Behandlingsrådet
The Danish Health Technology Council

Application to the Danish Health Technology Council regarding HAL-guided TUR-BT for Non-Muscle Invasive Bladder Cancer

Contents

1 List of abbreviations

Abbreviation	Meaning
AE	Adverse events
BCG	Bacillus of Calmette and Guerin
BLC	Blue light cystoscopy
CI	Confidence interval
CIS	Carcinoma in situ
CKD	Chronic kidney disease
CT	Computed tomography
CUA	Cost utility analysis
DaBlaCa	Danish Bladder Cancer
DRG	Disease related group
DTC	Danish Treatment Council
EAU	European Association of Urology
EC	Expert Committee
EORTC	European organisation for research and treatment of cancer
G1	Grade 1
G2	Grade 2
G3	Grade 3
GA	General aesthetic
HAL	Hexaminolevulinate
HEX	Hexvix
HG	High grade
HR	Hazard ratio
HRQoL	Health related quality of life
HTA	Heath technology assessment
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
INMB	Incremental net monetary benefit
IQR	Interquartile range
ITC	Indirect treatment comparison
K-M	Kaplan-Meier
LG	Low grade
MIBC	Muscle invasive bladder cancer
MMC	Mitomycin-C
NBI	Narrow Band Imaging
NMIBC	Non-muscle invasive bladder cancer
NR	Normalised ratio
NUF	Nordic Urology Forum
PDD	Photodynamic therapy
PICO	Population, Intervention, Comparator, Outcome
PPIX	Photoactive protoporphyrin IX
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QOL	Quality of life

RCT	Randomised control trials
RFS	Recurrence free survival
RR	Risk ratio
RWE	Real world evidence
SIIC	Singular immediate intravesical chemotherapy
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
TTO	Time trade off
TTR	Time to recurrence
TUR-BT	Trans urethral resection of bladder tumour
WLC	White light cystoscopy
WTP	Willingness to pay

2 Summary of the key results of the application

2.1 Data selection

A total of 39 studies out of the 1298 identified by the Danish Treatment Council for Systematic Literature Review (SLR) were identified for inclusion in this analysis. As per the research question and PICO criteria, only studies assessing recurrence at 12 months, progression, HRQoL and/or safety were retained: all other studies not including one or more of these end-points, including detection-only studies, were eliminated.

For the clinical and safety analysis, as per the Danish Treatment Council Methods Guide and Expert Committee request, only RCTs were used. Of the 39 retained studies, 13 were RCTs, 10 of which compared HAL-guided TUR-BT with WLC-guided TUR-BT [1-10]. None compared HAL-guided TUR-BT with NBI-guided TUR-BT. Although ultimately retained for the analyses for scenario purposes, two of the three RCTs comparing NBI-guided TUR-BT with WLC-guided TUR-BT [11-13] failed their primary end-point.

The SLR identified 16 publications that included meta-analyses/ITC's of the RCT data that were relevant to both the clinical question and PICO criteria, and which could be considered as appropriate to include as the comparative evidence. Seven of these [20-26] were carried out with a literature review that was more than 5 years old (range 2012 – 2016), so were not considered appropriate for this purpose. Of the remaining nine, five [15, 28-31] included at least one study with the wrong intervention, and one included an RCT which presented recurrence data for around one third of the patients [27].

Two of the remaining three, one compared HAL-guided TUR-BT with NBI-guided TUR-BT [16], and two compared HAL-guided TUR-BT with WLC-guided TUR-BT [17,18]. However, all were undertaken before publication of a 2023 RCT comparing HAL-guided TUR-BT with WLC-guided TUR-BT [6].

It was therefore decided that to compare HAL vs NBI on recurrence of NMIBC, we would repeat the Cochrane analysis carried out by Maisch et al [17] including data from the missing study [6], and carry out a new meta-analysis for NBI-guided TUR-BT, using the same analytical method as used by both Maisch et al [17] and Lai et al [29].

There were no studies with progression data for NBI. As per the Expert Committee guidance, a comparison between HAL and WLC would be considered appropriate. Only one meta-analysis study, Maisch et al., 2021

[17], was identified as appropriate, that compared HAL-guided TUR-BT with WLC-guided TUR-BT. This was therefore retained for the clinical and safety comparative analysis.

