For projector and public [noACIC]

Lead team presentation
Eribulin for treating locally advanced or metastatic breast cancer after two or more prior chemotherapy regimens – STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee A

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ERG: Liverpool Reviews & Implementation Group (LRiG)

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Background

- Current appraisal now focuses on the **review of TA250**, for a population of people with ‘locally advanced or metastatic breast cancer that has progressed **after two or more prior chemotherapeutic regimens for advanced disease** (including anthracycline and a taxane, unless these treatments were not suitable)’.
- In their submission, the company separated the population of the scope into two subgroups:
- Subgroup 1: HER2-negative patients with locally advanced or metastatic breast cancer (LABC/MBC), whose disease has progressed after one prior chemotherapy regimen in the advanced setting: **not relevant**
- Subgroup 2: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated): **relevant**

Eribulin

Marketing Authorisation in the UK (2014)	For the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least **one** chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. This appraisal only focuses on the original licence indication: locally advanced or metastatic breast cancer that has progressed after at least **two prior** chemotherapeutic regimens for advanced disease (including anthracycline and a taxane, unless these treatments were not suitable).
Mechanism of action	Synthetic analogue of halichondrin B, which inhibits tubulin polymerisation. The destabilisation of tubulin polymers disrupts the assembly and formation of microtubules, which in turn arrests cancer cell division.
Dosage and administration	Recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle
Costs	• £361 per 0.88mg/2ml solution for injection vial • £541.50 per 1.32mg/3ml solution for injection vial A Patient Access Scheme has been approved by the Department of Health for eribulin

Decision problem

	NICE Scope	Company
Population	Adults with locally advanced or metastatic breast cancer that has progressed **after at two or more prior chemotherapeutic regimens for advanced disease** (including anthracycline and a taxane, unless these treatments were not suitable)	**Subgroup 2:** Patients with LABC/MBC whose disease has progressed **after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine** (if indicated)
Intervention	Eribulin	
Comparators	• Vinorelbine • Capecitabine • Gemcitabine	• Treatment of Physician's Choice (TPC), including: Vinorelbine, Gemcitabine, Anthracyclines (Doxorubicin), Taxanes (Paclitaxel and Docetaxel)
Outcomes	• Overall survival • Progression free survival • Response rate • Adverse effects of treatment • Health related quality of life	

Key clinical effectiveness decision points

- Is there a high unmet medical need? What are the current options for this population?
- Are the results of the EMBRACE trial generalisable?
- Is the comparator TPC (Treatment physician's choice) used by the company appropriate?
- Is it appropriate to focus on Subgroup 2 of the company submission (previously treated with at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine) or is the ITT population of EMBRACE trial more relevant to the current appraisal?
- The utility values have an impact on the cost effectiveness in this appraisal, what is the committee’s view on the quality of life data?

Treatment pathway
for people having chemotherapy for advanced breast cancer

NICE Clinical Guideline 81: Advanced breast cancer: diagnosis and treatment

1st line	Anthracycline-based regimens	Docetaxel monotherapy or gemcitabine
2nd line	Capecitabine, vinorelbine or gemcitabine	
3rd line	Vinorelbine or capecitabine	Eribulin
4th line	Eribulin	

Impact on patients, family and carers

- Living with MBC is difficult for both the patient and their family
- It is a heavily pre-treated patient population, therefore there is an increased risk of drug resistance
- Many newer, very effective treatment have only been available through the CDF and are currently being reappraised by NICE, thus their future availability is uncertain
- Current treatment options are limited, therefore more options would be appreciated by patients
- Common side effects of these treatments include hair loss, nausea, vomiting, fatigue and neutropenia
- Willingness to accept side effects varies from patient to patient. Quality of life is valued as much as length of life. For some, spending quality time with their loved ones is more important than extra time with much reduced quality of life. Therefore for some, a modest survival benefit might not justify serious side effects
- People with triple negative breast cancer would likely benefit most from an additional treatment option, as there is no targeted treatment available for the condition, whereas cancers with ER and HER2 receptors have access to some targeted therapies.

