

Birch bark extract for treating epidermolysis bullosa

For committee papers – [redacted]

Highly specialised technologies evaluation committee [8th June 2023]

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Background on epidermolysis bullosa (EB)

Classification and causes

- Disrupted skin anchoring proteins resulting in fragile skin which blisters and breaks frequently
- Dominant and recessive dystrophic epidermolysis bullosa (DDEB and RDEB) and junctional epidermolysis bullosa (JEB) differ by mutation, skin proteins affected and clinical presentation

Diagnosis and epidemiology

- Diagnosed in ~1/17,000 births. UK point prevalence of 5,000. DEB makes up 25% of cases and JEB is very rare

Symptoms and prognosis

- Skin tearing after minor trauma, reduced wound healing, increased infections. Also affects eye, mouth, oesophagus and stomach with damage, scarring and pain
- Increased risk of skin cancers, dental problems, nutritional issues, anaemia and infections

Treatment pathway: Currently no licensed treatments for EB

- Multi-disciplinary management treats symptoms of EB, at 1 of 4 specialist centres in the UK
- Comparator for BBE is best supportive care (BSC) alone (BBE would be used in addition to BSC)

Best supportive care:

- **Wound management** is use of non-adhesive dressings and bandages, topical antimicrobials and steroids which are used off label. Bathing for supplemental cleaning of wounds and lancing and draining of blisters
- **Surgical procedures** are common and may be used to aid with nutritional issues (for example insertion of gastrostomy tubes or oesophageal dilation) or to manage contractures of the hands
- **Pain management** including pharmacological and non-pharmacological interventions is used to treat background and procedural pain from the above practices

Clinical perspectives: British Association of Dermatologists

Unmet need

- No approved treatments, unmet and urgent need to prevent recurrent wounds and aid healing

Wound healing

- Clinicians consider a clinically significant benefit to be:
 - For those over 10 years: a wound to heal and remain healed for 3 months
 - For those under 10 years: faster wound healing
 - BBE to be used in addition to existing care (such as dressings and other topical treatments) at home as part of daily routine
- Faster wound healing reduces pain and infections and possibly reduce risk of skin cancer

Other considerations

- BBE will not have any impact on mucosal, GI or eye manifestations of EB
- Appear to be no significant side effects
- Treatment start/stopping depends on wound response, assessment and patient preference

“ . . . If wound healing improves and the wound[s] improve or heal, this is likely to lead to improvement in quality of life for patients.”

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Abbreviations: EB, epidermolysis bullosa; BBE, birch bark extract; GI, gastro-intestinal

Patient perspectives: Submission from DEBRA (EB patient organisation) and patient expert

Skin and mucosal manifestations

- EB causes constant itching, swelling, blistering and pain. Areas of skin may simply be missing. 2-5 hours of dressing changes required daily (but can be as high as 6-8 hours)
- Scarring of oesophagus can make eating challenging and require repeated surgery

Mental health and quality of life

- Substantial treatment requirements and pain lead to personal, professional and educational exclusion
- Low awareness of condition can lead to feelings of loneliness and isolation

Effect on family and informal carers

- People with EB likely to have more than one unpaid carer.
- Close family may have to cut back their lives to care for people with EB. The total care requirements can add up to 35 – 45.5 hours per week.
- Financial and emotional effects on family due to loss of income from caring responsibilities, as well as additional costs of everyday life

Patient perspectives

Submission from patient organisation and patient expert

“It affects my swallowing, I choke on the smallest particles of food, I have to regurgitate the food back up or press on my throat to force it down”

“EB impacts our home life; our furniture, our bathroom, clothes we buy, holidays we go on, places we visit, it’s endless”

“People living with EB sometimes struggle to access care in their local area, due to the complexity of their condition and a lack of awareness amongst GPs”

“EB stops me having a normal life and that is what I want.”

Equality considerations

Some equality issues were identified

DEBRA UK Patient Organisation Submission

- EB has greatest impact on those who have limited resources. Those with fewer resources always struggle the most to access the care they need, due to costs associated with travelling to treatment centres or accessing care
- It may also have a larger impact in those who may find accessing specialist care more difficult due to cultural reasons

Question for clinical experts:

How are people referred to the specialist centres?

How often would people with EB be expected to attend the specialist centres?

Would recommending birch bark extract be likely to change requirements or ability to access specialist centres?



Would recommending birch bark extract be likely to improve health inequalities for those with EB?

Key issues



Key Issue	Resolved?	ICER impact
Method used to calculate and apply transition probabilities	No – for discussion	Large
Appropriate use of continuity corrections	Partially resolved	Large
Discontinuation rate	Yes (with scenarios)	Small
Modelling health state transitions after discontinuation	Yes	Moderate
Number of carers modelled and utility applied	Yes	Moderate
OLS versus GLM method to estimate health-state utility	Yes	Moderate

Other issues



Key Issue	Resolved?	ICER impact
Modelling of number of outpatient appointments	Yes	Small
Average age of people in the model	Yes	Small
The appropriate distribution amongst EB subtypes and health states	Yes (with scenarios)	Small
The efficacy of BBE in DDEB and JEB	Not resolvable	Unknown
The conduct of the SEE	Not resolvable	Unknown
Disparity between the company's PSA and deterministic results	Resolved	Small

Birch Bark Extract (Filsuvez, Amryt Pharmaceuticals)

Technology details

Marketing authorisation	<ul style="list-style-type: none">• Indicated for the treatment of partial thickness wounds associated with DEB and JEB in patients aged six months or older• MHRA marketing authorisation was granted in August 2022
Mechanism of action	<ul style="list-style-type: none">• The precise mechanism of action of birch bark extract is unknown
Administration	<ul style="list-style-type: none">• Applied topically at a thickness of 1mm to the surface of the wound or to a dressing which is then applied• BBE is intended for long term use and there is no long-term stopping rule defined in relation to efficacy
Price	<ul style="list-style-type: none">• List price is £275.33 per 23.4g tube of BBE• Mean tube usage per month is [REDACTED]• A confidential patient access scheme is applicable to birch bark extract

Decision problem

- Population: People aged 6 months and older with DEB or JEB
- Intervention: Birch bark extract
- Comparators: Current clinical management without BBE (including treatments which ease pain and infections)

	Final scope	Company	EAG comments
Outcomes	Wound healing and coverage measures, HRQoL, adverse events (see EAR Table 5 for details)	As per scope although focus on EBDASI and BSAP	The reporting of changes in EBDASI and BSAP is appropriate.
Subgroups	Subgroups of DEB (dominant and recessive), JEB (severe and intermediate) will be considered if evidence allows	Subgroup data are reported but the model applies pooled transition probabilities to the whole population	Due to the small number of patients with DDEB and JEB the clinical and cost-effectiveness estimates of BBE in these subtypes are uncertain.