2.2 Clinical effectiveness

2.2.1 Recurrence

Applicants Indirect Treatment Comparison

A Bayesian network meta-analysis (NMA) was carried out based on a systematic literature review carried out in 2022. Analysis of recurrence-free survival times demonstrate the following indirect treatment comparisons:

For WLC vs HEX: OR = 0.611 (95%CrI: 0.396-0.934; Estimated RR = 0.853; Estimated RD = 0.107
For NBI vs HEX: OR = 0.738 (95%CrI: 0.440-1.231; Estimated RR = 0.917; Estimated RD = 0.062
For WLC vs NBI: OR = 0.828 (95%CrI: 0.624-1.097; Estimated RR = 0.947; Estimated RD = 0.039

Applicants Meta-Analysis:

A re-analysis of Maisch et al, 2021 [17] was conducted, including the omitted study [6]. Given the substantial heterogeneity in the datasets, the random effects model was used. The meta-analysis outputs for recurrence free survival results were as follows:

- For HAL-guided TUR-BT vs WLC-guided TUR-BT, HR 0.632 (95%CI, 0.487 – 0.819), p=0.001
- For NBI-guided TUR-BT vs WLC-guided TUR-BT, HR 0.740 (95%CI, 0.415 – 1.320), p=0.308

Published Meta-Analyses:

Similarly, although Heer et al. [6] was not included in their HTA, Ontario Health [16] concluded that HAL-guided TUR-BT likely reduces the rate of recurrence at 12 months when compared to using white light alone and NBI-guided TUR-BT likely results in little to no difference in recurrence compared to WLC alone. Their indirect treatment comparison, while not statistically significant, showed a trend towards a lower rate of recurrence with HAL-guided TUR-BT than NBI-guided TUR-BT. The final recommendation from Ontario Health was to fund HAL-guided, and not NBI-guided TUR-BT, for all patients regardless of risk category.

Likewise, Maisch et al [17] and Veeratterpillay et al [18] concluded that HAL-guided TUR-BT was superior to WLC-guided TUR-BT. Maisch et al, 2021 [17] reported a Hazard Ratio of 0.69 (95%CI; 0.48 – 0.98) from a post-hoc analysis of HAL alone. Heterogeneity was low: Tau^2 = 0.00, Chi^2 0.21, df3 (p=0.98). Veeratterpillay et al., concluded that at 12 months, the RR for disease recurrence with HAL-guided TUR-BT was 0.73 (95% CI 0.59-0.91) and at 24 months was 0.72 (95%CI 0.57, 0.90). Recurrence free survival at 12 months for both HAL and 5-ALA showed a HR (in favour of PDD) of 1.14 (95%CI 1.05-1.23) and at 12 months, HR 1.25 (95%CI 1.15-1.35, p<0.001).

Individual RCT studies concluded as follows:

Recurrence at 12 months

HAL: The majority of the evidence suggests that HAL-guided TUR-BT significantly reduces recurrence rate in the short term (at 12 months) in low, medium and high-risk patients [1-10].

NBI: Although the evidence suggests that NBI-guided TUR-BT significantly reduces recurrence rate in low-risk patients in the short term (at 12 months) [11-13], two of the three RCTs failed their end-point [12,13].

The majority of the evidence suggests that NBI-guided TUR-BT is of no benefit in medium and high-risk patients at 12 months [11-13].

Recurrence at up to 5 years

HAL: The majority of the evidence suggests that HAL-guided TUR-BT significantly reduces recurrence rate in the mid to long term (2-5 years) [1-3, 19].

NBI: There is no evidence that NBI-guided TUR-BT reduces recurrence rate in the long term.

2.2.2 Disease progression

The meta-analysis for progression results from Maisch et al, 2021 [17] for the HAL sub-analysis was as follows:

- HAL-guided TUR-BT vs WLC-guided TUR-BT: HR 0.69 (95%CI; 0.48 – 0.98).

Individual RCTs concluded as follows:

Disease progression

HAL: The impact of HAL-guided TUR-BT on progression is less well quantified since progression takes place over a longer timeframe than recurrence, numbers of people progressing are low and there are differences in the definitions of progression. Furthermore, the utilisation of different adjuvant treatments and treatment lengths are considerable confounders in the outcome. However, HAL-guided TUR-BT has shown a significant improvement in time to progression [5,8] and a trend towards a reduction in progression [8].