Impact on patients and carers

- Eribulin is not an expensive treatment and it has been shown in trials to extend life by an average of three months longer than capecitabine
- This survival benefit is greater when looking specifically at patients with HER2-negative breast cancer, an indication where very little progress has been seen in recent years
- Eribulin controls the symptoms of the disease (including pain) better
- Five audits of the use of eribulin were carried out at hospitals in England with 270 patients and shown that eribulin:
  - is generally well tolerated
  - performs as well in clinics as it does in trials with similar survival benefits and toxicities, particularly for patients who have previously received more than one previous chemotherapy regimen for metastatic breast cancer
- In addition, the contacted clinicians said that they value having the option of eribulin for patients nearing the end of their lives

Overview of the clinical evidence

- The company presented the results of 2 randomised controlled trials (RCT) in the submission:
  - EMBRACE trial (Study 305) - pivotal trial for the current appraisal, main source of clinical evidence
  - Study 301 trial was used for applying for the licence extension, in the context of this appraisal, only used to provide HRQoL data, which was not evaluated in the EMBRACE trial.

Clinical trial evidence
EMBRACE trial

Design	Phase III, open label, multicentre, randomised controlled trial	
Population	N=762, women with locally advanced or metastatic breast cancer, who had received 2 to 5 chemotherapy regimens for advanced disease	
Intervention	n=508; Eribulin mesylate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle	This is equivalent to the licensed dose specified in the SMPC (1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle
Comparator	n=254; TPC (any available single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer, radiotherapy or best supportive care). The selection of the TPC agent took place before randomisation	
Outcomes	Primary outcome: OS	
	Secondary outcomes: PFS, ORR, safety	
Subgroups	**Previously treated with capecitabine (73.4% of ITT)**	

Patient characteristics
EMBRACE trial (ITT population)

		Eribulin (n=508)	TPC (n=254)
Median age, years (range)		55.0 years (28–85)	55.0 years (27–81)
Geographic region, n (%)	• **North America, Western Europe, Australia**	**325 (64.0%)**	**163 (64.2%)**
	• Eastern Europe	129 (25.4%)	64 (25.2%)
	• Latin America, South Africa	54 (10.6%)	27 (10.6%)
HER2 status, n (%)	+	83 (18.0%)	40 (17.2%)
	–	**373 (81.1%)**	**192 (82.8%)**
	Unknown	4 (0.9%)	0
Triple negative, n (%)	(ER/PR/HER2-negative)	93 (18.3%)	51 (20.9%)

Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice; HER2, Human epidermal growth factor receptor 2
Source: Table 19 and 20, Company submission

Prior treatments
EMBRACE trial (ITT population)

		Eribulin (n=508)	TPC (n=254)
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)	1	1 (0.2%)	0
	2	65 (12.8%)	31 (12.2%)
	3	176 (34.6%)	83 (32.7%)
	4	166 (32.7%)	79 (31.1%)
	5	85 (16.7%)	51 (20.1%)
	≥ 6	13 (2.6%)	9 (3.5%)
No. of patients who previously (adjuvant and LABC/MBC setting) received n (%)	Taxanes	503 (99.0%)	251 (98.8%)
	Anthracyclines	502 (98.8%)	250 (98.4%)
	Capecitabine	**370 (72.8%)**	**189 (74.4%)**

Abbreviations: TPC, Treatment of Physician's Choice; LABC, locally advanced breast cancer; MBC, metastatic breast cancer

Source: Table 21, Company submission

EMBRACE results

- Comparator was Treatment of Physician's Choice (TPC):
  - Chemotherapy (vinorelbine, gemcitabine, capecitebine, taxanes anthracyclines, others)
  - Hormonal therapy (fulvestrant, letrozole, exemestane, tamoxifen)

- The company conducted a primary analysis of overall survival, when the primary endpoint was met, when 55% of patients died
- The company conducted updated analysis when 77% of patients died.
- The company presented the results of a **further updated analysis when 95% of patients died**. The result of this analysis has been used for the cost-effectiveness analysis

