CPAG Summary Report for Clinical Panel – URN 1827: Local therapy (surgery/ radiotherapy) in the form of Ablative surgery, Mould technique brachytherapy and surgical Reconstruction (AMORE) treatment for non-metastatic rhabdomyosarcoma of the head and neck

The Benefits of the Proposition – Outcomes with AMORE available as a treatment option Vs. outcomes when AMORE was not available to treat rhabdomyosarcoma of the head and neck		
No	*Metric*	*Summary from evidence review*
1.	Survival	Overall survival is the proportion of patients alive at specified intervals. Schoot et al (2015a) reported 5 year overall survival. There was no significant difference in 5 year overall survival between Amsterdam cohort survivors (where AMORE was available as a treatment option) (76.9%) and London cohort survivors (where AMORE was not available) (75.0%) (p=0.56). Median follow-up was 9.7 years for the Amsterdam cohort and 11.0 years for the London cohort. There was no difference in 5 year overall survival between the different treatment centres. Overall survival is important to clinicians, patients and their families. These results should be treated with caution as they are from a small, non-randomised study which included 49 patients who received treatment in Amsterdam and 31 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received External Beam Radiotherapy (EBRT) when AMORE was not available or not feasible. 73% of the Amsterdam cohort had AMORE treatment at

		some stage, either as initial treatment or after recurrence. 94% of the London cohort had EBRT as initial treatment or after recurrence. There were no significant differences in the reported patient characteristics between the treatment centres. There were significant differences between the Amsterdam and London cohorts in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
2.	Progression free survival	Failure-free survival was not defined, but this is generally the proportion of patients who have not experienced disease recurrence at specified intervals after completion of treatment. Schoot et al (2015a) reported 5 year failure-free survival. There was no significant difference in 5 year failure-free survival between Amsterdam cohort survivors (where AMORE was available as a treatment option) (53.2%) and London cohort survivors (where AMORE was not available) (63.8%) (p=0.37). Median follow-up was 9.7 years for the Amsterdam cohort and 11.0 years for the London cohort. There was no difference in 5 year failure-free survival between the different treatment centres. Failure-free survival is an important outcome for clinicians, patients and their families. See metric 1, paragraph 4 for further study notes.
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver /	

	supporting independence	
10.	Safety	Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAEv4[1]). The 5 severity grades were grade 1 ‘mild’; grade 2 ‘moderate’, grade 3 ‘severe or medically significant but not immediately life-threatening’; grade 4 ’life-threatening consequences’; grade 5 ‘death’. Schoot et al (2015a) also developed a burden of treatment score ranging from ‘none’ to ‘severe’, based on the number and severity of adverse events. For example a ‘severe’ score was given to 2 patients who experienced ≥2 grade 4 adverse events and 3 patients who experienced 1 grade 4 adverse event and ≥2 grade 3 adverse events. Patients were followed-up for a median of 10.5 years. Amsterdam cohort survivors (where AMORE was available as a treatment option) were significantly less likely to experience a grade 3 or 4 adverse event (53%) compared to London cohort survivors (where AMORE was not available) (77%) (p=0.028). This significant difference was retained in multivariate analysis adjusted for primary tumour site, age at diagnosis and follow-up duration (Odds Ratio (OR) 0.29 95% Confidence Intervals (CI) 0.10 to 0.90, p=0.032). Amsterdam cohort survivors were less likely to develop ≥10 adverse events of any grade (18% vs 48%) (p=0.04). In multivariate analysis Amsterdam cohort survivors were also significantly less likely to have ≥5 adverse events of any grade, after adjustment for primary tumour site, age at diagnosis and follow-up duration (OR 0.11 95%CI 0.02 to 0.60, p=0.01). Parameningeal tumour site was an independent risk factor for the development of ≥5 adverse events of any grade (OR 13.34 95%CI 2.52 to 70.60, p=0.002). Availability of AMORE treatment (in Amsterdam) was associated with a significantly lower burden of adverse events than no availability of AMORE (in London) (p=0.04). The number of patients scoring severe or high was similar between the treatment centres (Amsterdam n=15; London