Abbreviations: DEB, dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa; EB, epidermolysis bullosa; DDEB, dominant dystrophic epidermolysis bullosa; HRQoL, health related quality of life; EBDASI, epidermolysis bullosa disease activity and scarring index; BSAP, body surface area percentage; EAG, external assessment group; EAR, external assessment report

Clinical effectiveness

EASE: Phase 3 double blind trial with open label extension

Key clinical trial

Clinical trial designs and outcomes

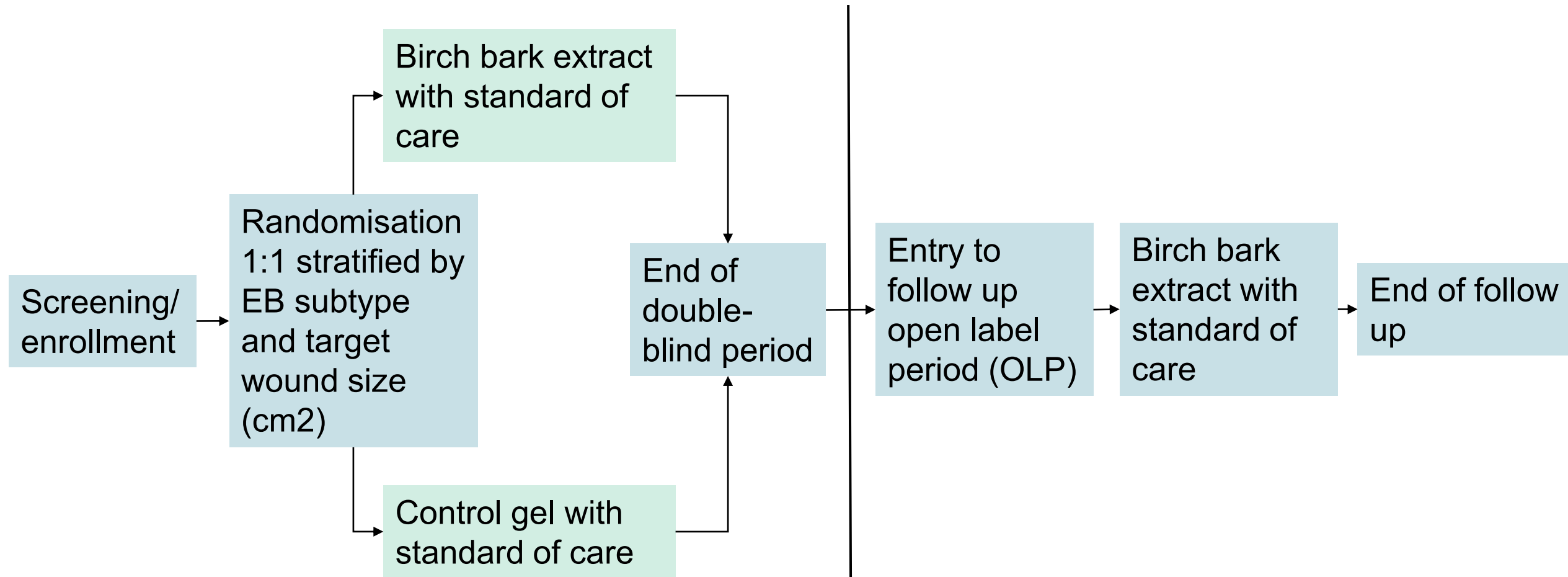
	EASE (NCT03068780)
Design	Phase 3, randomised double blind trial with open label extension
Population	People over 21 days of age with an EB target wound 10-50cm ² diameter which has been present for over 21 days and less than 9 months
Intervention	Birch bark extract (BBE) gel administered 1mm thickness applied to target and all wounds during all dressing changes (at least every 4 days)
Comparator(s)	Control gel applied in the same fashion
Duration	90 day double blind period, followed by a 24 month open label extension where all people have BBE gel
Primary outcome	Proportion of patients with first complete target wound closure (within 45 days)
Key secondary outcomes	Range of measures to assess wound healing, infection, itching, total body wound burden (including EBDASI and BSAP change from baseline)

NICE Abbreviations: EB, epidermolysis bullosa EBDASI, Epidermolysis bullosa disease area severity index; BSAP, body surface area percentage (EBSASI and BSAP are measures of disease severity with higher scores representing more severe disease)

Clinical trial study design: EASE trial

Double blind period: 90 +/- 7 days

Open label period: 24 months +/- 14 days



Clinical trial results

Outcome (Yes/No)	BBE gel [N=109] Numbers (%)	Control gel [N=114] Numbers (%)	Odds ratio (95% CI)
Proportion of patients with first complete target wound closure within 45 days	Closure: 45 (41.3%)	Closure: 33 (28.9%)	1.84 (1.02 to 3.30)*
Proportion of patients with first complete target wound closure within 90 days	Closure: 55 (50.5%)	Closure: 50 (43.9%)	1.34 (0.78 to 2.32)
Incidence of target wound infection up to day 90	Infection: 2 (1.8%)	Infection: 5 (4.4%)	0.43 (0.08 to 2.33)

Abbreviations: BBE, birch bark extract; CI confidence interval

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*Odds ratios highlighted in bold illustrates statistical significance achieved

