant	PRO-806# and PRO-814#	Evidence of of illicit opioid use	290	0.01	201	2	0.00	89	0	0.01	0.00	0.02			
Clinically Significant Implant Breakage	PRO-806#, PRO-814# and post-marketing reports in PADER	Evidence of of illicit opioid use	1233	0.01	1144	6	0.00	89	0	0.01	0.00	0.01			
Infection at insertion / removal site	PRO-806# and PRO-814#	Evidence of of illicit opioid use	290	0.09	201	18	0.01	89	1	0.08	0.03	0.12			
Implant related allergic reaction	PRO-806# and PRO-814#	Evidence of of illicit opioid use	290	0.08	201	16	0.01	89	1	0.07	0.03	0.11			

BPN=Buprenorphine; S/L=sublingual; RD=Risk difference; CI= Confidence Interval; ROR=Reporting odds ratio; FAERS= FDA Adverse Event Reporting System; PADER= Periodic Adverse Drug Experience Report; *=minimum 80% power to detect difference; # clinical trials were powered to detect a difference between sublingual buprenorphine and buprenorphine implant for the primary outcome

Supplementary Table 2. Benefit-Risk summary table for key benefits and risks identified for buprenorphine implant and sublingual buprenorphine

Outcome name	Implant BPN risk/1000 pts	S/L BPN risk/1000 pts	RD (95% CI)/1000 pts	ROR (95% CI)
Benefits				
Improved compliance and convenience	780	580	200 (-, -)	
Reduced risk of illicit opioid use	964	876	88 (9, 167)	
Quality of life measures	832	801	31 (-, -)	
Risk of misuse and diversion	-	-	-	0.13
Risks				
Migration/missing implant	10	0	10 (-4, 24)	
Clinically Significant Implant Breakage	5	0	5 (1, 9)	
Infection at insertion / removal site	90	11	78 (33, 123)	
Implant related allergic reaction	80	11	68 (25, 112)	

BPN=buprenorphine; S/L= sublingual; RD=risk difference; CI=confidence interval; ROR=reporting odds rati

Supplementary Table 3. Swing weights assigned to key benefits and risks (normalised)

Ranking	Outcome	Swing Weight (normalised)
1	Improved compliance and convenience	100
2	Reduced risk of illicit opioid use	100
3	Migration/missing implant	80
4	Clinically significant implant breakage	70
5	Quality of life measures	60
6	Infection at insertion/removal site	35
7	Implant related allergic reaction	25

Formula for calculation of wNCB (Sutton et al., 2005)

Expected net = ∑ Expected benefits - ∑ Expected harms
Clinical benefit from treatment from treatment

Expected benefits = (Probuphine proportion – S/L BPN proportion) x weight
From treatment

Expected harms = (Probuphine proportion - S/L BPN proportion) x weight
From treatment

Supplementary Table 4. Weighted net clinical benefit (wNCB) for buprenorphine implant

Outcomes	Weights (%)	Point estimate difference x weight
Benefits		
Reduced risk of illicit opioid use	21	1.68
Improved compliance and convenience	21	4.20
Quality of Life	13	0.39
Risks		
Migration/missing implant	17	0.17
Clinically significant implant breakage	15	0.15
Infection at insertion/removal site	8	0.64
Implant related allergic reaction	5	0.35
	Overall wNCB	**4.96**

wNCB=weighted net clinical benefit

Sensitivity analysis of weighting approach

To examine the robustness of the assigned weights and whether significant changes would alter the benefit-risk profile for buprenorphine implant, we examined three scenarios where different swing weights were assigned.

The first scenario examined the change in wNCB if the weights for each benefit were reduced by a third and the weights for each risk increased in equal proportions. The wNCB remained positive at 2.12, despite the total weighting of the benefits decreasing to 37%.

The second scenario examined the change in wNCB if the weights for each benefit were halved and the weights for each risk increased in equal proportions. The wNCB remained positive at 0.66, despite the total weighting of the benefits decreasing to 27.5%.

For the final scenario, the change in wNCB was examined if the weights for each benefit were decreased by two-thirds and the weights for each risk increased in equal proportions. The wNCB would become negative in this scenario at -0.80, because the benefit weights are only contributing a total of 18%.