[1] https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

		n=12) but more Amsterdam cohort survivors had a burden score of low or none (11 vs 4). Five types of adverse event (any grade) were significantly less common in Amsterdam cohort survivors than London cohort survivors. These were dry eye (25% vs 55% OR 4.20 95%CI 1.55 to 11.40); alopecia (21% vs 42% OR 2.99 95%CI 1.10 to 8.15); cataract (19% vs 39% OR 2.95 95%CI 1.05 to 8.28); growth hormone deficiency (12% vs 48% OR 7.56 95%CI 2.42 to 23.58) and dysarthria (10% vs 32% OR 4.63 95%CI 1.39 to 15.40). The effect size (ES) represented by the odds ratios (ORs) reported varied from small to moderate and the confidence intervals are wide reducing confidence in the results. Number and severity of adverse events is an important outcome for patients, families and clinicians. See metric 1, paragraph 4 for further study notes.
11.	Delivery of intervention	

AMORE – Ablative surgery, MOuld technique brachytherapy and surgical REconstruction; CI – confidence intervals; EBRT – external beam radiotherapy; ES – effect size; IQR – Inter-quartile range; OR – odds ratio; RT – radiotherapy

Other health metrics determined by the evidence review		
No	Metric	Summary from evidence review
1.	Health-related quality of life	Health-related quality of life was assessed using the self-reported Peds QL, a validated standardised questionnaire assessing health-related quality of life in physical, emotional, social and school domains. Schoot et al (2015a) reported the total score (0-100) and psychosocial health score (mean of the emotional, social and school functioning scales) (0-100) for 3 groups (all patients aged >8 years; patients aged 8 to 17 and patients aged ≥18). Higher scores indicate better health-related quality of life with 100 meaning 'never'; 75 'almost never', 50 'sometimes', 25 'often' and 0 'almost always'[2]. Health-related quality of life scores were also compared to country-specific weighted norms adjusted for

[2] https://www.corc.uk.net/outcome-experience-measures/paediatric-quality-of-life/

		sex and attained age. The authors considered an effect size of 0.2 as small, 0.5 as moderate and 0.8 as large. For Amsterdam cohort survivors (where AMORE was available as a treatment option) PedsQL total scores ranged from 81.0 to 82.3 for the 3 age groups. Psychological health scores ranged from 76.8 to 80.0. For London cohort survivors (where AMORE was not available) total scores ranged from 74.3 to 82.5 for the 3 age groups. Psychological health scores ranged from 72.6 to 78.9. The authors reported no difference in mean health-related quality of life scores between the treatment centres (p value not reported). There was no significant difference in total score or psychological health score between the Amsterdam cohort survivors and weighted norms for any of the 3 age groups. For London cohort survivors there was no significant difference with weighted norms for patients aged 8 to 17 on the total or psychological scores, or on the total score for all patients aged >8 years. There was a statistically significant difference between London cohort survivors and weighted norms for psychological health score for patients all aged >8 years (ES -0.55, p=0.037) for patients aged ≥18 years on total (ES -0.25, p=0.030) and psychological health (ES -0.35, p=0.022) scores. There was no reported difference between the treatment centres in health-related quality of life scores. Some statistically significant differences were found between London survivors and weighted norms, with effect sizes that were considered to be between small and moderate. The health-related quality of life scores reported were all between 72 and 82 out of 100. On the Peds QL scale, higher scores indicate better health-related quality of life and a score of 75 represents ‘almost never’. These results should be treated with caution as they are from a small, non-randomised study which included 49 patients who received treatment in Amsterdam and 31 patients who