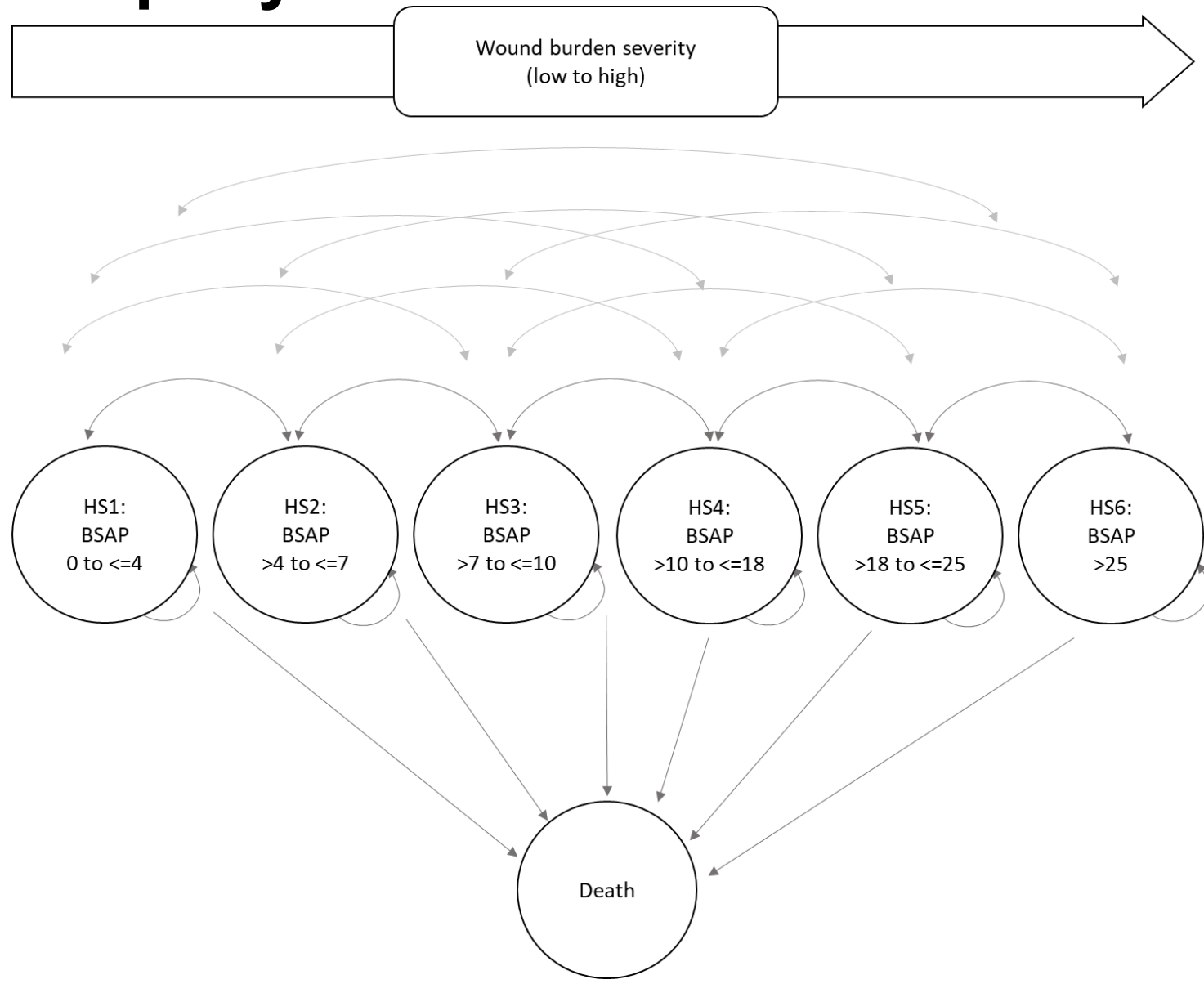
Clinical trial results

Outcome (Change from baseline)	BBE gel (N=109) Mean change	Control gel (N=114) Mean change	Mean difference (95% CI)
Change from baseline in BSAP by day 90	-4.3	-2.5	-1.3 (-2.9 to 0.3)
Change from baseline in EBDASI by day 90	-3.4	-2.8	0.1 (-1.6 to 1.8)

Cost effectiveness

- Cohort level state transition model
- 7 mutually exclusive health states (including death)
- People in each health state generate specific costs and utilities
- Discounting and half cycle correction applied

Company's model overview: Model structure



Model function

- People move through health states according to transition probabilities
- Can move from any given health state to another or to death
- CCM Transition probabilities applied until 90 days, then steady state (no more transitions)
- BBE Transition probabilities applied for 12 months before steady state
- No stopping rule in model, BBE used for life, annual discontinuation applied (1% in company base case)
- Note: Health state ranges were defined so that the EASE baseline population range was split equally across all 6 health states

Company's model overview:

- Technology affects **costs** by:
 - Inclusion of the acquisition costs of BBE
 - Reducing resource use (e.g dressings, additional care or outpatient costs)
- Technology affects **QALYs** by:
 - Increasing utility gained by people with EB and their carers by moving people to less severe health states where they and their carers experience greater health related quality of life.
- Assumptions with greatest ICER effect:
 - Use of transition probabilities estimated directly from EASE trial for 90 days
 - Steady state assumption for both BBE and CCM after 90 days
 - Assuming a single carer per health state (resolved at TE)
 - The discontinuation rate of BBE (resolved at TE)
 - If and how continuity corrections are applied to the transition probabilities

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	Generally taken from EASE trial. Health state distribution was calculated equally (split into 6 equal BSAP health states) for both arms. EB subtype distribution in model (DDEB, RDEB and JEB) was taken from the Petrof (2022) study ¹
Intervention efficacy	Transition probabilities for CCM and BBE are calculated with an approximation method that uses mean change in BSAP and its standard deviation from the EASE trial to calculate the probability of transitioning between health states at another given time
Comparator efficacy	
Patient Utility	Informed in the base case by GLM regression of EASE 24 month data. Alternative scenarios use an OLS regression and also explored utility derived from a cross-sectional study and a TTO study
Carer Utility	Derived from a TTO study which used vignettes to estimate carer disutility
Costs	Costs taken from PEBLES study (Pilay et al 2020 ²)
Resource use	Resource use estimated using structured elicitation exercise with clinicians

Abbreviations: EB, epidermolysis bullosa; CCM, current clinical management; BBE, birch bark extract; TTO, time trade off; BSAP, body surface area percentage; GLM, generalised linear model; OLS, ordinary least squares; D/RDEB dominant/recessive dystrophic epidermolysis; JEB, junctional EB

Key issue: Modelling of transition probabilities

Background

- Company approximates transition probabilities (TPs) using BSAP mean change and variance from the EASE trial (requires assumption that change in BSAP is normally distributed)
- Almost all transitions under this approach lead to health state maintenance or improvement

Company

- Using TPs derived from EASE is not sensitive enough to capture the various changes in BSAP observed during the OLP, particularly when interpolating between visits.
- Accepts uncertainty: scenario with EASE TPs to 90 days approximated TPs to 12 months

EAG comments

- This method more favourable to BBE and less favourable to CCM than EASE observed TPs
- E.g for BBE, all people in HS1 remain in HS1 in the first model cycle under the approximated approach, however only ■ remain in HS1 using EASE observed TPs
- For CCM, 97.8% of people in HS2 in the first model cycle stay in HS2 and 2.2% move to HS1, however ■ of people move from HS2 to HS1 using EASE observed TPs
- Also, large changes in BSAP suggest that change in BSAP is not normally distributed



How should transition probabilities be modelled up to 90 days?

Key issue: Modelling of transition probabilities

Company approximation approach

EASE observed (EAG base case)

BBE

Day 0-30						
	HS1	HS2	HS3	HS4	HS5	HS6
HS1	1	0	0	0	0	0
HS2	0.109	0.891	0	0	0	0
HS3	0	0.382	0.618	0	0	0
HS4	0	0	0.368	0.632	0	0
HS5	0	0	0	1	0	0
HS6	0	0	0	0	1	0