NBI: There is no data on the impact of NBI-guided TUR-BT on progression.

Overall survival

HAL: There is emerging data supporting overall survival benefit in HAL-guided TUR-BT [2] compared to WLC-guided TUR-BT alone.

NBI: There is no data on the impact of NBI-guided TUR-BT on overall survival.

2.2.3 HRQoL

No data was available on HRQoL for NBI.

One study [6] did collect self-reported HRQoL data for HAL-guided TUR-BT vs WLC-guided TUR-BT and reported similar responses using EQ-5D-3L, for both arms at all time points. At 12 months, the mean difference was -0.006 (-0.067-0.056), p=0.854. There was no evidence of a difference in QALYs gained between treatment groups at 3 years (mean difference -0.096, 95%CI, -0.342-0.151), p=0.444.

No further analysis was undertaken.

2.2.4 Number of TUR-BTs

The Danish guidelines [32] recommend only one primary TUR-BT in patients, with all follow-up surveillance procedures undertaken in an outpatient setting with flexible cystoscopy using either NBI or HAL. This is out

of scope of this analysis. In certain circumstances, patients will undergo a second TUR-BT when the initial TUR-BT may be incomplete and there is a risk of residual tumours (NMIBC guideline recommendation).

It can be assumed, however, that a reduction in recurrence is a surrogate measure of the need to perform a TUR-BT. Studies identified concluded that in reducing recurrence, a similar reduction in the number of TUR-BTs is reduced [33,34].

No further analysis was undertaken.

2.3 Safety

HAL and NBI were both found to be safe.

Maisch et al., 2021 [17] were unable to draw conclusions regarding how HAL-guided TUR-BT affects AE of any grade but noted participants with WLC TUR-BT had 36 more (48 fewer to 131 more) AE per 1,000 participants with HAL-guided TUR-BT, which falls below their predefined threshold for MCID of 50 per 1,000.

The Ontario Health HTA 2021 review [16] also considered safety but the SLR and criteria included only one study that reported on safety outcomes for Hexvix. Reviewers concluded that Hexvix is "generally safe".

Two HAL studies [6,10] and one NBI study [12] reported on adverse events. Heer et al [6] reported no difference between WLC and HAL groups (RR 0.62;95%CI (0.24-1.60), p=0.33). O'Brien et al [10] reported that there were no adverse events related to HAL in their study. Naito et al [12] saw no significant differences between NBI and WLC.

Comprehensive information regarding the safety of Hexvix is available in the Summary of Product Characteristics [35]. Most of the reported adverse reactions were transient and mild or moderate in intensity. The adverse reactions observed were expected, based on previous experience with standard cystoscopy and TUR-BT procedures. This data is supported by an analysis of post-marketing data [36], an RCT looking specifically at the safety of repeat HAL-guided TUR-BTs [37] and data from a large prospective registry [38].

Adverse reactions with either HAL or NBI have therefore not been observed other than those associated with standard cystoscopy and TUR-BT procedures.

Due to the paucity of safety data, no further analysis was undertaken.

2.4 Patient perspective

Although detection is out of scope of this analysis, patients can be reassured that HAL-guided TUR-BT with Hexvix improves tumour detection vs conventional WLC-guided TUR-BT [39] alone, consequently improving resection quality and improving diagnosis and care, giving patients more time in remission [17, 18]. A reduction in recurrence and progression of tumours results in fewer surgical resections (TUR-BTs), which greatly benefits the patient.

As a procedure carried out by physicians, the procedure does not have an impact on the patient's daily life. With the exception of instillation into the bladder for HAL, there is no difference between HAL, NBI and WL guided TUR-BTs from the patient's perspective.

2.5 Organisational implications

The major barrier to adoption in Denmark is the lack of availability of HAL-enabled equipment. All equipment, regardless of whether HAL or NBI, consists of a processor, a light source, a camera head, a light cable and a cystoscope. There are three manufacturers of HAL-enabled equipment (Richard Wolf, Karl Storz and Olympus), and one manufacturer of NBI (Olympus). The majority of urology departments in Denmark contain the Olympus NBI equipment which in many hospitals may not yet be adaptable to accommodate HAL. Thus, HAL-guided TUR-BT may not currently be possible in many hospitals in Denmark without a change or the addition of equipment. This is reflected in the Budget Impact Model.