		received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible.73% of the Amsterdam cohort had AMORE treatment at some stage, either as initial treatment or after recurrence. 94% of the London cohort had EBRT as initial treatment or after recurrence. There were no significant differences in the reported patient characteristics between the treatment cohorts. There were significant differences between the Amsterdam and London cohorts in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
2.	Clinical assessment of facial asymmetry	In Schoot et al (2017) clinicians graded facial asymmetry using the Common Terminology Criteria for Adverse Events (CTCAEv4[3]). There were 4 grades, where grade 1 = 'cosmetically and functionally insignificant hypoplasia'; grade 2 = 'deformity, hypoplasia or asymmetry able to be covered'; grade 3 = 'significant deformity, hypoplasia or asymmetry unable to be remediated by prosthesis or covered by clothing, disabling'; grade 4 = 'orbital exenteration, which results in asymmetry which cannot be covered and in blindness of at least 1 eye'. The severity of clinically assessed facial asymmetry was significantly lower for Amsterdam cohort survivors (where AMORE was available as a treatment option) (median 1, Inter-Quartile Range (IQR) 0 to 2) compared to London cohort survivors (where AMORE was not available) (median 1.5, IQR 0 to 3)

[3] https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

		(p=0.039). Median follow-up was 9.7 years for the Amsterdam cohort survivors and 11.0 years for the London cohort survivors. The median severity scores are associated with facial asymmetry that is either 'insignificant' or between 'insignificant' and 'able to be covered'. The importance of this degree of facial asymmetry to patients, families and clinicians is not clear. These results should be treated with caution. Patients were treated in 2 countries (The Netherlands and England). The authors reported significant differences in facial asymmetry between a cohort of British and Dutch healthy controls raising uncertainty about the direct comparison of patients from the different treatment centres. The results are from a small, non-randomised study including 49 patients who received treatment in Amsterdam and 26 patients who received treatment in London and had a 3-dimensional (3D) photograph taken. Only patients who had survived at least 2 years after treatment were included in the analysis. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible. 51% of the Amsterdam cohort received AMORE as an initial treatment. The proportion of patients who had AMORE or EBRT treatment at some stage (as initial treatment or after recurrence) was not reported in this paper, but other papers about the same patient cohort reported that 73% of the Amsterdam cohort had AMORE treatment at some stage and 94% of the London cohort had EBRT treatment at some stage. Significantly more of the London cohort were of non-Caucasian ethnicity. The Amsterdam cohort received a significantly higher number of radiotherapy treatments than the London cohort. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed

		in that period and may not reflect current practice.
3.	Pituitary dysfunction	Pituitary dysfunction encompassed growth hormone deficiency, thyroid-stimulating hormone deficiency, adrenocortcotropic deficiency, gonodotropin deficiency and precocious puberty[4]. No further definition of pituitary dysfunction was provided by Clement et al (2016). 24 (of 80) patients developed pituitary dysfunction at median follow-up of 11.8 years, consisting of 7 of the 49 Amsterdam cohort survivors and 17 of the 31 London cohort survivors. In multivariate analysis, there was a significantly lower risk of pituitary dysfunction among survivors treated in Amsterdam (where AMORE was available as a treatment option), compared to those treated in London (where AMORE was not available) (OR 2.06 95%CI 1.79 to 2.46, p<0.05). The authors reported that adjustment for follow-up time produced similar results (precise figures not reported). Pituitary dysfunction can develop as an adverse effect of radiotherapy to the pituitary area. The clinical significance of the pituitary dysfunction observed, and its importance to patients, families and clinicians, is unclear. See metric 1, paragraph 4 for further study information.
4.	Hearing threshold	Hearing threshold is the sound level below which a person is unable to detect any sound with 0 decibel (dB) as the reference level[5]. Median hearing threshold was assessed at 0.5 to 1-2 kilohertz (kHz) AC (speech frequency) and 4kHz.AC. Schoot et al (2015b) defined clinically relevant hearing loss as a deterioration of ≥20 decibels at pure-tone average 0.5 to 1-2kHz AC or 4kHz AC. Median follow-up was 11.0 years for survivors at both treatment centres. Median hearing

[4] Pubertal stage was assessed using the Tanner criteria (https://patient.info/doctor/normal-and-abnormal-puberty)