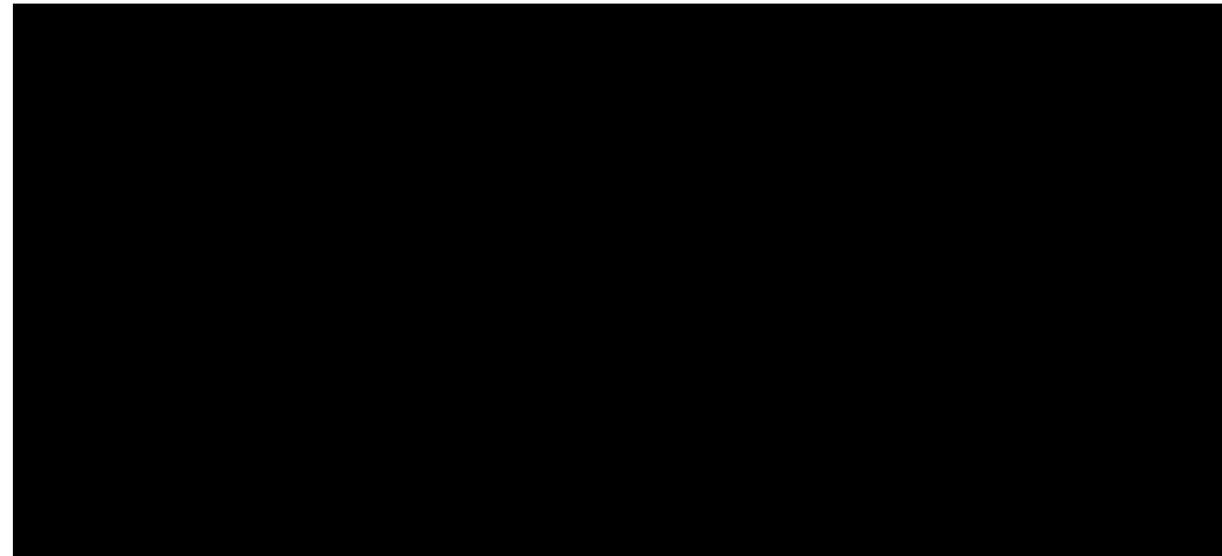


Starting health state

Ending health state

CCM

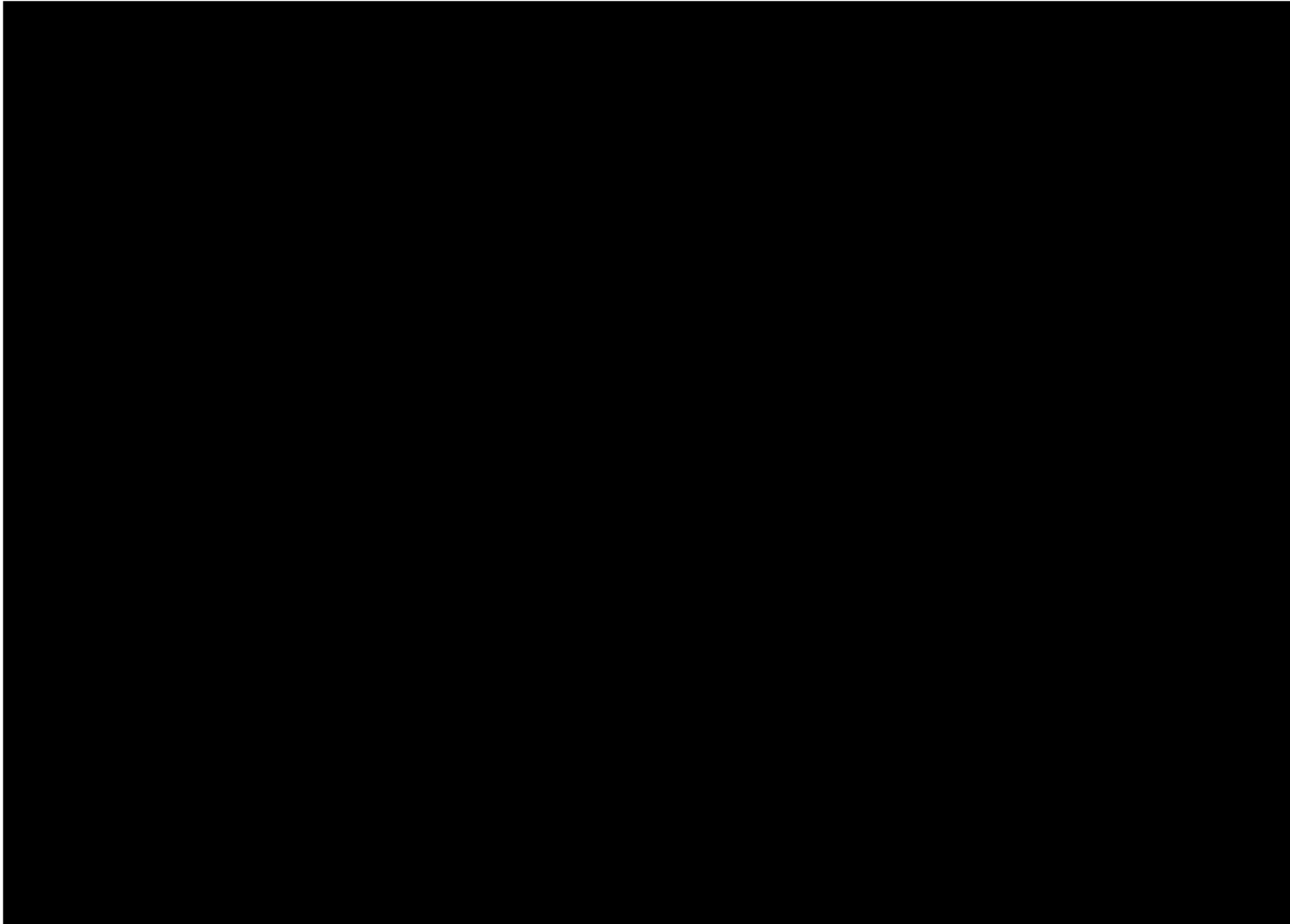
Starting health state	Day 0-30					
	HS1	HS2	HS3	HS4	HS5	HS6
HS1	1	0	0	0	0	0
HS2	0.022	0.978	0	0	0	0
HS3	0	0.358	0.642	0	0	0
HS4	0	0	0.284	0.716	0	0
HS5	0	0	0	0.999	0.001	0
HS6	0	0	0	0	1	0



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Abbreviations: HS, health state; BBE, birch bark extract; CCM, current clinical management

Key issue: Modelling of transition probabilities



EAG on change in BSAP:

- Approximation method relies on assumption that change in BSAP normally distributed
- If normally distributed, most changes would be grouped around 0 (on or near the line)
- Only a small proportion would have large changes (improving or worsening)
- Figure 2 suggests this is not the case, as there are many with large changes.

Key issue: Applying transition probabilities and steady state

Background

- Both EAG and company apply transition probabilities to CCM for 90 days, then steady state
- Uncertainty around how long to apply TPs to BBE arm for, before steady state assumption.

Company

- Apply transition probabilities (approximated) to BBE arm for 12 months before steady state
- BSAP reductions in BBE arm not fully achieved until 12 months (based on EASE)
- Offers RWE study (████████) showing mean BSAP over time

EAG comments

- RWE study has small sample size and wide 95% CI (OLP of EASE is larger █████████)
- Plausible that steady state reached after 12 months, but submission data indicate steady state may be reached after 90 days
- Prefers to apply transition probabilities to BBE for 90 days after which steady state assumed
- If scenarios modelling transitions beyond 90 days are conducted they should use EASE observed data (not the company approximation method)



At what point should the steady state assumption be applied to the BBE arm?

How should transition probabilities be calculated if they are applied beyond 90 days?