Some work order changes would be required, namely the instillation of HAL into the bladder prior to the TUR-BT. In most hospitals patients are currently seen by nursing staff prior to the procedure. Prior to the introduction of the NBI equipment in Danish urology departments, these nurses broadly instilled HAL at the same time as undertaking other pre-procedure processes. As such, re-introduction of HAL is not anticipated to be a major barrier.

Overall, there is less burden to the health care system with the use of a technology that improves resection completeness and reduces the number of surgical TUR-BTs in the operating room due to tumour recurrence and progression.

The training of staff to use HAL-capable equipment is provided by the manufacturer and peers.

2.6 Health economics

HAL was found to be cost-effective compared to NBI.

A de novo meta-analysis and a cost-utility analysis were undertaken comparing HAL-guided TUR-BT to NBI-guided TUR-BT. The results of the cost-utility analysis fall well within the range of ICERs that would normally be considered cost-effective (<100,000 DKK/QALY for most simulations). This gives confidence that, even allowing for structural and parameter uncertainty, HAL-guided TUR-BT is highly likely to represent a cost-effective option in the management of NMIBC.

Table 1: Results of the health economic analysis

Intervention	Total cost, DKK	Total benefit QALY	ΔC, DKK	ΔE	ICER	Statement of dominance
			vs. relevant comparator			
HAL-guided TUR-BT	60,070	6.672	-	-		
NBI-guided TUR-BT	52,453	6.779	7,616	0.108	70,707 DKK/QALY	No dominance

The results of a budget impact analysis was constructed in line with Danish practice and the DTC specification, HAL-guided TUR-BT would be used for one initial TUR-BT procedure following a suspected diagnosis of NMIBC. This would represent a net budget impact of 3,037,505 DKK at five years, assuming 30% of patients would be switched to HAL from NBI, and inclusive of anticipated equipment costs to replace existing equipment. The budget impact analysis solely considered only direct hospital costs attributable to the use of HAL-TUR-BT: no offset was applied to take into account the consequential delay

in requirement for repeat TUR-BT for recurrent disease, or potentially later-stage treatments. Although this aspect of the benefit was fully explored in the cost utility model, essentially being an opportunity cost rather than a direct reduction in budgetary spend, it was decided to omit it. This means that the estimated cost impact may be considered an upper estimate.

3 Introduction

Bladder cancer is the sixth most common cancer in Denmark [40] and accounts for just under 5% of all new cancers in Denmark [40] with 5-year survival of around 70% [41]. The risk of bladder cancer increases significantly with age, and it is more common in men than in women; it is the fourth leading cause of cancer in men in Denmark, compared to being the seventh in women [40].

Approximately 75% of patients with bladder cancer present with non-muscle invasive bladder cancer (NMIBC), a disease confined to the mucosa (stage Ta or carcinoma in situ, CIS) or lamina propria/submucosa (stage T1) [18] which is a heterogenous disease with differing clinical outcomes. NMIBC has a high recurrence rate (50-70% of patients), and 10-20% of NMIBCs will progress to muscle-invasive disease (depending on stage and grade at diagnosis) [42-44]. In Denmark, diagnosis depends on the outcome of a cystoscopy and CT urogram. Patients with tumours then undergo a TUR-BT procedure where tumours are removed and pathology is obtained for tumour staging.

Initial treatment for NMIBC focuses on visualisation and complete surgical removal of all visible tumours using trans-urethral resection of bladder tumour (TUR-BT), during which detected tumours in the bladder are resected, pathologically examined and biopsies from suspected flat lesions are taken. TUR-BT is a standard procedure performed by conventional white-light cystoscopy (WLC), and as recommended by guidelines, in some patients this is aided by enhanced cystoscopy techniques. Unfortunately for patients, NMIBC has a high risk of recurrence (approximately 50%) and progressive disease (approximately 11%) after a median follow up of 3.9 years [34]. Poor visualisation and incomplete removal of tumours during TUR-BT means that patients are at increased risk of recurrence and progression [42,43,45,46]. It is therefore imperative to ensure the effective detection and complete removal of malignant bladder tumours.