[5] http://ec.europa.eu/health/scientific_committees/opinions_layman/en/hearing-loss-personal-music-player-mp3/glossary/ghi/hearing-threshold.htm)

		threshold at pure-tone average 0.5 to 1-2kHz AC was significantly better in Amsterdam cohort survivors (where AMORE was available as a treatment option) (5dB, range 0 to 118) compared to London cohort survivors (where AMORE was not available) (10dB, range 0 to 75) (p=0.002). Median hearing threshold at pure-tone average 4kHz AC was significantly better in Amsterdam cohort survivors (5dB, range 0 to 115) compared to London cohort survivors (10dB, range 0 to 85) (p=0.0007). For all survivors, hearing threshold was worse than age-corrected normal hearing levels. In multivariate analysis the difference between treatment centres remained significant after adjustment for tumour localisation (difference in expected hearing threshold.5.4dB, p=0.001). In multivariate analysis, hearing threshold was worse in patients with parameningeal tumours compared to non-parameningeal tumours after adjustment for treatment centre (difference in expected hearing threshold 6.6dB, p=0.008). Hearing thresholds were worse than normal hearing levels for head and neck RMS patients, with worse outcomes for London cohort survivors (where AMORE was not available). It is not clear how important the hearing threshold observed would be for patients and families. These results should be treated with caution as they are from a small, non-randomised study which included 46 patients who received treatment in Amsterdam and 27 patients who received treatment in London. Only patients who had survived at least 2 years after treatment were included in the analysis. Baseline audiometry was not available. The authors assumed that children had normal hearing at the start of treatment. Patients in Amsterdam received AMORE treatment where feasible. This was determined by whether it was considered possible to carry out resection and the placement of a mould for internal radiotherapy. AMORE was not available as a treatment option in London. Most patients received EBRT when AMORE was not available or not feasible. 72% (33/46) of the Amsterdam cohort survivors had AMORE

		treatment at some stage, either as initial treatment or after recurrence. 96% (26/27) of London cohort survivors had EBRT. There were no significant differences in the reported patient characteristics between the treatment cohorts. Differences in treatment characteristics were not reported, but other papers on the same patient cohort reported significant differences in the number of radiotherapy treatments received and the proportion of patients who had major surgery. Patients were treated over a 20 year period between 1990 and 2010. Treatment techniques and protocols changed in that period and may not reflect current practice.
5.	Hearing loss	Hearing loss was assessed using the Common Terminology Criteria for Adverse Events[6] (CTCAE) and the Boston criteria[7], both of which have 4 severity grades with higher grades indicating more severe impairment. Schoot et al (2015b) defined clinically relevant hearing loss as a deterioration of ≥20 decibels at pure-tone average 0.5 to 1-2kHz Air Conduction (AC) or 4kHz AC. There was no significant difference in the proportion of patients with any grade (1 to 4) of hearing loss between Amsterdam cohort survivors (where AMORE was available as a treatment option) and London cohort survivors (where AMORE was not available). For CTCAE this was 41% and 44% respectively (p=0.55) and for the Boston criteria this was 52% and 59% respectively (p=0.67). There was no significant difference between Amsterdam cohort survivors (15%) and London cohort survivors (26%) in the proportion of patients with clinically significant hearing loss at 0.5 to 1-2kHz AC (p=0.26). There was no significant difference between Amsterdam cohort survivors (20%) and London cohort survivors (33%) in the proportion of patients with clinically significant hearing loss at 4kHz AC (p=0.19). Median follow-up was 11.0 years for survivors at both treatment centres.

[6] https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
[7] https://www.researchgate.net/figure/SIOP-Boston-Ototoxicity-Scale_tbl2_224871212

		Clinically significant hearing loss is an important outcome. Whilst up to a third of survivors experienced clinically significant hearing loss, the proportion who did so did not differ significantly between the treatment centres. See metric 4, paragraph 4 for further study information.

3D – 3-dimensional; AC – air conduction; AMORE – Ablative surgery, MOuld technique brachytherapy and surgical REconstruction; CI – confidence intervals; dB – decibel; EBRT – external beam radiotherapy; ES – effect size; IQR – Inter-quartile range; kHz –kilohertz; OR – odds ratio; RT – radiotherapy