Key issue: Applying transition probabilities and steady state

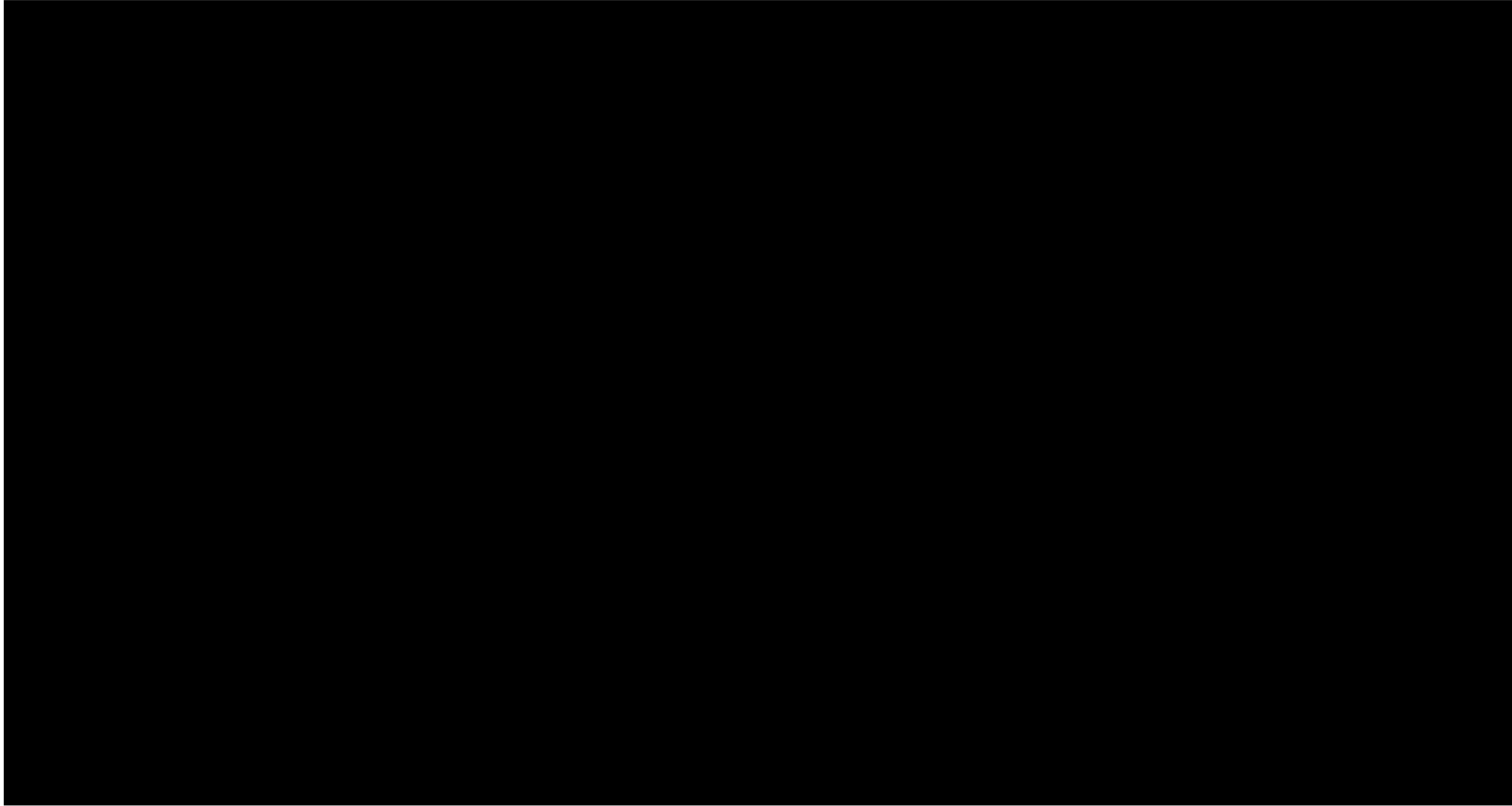
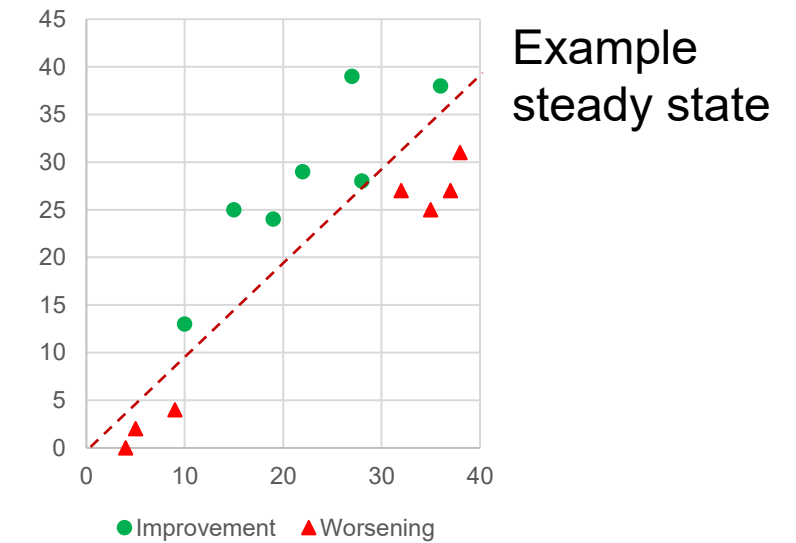