EMBRACE results

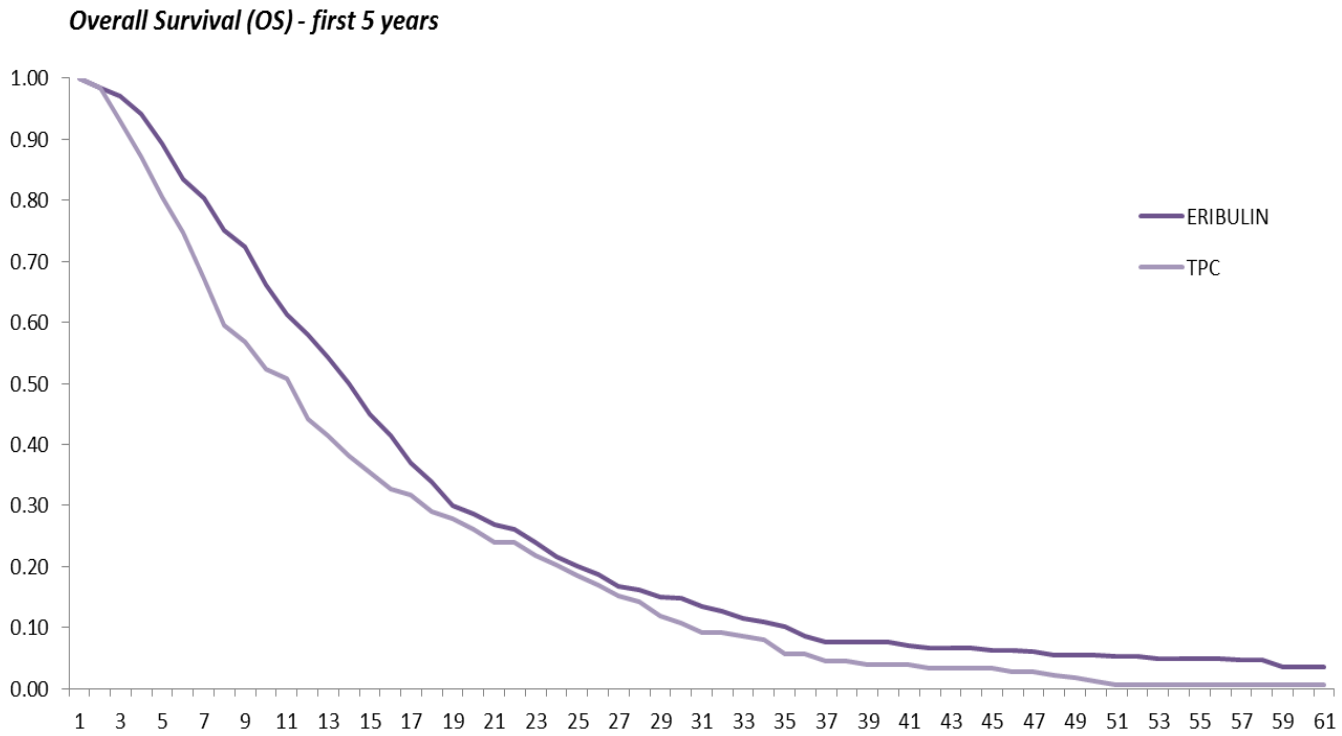
Survival results (further updated analysis after 95% of patients died)

	ITT population		Subgroup 2	
	Eribulin (n = 508)	TPC (n = 254)	Eribulin (n = 370)	TPC (n = 189)
Overall survival (OS), months (95% CI)				
Median	13.24 (12.06, 14.4)	10.55 (9.23, 12)	13.0 (11.7, 13.8)	10.1 (7.7, 11.4)
Difference in medians	**2.7 (1, 4.4)**		**2.9 (CIs N/A)**	
	p = 0.011		p = 0.008	
Hazard ratio	**0.815 (0.696, 0.955)**		**0.78 (0.65, 0.94)**	
Progression-free survival (PFS) - investigator review, months (95% CI)				
Median	3.61 (3.29, 3.75)	2.17 (1.97, 2.76)	3.6 (3.3, 3.8)	2.1 (1.9, 2.2)
Difference in medians	**1.4 (CIs N/A)**		**1.5 (CIs N/A)**	
	p = 0.002		p < 0.001	
Hazard ratio	**0.77 (0.65, 0.91)**		**0.68 (0.56, 0.83)**	