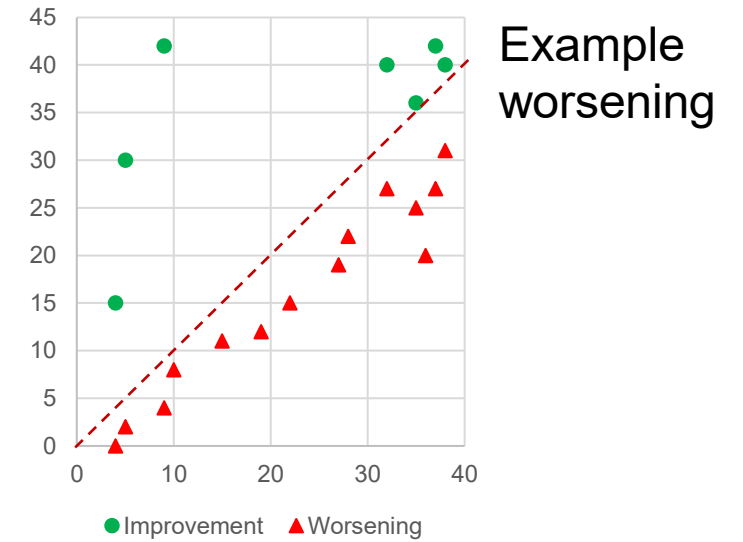
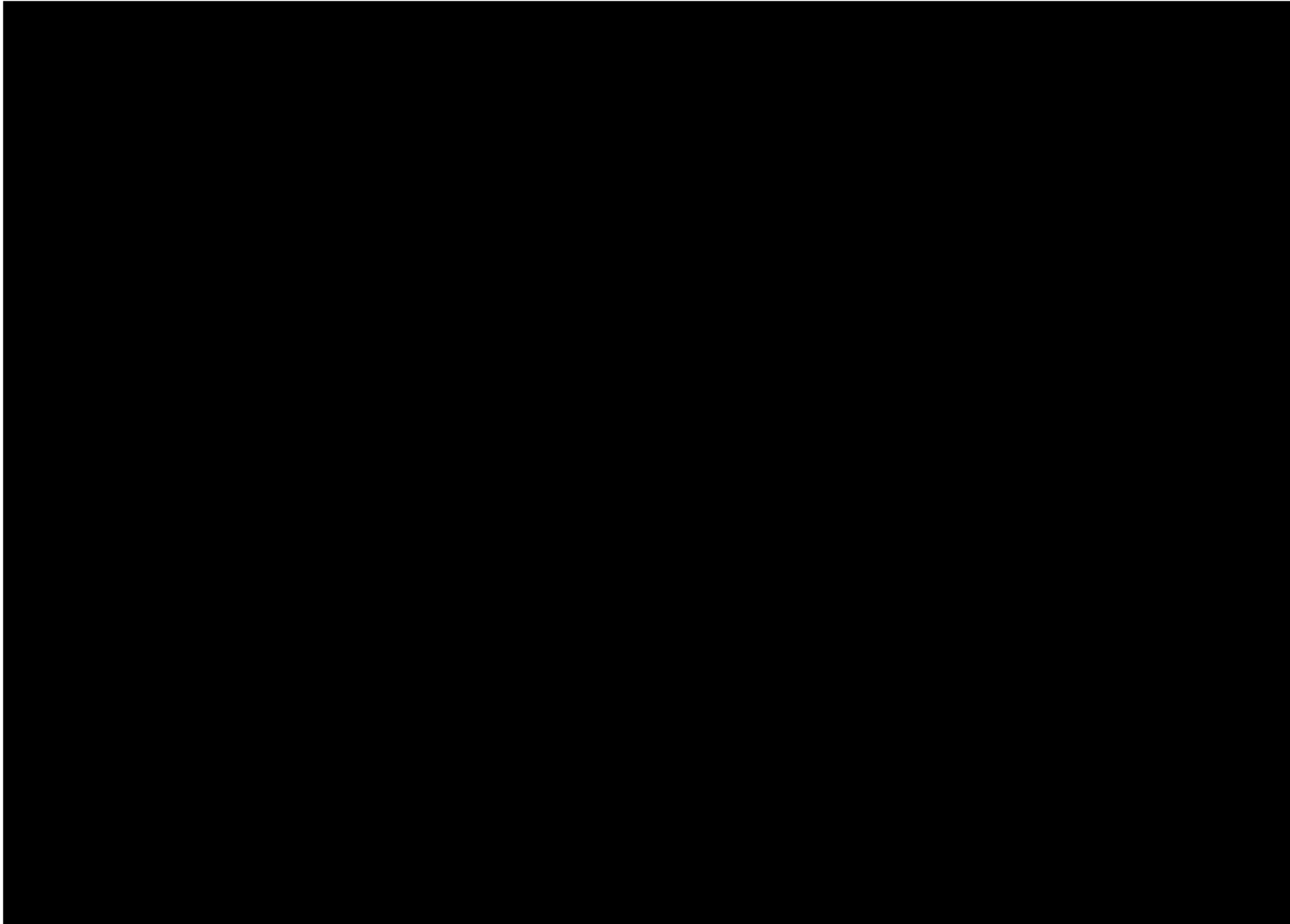
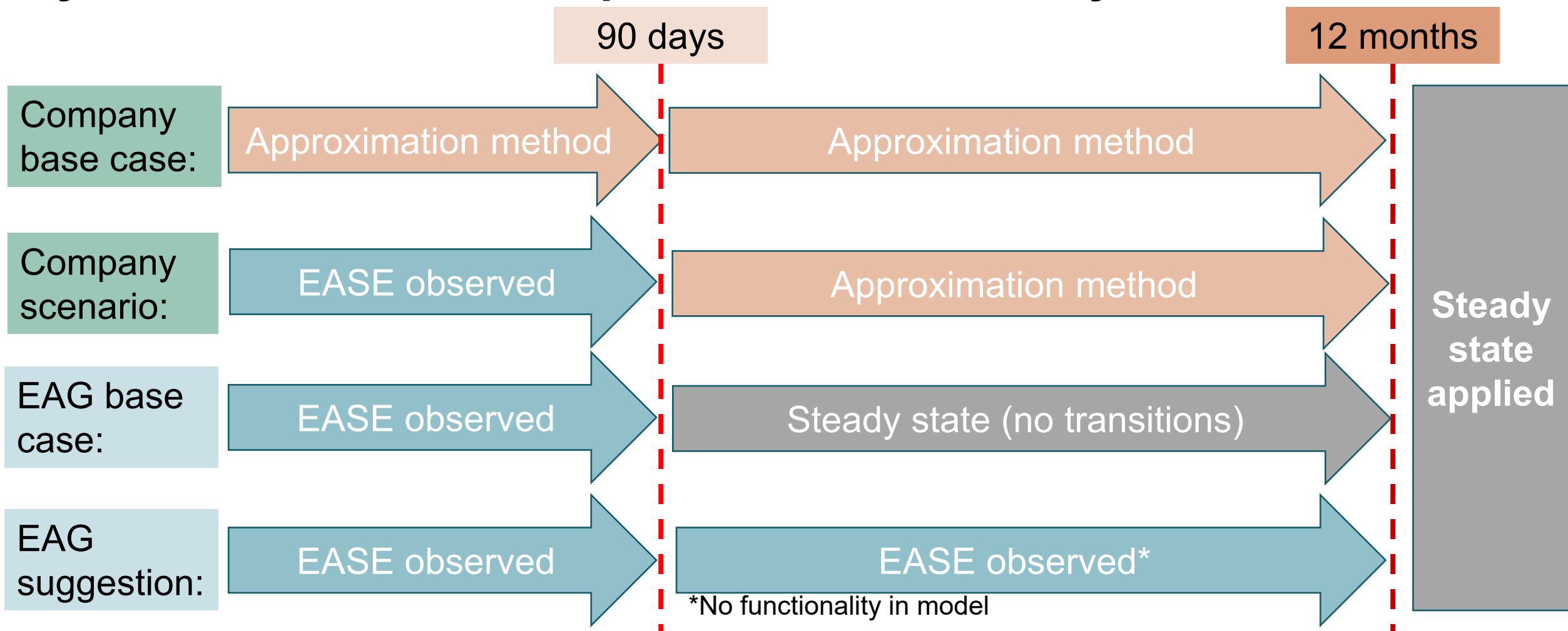


Figure: Company submitted RWE study, % BSAP at various time points after commencing BBE (■)

Key issue: Applying transition probabilities and steady state



Key issue: BBE transition probabilities summary



How should transition probabilities be modelled up to 90 days?

At what point should the steady state assumption be applied to the BBE arm?

How should transition probabilities be calculated if they are applied beyond 90 days?

Key issue: Appropriate use of continuity corrections

Background

- Continuity corrections applied when small sample sizes inform transition probabilities
- They allow for unobserved transitions to be better represented in a model
- E.g. transitions from health state 2 to health state 6 occur rarely but were not observed due to small sample size. A continuity correction will allow for their representation in the model

Company

- Doesn't include continuity corrections in base case but notes they should be explored
- Implementable in model for transitions between any health states, or only adjacent states

1. Adjacent only (*dummy data*)

X - Y	HS1	HS2	HS3	HS4	HS5	HS6
HS1	15 +0.5	5 +0.5	2	4	0	0
HS2	20 +0.33	5 +0.33	6 +0.33	8	2	1
HS3	2	4 +0.33	9 +0.33	3 +0.33	1	0
HS4	0	3	5 +0.33	13 +0.33	3 +0.33	0
HS5	0	0	5	19 +0.33	20 +0.33	2 +0.33
HS6	1	2	5	18	22 +0.5	4 +0.5

2. All transitions (*dummy data*)

X - Y	HS1	HS2	HS3	HS4	HS5	HS6
HS1	15 +0.167	5 +0.167	2 +0.167	4 +0.167	0 +0.167	0 +0.167
HS2	20 +0.167	5 +0.167	6 +0.167	8 +0.167	2 +0.167	1 +0.167
HS3	2 +0.167	4 +0.167	9 +0.167	3 +0.167	1 +0.167	0 +0.167
HS4	0 +0.167	3 +0.167	5 +0.167	13 +0.167	3 +0.167	0 +0.167
HS5	0 +0.167	0 +0.167	5 +0.167	19 +0.167	20 +0.167	2 +0.167
HS6	1 +0.167	2 +0.167	5 +0.167	18 +0.167	22 +0.167	4 +0.167



Key issue: Appropriate use of continuity corrections

EAG comments

- The appropriateness of applying a continuity correction to analyses using the approximation method is unclear
- Not included in EAG base case but presented as sensitivity analyses
- Both “adjacent only” and “all transitions” are plausible. Likely that people only move one health state each 30 days, however 2 plus health state movements were observed in EASE.



Key issues resolved by technical engagement

Number of carers and carer disutility

- Number of carers based on health state severity (0.5 for states 1-2, 1 for 3-4 and 1.78 for 5-6), this was based on a TTO study with vignettes describing participants as “the main carer”
- EAG questioned whether the results of this study could be applied to health states 5 and 6 where more than one carer was present, due to issue with the vignettes
- Company data (N=6) suggest secondary carers have 77% QoL reduction of primary carers
- Company maintain health state specific number of carers and apply 77% modifier to disutility accrued by secondary carers in health states 5 and 6.
- EAG accept this and include company modelling of carers and carer utility in its base case

Estimating health state utility

- Company initially used an OLS regression method to estimate health state utility whereas the EAG preferred a GLM regression.
- Company acknowledged that GLM was a better statistical fit and has been used in both base cases

Key issues resolved by technical engagement

Discontinuation rate

- Annual discontinuation rate of 1% modelled by company, EASE trial had [REDACTED] rate
- Company explained many trial discontinuations would not result in discontinuation in practice (for example not attending follow ups) so EASE rate is an overestimate
- Raising discontinuation rate lowers ICER, assuming 1% is conservative
- Company and EAG base case use 1% (scenario with EASE observed rate)

Modelling health state occupancy after discontinuation

- Company initially modelled those discontinuing BBE after 90 days would adopt transition probabilities of CCM
- However, as CCM was in steady state from 90 days this would effectively mean the effect of BBE at 90 days was preserved for the lifetime of the model
- EAG suggested that those discontinuing BBE after 90 days should move to CCM health state distribution.
- Company agreed and this is present in both base cases



Other issues resolved by technical engagement

Issue	Description	In company and EAG base case?	Scenarios presented?
Number of outpatient appointments	Company JEB-S patients (not in main model) in outpatient appointment calculations	JEB-S excluded when calculating outpatient appointments	None
Baseline age in model	Company modelled at 0.5 years in line with MA. However average age from EASE was 16.67	Age in the model set to 16.67	None
Distribution amongst EB subtypes	Company used distributions from Petrof* study as EASE not expected to represent clinical practice.	Both base cases use Petrof study proportions to model subtype distribution	Scenario using EASE observed distributions
Distribution among health states	People distributed equally between health states 1-6, not as per proportions in EASE.	Both base cases split population equally between health states	EASE observed scenario



Non-resolvable other issues

Issue	Description	EAG conclusion
Efficacy of BBE in DDEB and JEB	Efficacy of BBE may differ between RDEB, DDEB and JEB, EASE suggests this could be the case. Company assumed constant effect across subtypes.	Given small DDEB and JEB patient numbers, unclear whether company base case results only generalisable to RDEB population.
The conduct of the SEE	EAG noted deviations from IDEA protocol used to run the SEE. Also notes it would have been preferable to use clinical nurse specialists for SEE, not UK based clinicians.	“The EAG does not know what the impact on the ICER would be had the limitations identified in the SEE been removed”
Assumption to ensure face validity of the PSA	Company capped HRQoL in the PSA so that utility in more severe states could not exceed less severe states. This changes distributions for utility and could explain why probabilistic ICERs were low when capping was applied.	The EAG presents probabilistic results without capping It believes that the deterministic values are appropriate estimates of the ICERs. Company accepts.

Abbreviations: BBE, birch bark extract; R/DDEB recessive/dominant dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa; SEE, structured elicitation exercise; HRQoL, health related quality of life; PSA probabilistic sensitivity analysis; ICER, incremental cost effectiveness ratio

Summary of company and EAG base case assumptions

<u>Remaining differences between base cases</u>	Company base case	EAG base case
TPs to 90 days	Approximation method	EASE observed TPs
Time until steady state assumption in BBE arm	12 months. Transitions after 90 days modelled using approximation method.	90 days. With steady state assumption applied afterwards.

<u>Common assumptions</u>	Agreed upon assumption	Scenarios provided
Discontinuation rate	Annual BBE discontinuation rate of 1%	EASE observed ██████
Continuity corrections	None applied	Both continuity corrections applied to EAG base case.
Health-states post discontinuation	Discontinuers move to the CCM distribution	-
Health state utility	GLM regression model EASE 24 month data.	-
Carers and their utility	Carers scaled by health state severity. Secondary carers utility loss 77% of primary.	-

Note: Company have not made a case for 1.5% QALY discounting or HST QALY upweighting

Company base case results – Post technical engagement

ICERs

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£100k/QALY)
CCM	£1,061,671	50.74				
BBE	£1,279,800	53.46	£218,129	2.72	£80,199	0.54

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£100k/QALY)
CCM	£935,337	45.80				
BBE	£1,152,657	48.11	£217,320	2.30	£94,345*	0.13

*The company probabilistic results are calculated without the capping of health state utility estimates.

Note: All QALYs presented here are discounted

EAG base case results – Post technical engagement ICERs

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs**	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£100k/QALY)
CCM	£1,029,709	51.88				
BBE	£1,327,662	53.20	£297,954	1.32	£225,781	-1.66

** Discounted QALYs

EAG comment: “The functionality to run probabilistic sensitivity analyses appears to have been removed in the company’s model after TE. However, as the model was previously shown to be relatively linear when the company’s restriction on utilities was removed this was not deemed by the EAG to be a major limitation.”

Before tech engagement (and with utility capping removed) the EAG base case deterministic ICER was £302,808 and probabilistic was £304,178.