Abbreviations: ITT, intention to treat; TPC, treatment physician's choice; CI, confidence interval; OS, overall survival; PFS, progression –free survival

EMBRACE results

Kaplan-Meier analysis of overall survival: Study 305 (EMBRACE), Subgroup 2; further updated analysis after 95% of patients died)

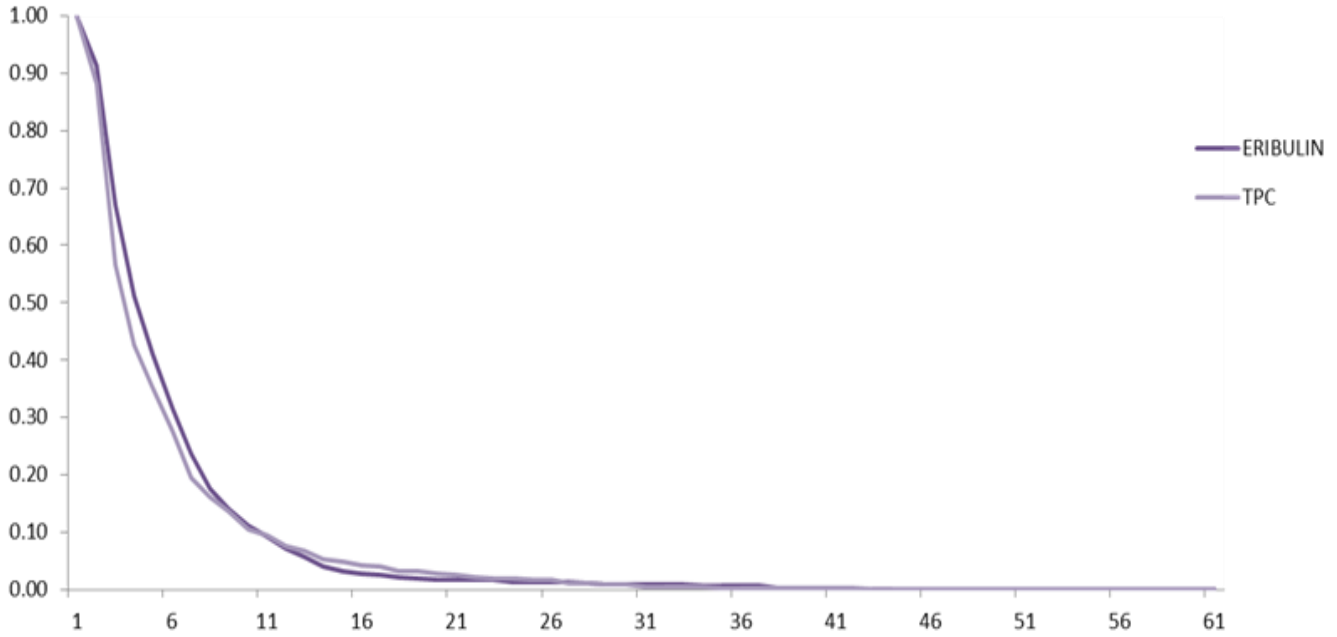


Source: Figure 34 of company submission

Kaplan-Meier results for the ITT population for the further updated analysis after 95% of patients died were not presented in the company submission.

EMBRACE results

Kaplan-Meier analysis of progression-free survival: Study 305 (EMBRACE, Subgroup 2, further updated analysis after 95% of patients died)



Source: Figure 33 of company submission

Kaplan-Meier results for the ITT population for the further updated analysis after 95% of patients died were not presented in the company submission.

EMBRACE results

Objective response rate results (ITT population, primary analysis after 55% of patients died)

Investigator review		
	Eribulin (n=468) n (%)	TPC (n=214) n (%)
ORR [CR or PaR]	**62 (13.2)**	**16 (7.5)**
95% CI	(10.3, 16.7)	(4.3, 11.9)
p-value	0.028	
CR	1 (0.2)	0
PaR	61 (13.0)	16 (7.5)

Abbreviations: ORR, objective response rate; CR, complete response; PaR, partial response; CI, confidence interval
Source: table 27 of company submission

Objective results rate results for the further updated analysis after 95% of patients died were not presented.
The results of the investigator review have been used in the cost-effectiveness model, because it was considered to represent UK clinical practice.

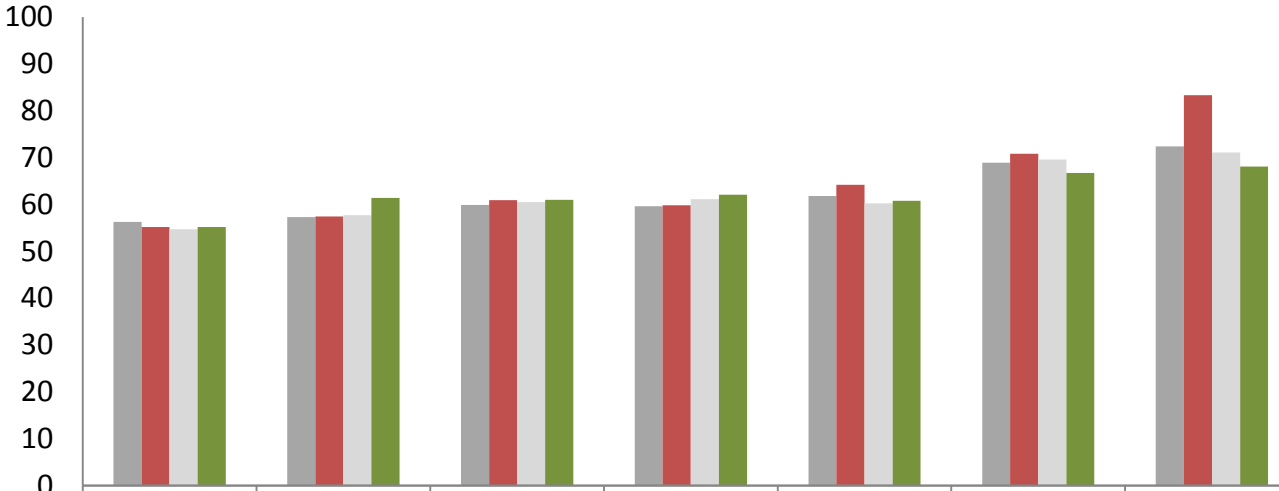
Health Related Quality of Life evidence – Study 301

- Health-related quality of life data was not collected in the EMBRACE
- Company used HRQoL results from Study 301 in the analysis.
- Data from EORTC QLQ-C30 (version 3.0) and the breast module QLQ-BR23 (version 1.0) instruments collected
- Global health status results from the EORTC QLQ-C30 questionnaire was mapped to EQ-5D using mapping algorithm published by Crott and Briggs.

Design	Phase III, open label, multicentre, randomised controlled trial
Population	N=1102, women with locally advanced or metastatic breast cancer, who had received up to 3 chemotherapy regimens, **no more than 2 for advanced disease**
Intervention	n=554; Eribulin 1.23mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle
Comparator	n=548; capecitabine
Outcomes	Primary outcome: OS, PFS
	Secondary outcomes: ORR, HRQoL
Subgroups	By geographic region and by HER2 status

Health-related quality of life results

Global Health Status by Treatment (ITT and 3rd Line Plus)



	Baseline	6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Eribulin ITT	56.3	57.3	59.9	59.6	61.8	68.9	72.4
Eribulin 3rd Line Plus (N=158)	55.2	57.4	60.9	59.8	64.2	70.8	83.3
Capecitabine ITT	54.7	57.7	60.5	61.1	60.2	69.6	71.1
Capecitabine 3rd Line Plus (N=151)	55.2	61.4	61	62.1	60.8	66.7	68.1