Company & EAG deterministic scenario analysis

Company base case– BBE vs CCM (deterministic)

No.	Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£) versus CCM	NHB (£100k/QALY)
1	Company base case	£218,129	2.72	£80,199	0.54

EAG base case and scenario analyses – BBE vs CCM (deterministic)

No.	Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£) versus CCM	NHB (£100k/QALY)
1	EAG base case	£297,954	1.32	£225,781	-1.66
2	With continuity correction (adjacent transitions only)	£319,114	1.20	£266,911	-1.99
3	With continuity correction (all transitions)	£332,690	1.09	£306,598	-2.24

Company & EAG additional deterministic scenario analysis

Company scenario analyses – BBE vs CCM (deterministic)

#	Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£) versus CCM	NHB (£100k/QALY)
1	Company base case	£218,129	2.72	£80,199	0.54
2	Assume █████ discontinuation	£190,079	2.44	£77,978	0.54
3	EASE observed EB distribution	£212,102	2.64	£80,275	0.52
4	EASE observed TPs to 90 days	£130,414	2.91	£44,801	1.61

EAG scenario analyses – BBE vs CCM (deterministic)

#	Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£) versus CCM	NHB (£100k/QALY)
1	EAG base case	£297,954	1.32	£225,781	-1.66
2	Assume █████ discontinuation	£261,430	1.18	£220,809	-1.43
3	EASE observed EB distribution	£289,586	1.28	£225,820	-1.62

Key issues



Key Issue	Resolved?	ICER impact
Method used to calculate and apply transition probabilities	No – for discussion	Large
Appropriate use of continuity corrections	Partially resolved	Large
Discontinuation rate	Yes (with scenarios)	Small
Modelling health state transitions after discontinuation	Yes	Moderate
Number of carers modelled and utility applied	Yes	Moderate
OLS versus GLM method to estimate health-state utility	Yes	Moderate

NICE Abbreviations: OLS, ordinary least squares; GLM, generalised linear model; BBE, birch bark extract; DDEB dominant dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa; SEE solicited elicitation exercise; PSA, probabilistic sensitivity analysis

Other issues



Key Issue	Resolved?	ICER impact
Modelling of number of outpatient appointments	Yes	Small
Average age of people in the model	Yes	Small
The appropriate distribution amongst EB subtypes and health states	Yes (with scenarios)	Small
The efficacy of BBE in DDEB and JEB	Not resolvable	Unknown
The conduct of the SEE	Not resolvable	Unknown
Disparity between the company's PSA and deterministic results	Resolved	Small

Managed access

Criteria for a managed access recommendation

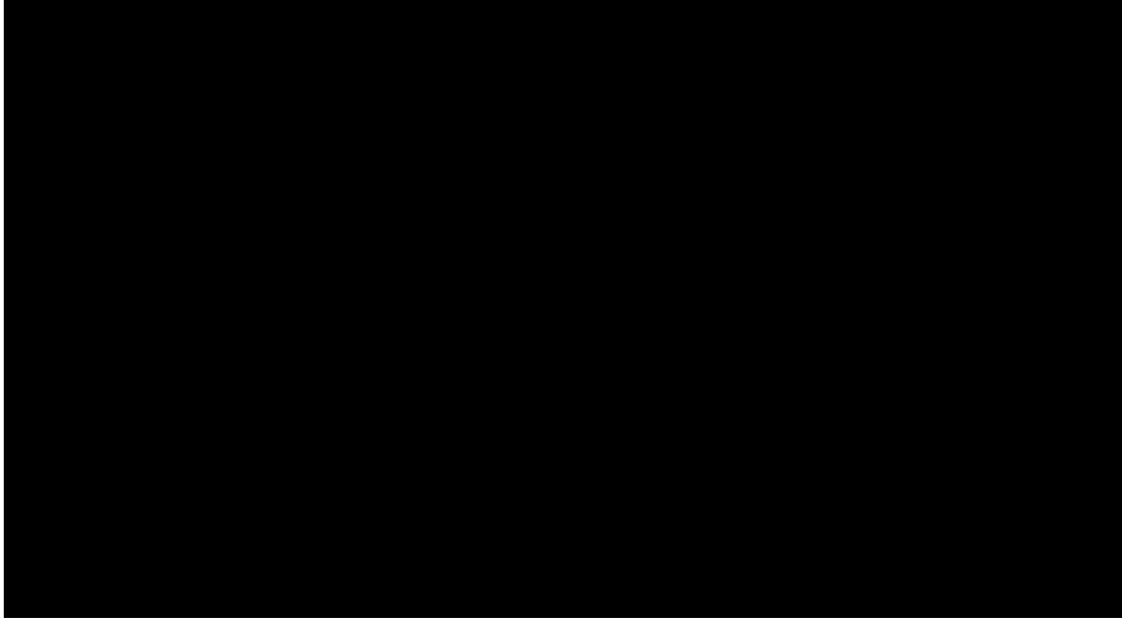
The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.
- A managed access recommendation can only be made if the company has submitted a proposal for managed access.

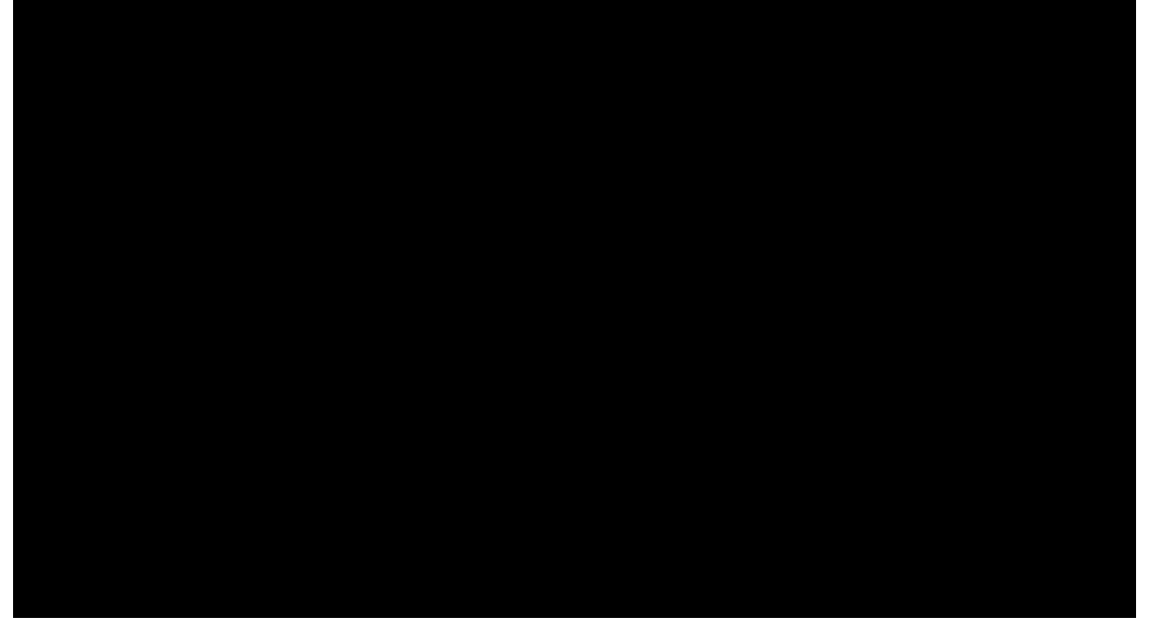
Thank you.

Backup slides

Key issue: Modelling of transition probabilities



EBDASI improvements for people having BBE



BSAP improvements for people having BBE

EAG comments

- Examination of BSAP and EBDASI indicates [REDACTED]
- [REDACTED]
- Note: model does not currently allow implementation of steady state at 180 days