Source: Figure 18 of company submission

Adverse events

AEs	EMBRACE Study 305		Study 301	
	Eribulin n=503	TPC n=247	Eribulin n=544	Capecitabine n=546
Any AE	497 (98.8%)	230 (93.1%)	512 (94.1%)	494 (90.5%)
Any treatment-related AE	474 (94.2%)	192 (77.7%)	460 (84.6%)	421 (77.1%)
Fatal serious AEs	20 (4.0%)	18 (7.3%)	26 (4.8%)	36 (6.6%)
Any treatment-related serious AEs	59 (11.7%)	17 (6.9%)	7.7%	8.1%
AEs that led to discontinuation	67 (13.3%)	38 (15.4%)	43 (7.9%)	57 (10.4%)
AEs that led to dose interruption	25 (5.0%)	25 (10.1%)	10 (1.8%)	1 (0.2%)
Common AEs				
Asthenia/ fatigue	270 (53.7%)	98 (39.7%)	174 (32%)	163 (30%)
Neutropenia	260 (51.7%)	73 (29.6%)	295 (54.2%)	87 (15.9%)
Alopecia	224 (44.5%)	24 (9.7%)	188 (34.6%)	22 (4.0%)
Peripheral neuropathy	174 (34.6%)	40 (16.2%)	73 (13.4%)	38 (7.0%)
Arthralgia/ myalgia	109 (21.7%)	29 (11.7%)	72 (12.2%)	39 (7.1%)
Febrile neutropenia	23 (4.6%)	4(1.6%)	7 (1.3%)	4 (0.7%)
Source: table 33 of company submission				

ERG critique of clinical evidence (I)

- The company's literature search was appropriate
- The EMBRACE trial appears to be of good quality, the results appear to be generalisable to NHS clinical practice
- For the statistical analysis of the EMBRACE study the results of the latest data cut (after 95% of patients died) should have been presented, instead of the updated data cut (after 77% of patients died); the availability of mature clinical effectiveness data is considered one of the strengths of the EMBRACE trial
- Considered the use of the TPC comparator to be appropriate as it represented 'real life' treatment options for LABC/MBC
- Proportional hazards assumption was not tested by the company, however the HRs only valid if this assumption holds.
  - The ERG tested whether the proportional hazards assumption holds and found that the only reliable HR is for OS in the ITT population for all patients receiving ≥3 chemotherapy regimens for LABC/MBC
  - HRs for OS for Subgroup 2 and for PFS in both populations are derived from K-M data that are not proportional to one another

  Nonetheless, the ERG considers the estimates for median OS and PFS in both populations are valid

ERG critique of clinical evidence (II)

- The main difference between the ITT and Subgroup 2 populations in the EMBRACE trial is that Subgroup 2 patients appear to be slightly more heavily pre-treated:
  - approximately 64% of Subgroup 2 patients had received 4 or more prior chemotherapy regimens (in any setting) compared with approximately 53% of all patients in the ITT population
  - approximately 65% of Subgroup 2 patients had received 3 or more prior chemotherapy regimens in the LABC/MBC setting compared with approximately 57% of all patients in the ITT population
- Safety data from the EMBRACE trial and from 'real world' observational studies show that eribulin has an acceptable safety profile
- The EMBRACE trial results appear to be generalisable to NHS clinical practice
- The generalisability of HRQoL data from Study 301 (only 28% of patients in this trial had received study treatment as a 3rd line option) compared with the population of the appraisal may be questioned, given the different designs of the EMBRASE and Study 301 trials.

Key clinical effectiveness decision points

- Is there a high unmet medical need? What are the current options for this population?
- Are the results of the EMBRACE trial generalisable?
- Is the comparator TPC (Treatment physician's choice) used by the company appropriate?
- Is it appropriate to focus on Subgroup 2 of the company submission (previously treated with at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine) or is the ITT population of EMBRACE trial more relevant to the current appraisal?
- The utility values have an impact on the cost effectiveness in this appraisal, what is the committee’s view on the quality of life data?