The use of WLC alone can lead to missed lesions [47] and identifying tumour margins can be challenging [48]. This is particularly true for identification of difficult-to-find small or flat, high-risk tumour lesions, e.g., carcinoma in situ (CIS) [47,49] papillary tumours, e.g., small (micropapillary), and/or multifocal Ta/T1-tumours. Early dysplasia can also be missed if using WLC alone [49-51]. TUR-BT can remove a Ta/T1 tumour completely, however, these tumours commonly recur and can progress to MIBC. With WLC alone, for a Ta/T1 tumour there is a 51% risk of incomplete resection and an 8% risk of under staging [46]. Incomplete resection leaves a residual tumour burden, which increases the risk of progression and recurrence. Adjuvant therapy should be considered for all intermediate and high-risk patients, the type of which is given on the basis of risk [52]. It is reported that WLC identifies CIS in 38–71% of cases, varying with the urologist's skill and experience [38].

Having visual enhanced cystoscopy techniques to aid the WLC-guided TUR-BT is essential to improve initial detection and completeness of resection of bladder cancer tumours, as well as taking guided biopsies for improving the chance of getting a correct diagnosis (staging and grading) and risk stratification: an accurate diagnosis depends on the quality of the histological evaluation of suspect tissue obtained via TUR-BT or biopsies obtained from suspicious lesions during cystoscopy [53]. A resection tissue sample or biopsy should preferably include detrusor muscle for evaluation of potential muscle invasiveness. Very small or high-risk flat CIS tumours are particularly vulnerable to not being seen or to being misdiagnosed if not biopsied. Improved tumour visualisation methods include the intervention, HAL-guided TUR-BT using Hexvix® and the comparator, Narrow Band Imaging (NBI).

In malignant cells, dysregulation in the activity of transport proteins leads to the accumulation of photoactive protoporphyrin IX (PPIX) [35,54]. After intravesical instillation of the optical imaging agent

Hexvix® (hexaminolevulinate), also referred to as HAL or HEX, porphyrins (including PPIX) accumulate preferentially intracellularly in malignant bladder wall lesions. The intracellular porphyrins (including PPIX) are photoactive, fluorescing compounds, which emit red light upon blue light exposure. As a result, premalignant and malignant lesions will glow red on a blue background, making them easier to visualise and remove [35,54].

Improved tumour visualisation with HAL-guided TUR-BT in adjunct to WLC results in significantly improved tumour detection versus (vs) WLC-guided TUR-BT only [55]. The procedure is often referred to as Blue Light Cystoscopy (BLC) or Photodynamic Diagnosis (PDD), noting the latter is the nomenclature used in the Danish Guidelines for Bladder Cancer [53].

Use of HAL-guided TUR-BT has shown a significant reduction in disease recurrence, improvements in time to disease recurrence and in recurrence-free survival (RFS) [16,18] and a reduction in disease progression [54] vs WLC-guided TUR-BT. Data suggests a trend towards the use of HAL-guided TUR-BT improving overall survival compared to WLC-guided TUR-BT. Such potential impact of HAL guided TUR-BT on survival was initially reported by Gakis in 2016 [22] and a recent (May 2024) observational study comparing the impact of BLC on the oncologic outcomes of NMIBC patients in a real-world equal-access setting at the Veterans Affairs (VA) Healthcare System in the US [56]. This data was not further analysed as part of this submission as this is out of scope.

Narrow Band Imaging (NBI) is an endoscopic visualisation-assisted (VA) technique, which makes use of blue and green wavelengths of light to enhance the contrast between mucosa and vascular structures without the prior application of dyes. These wavelengths of light are absorbed by haemoglobin, so blood vessels appear dark, providing contrast to surrounding tissue to allow for the detection of changes. Since malignant solid tumours usually demonstrate rich vascularity due to angiogenesis, the increased vascularisation is used as an indirect sign to improve detection of malignant tumours by the NBI technique. NBI is a technology unique to manufacturer Olympus.

Although out of scope of the analysis, the reported sensitivity and specificity with BLC and NBI are in the ranges of 87%–97% and 43%–67% for detecting tumor lesions, respectively; the sensitivity and specificity of standard WLC are 68%–78% and 43%–89% in the comparison groups, respectively. The performance with BLC and NBI is higher for detecting CIS lesions vs WLC, and differs with surgeons' experience [57,58].

Both visual enhancement techniques have higher detection rates on lesion basis compared to WLC. False-positive rates for BLC ranging from 14.7% to 36.5% versus 11.6–45.1% in the WLC groups. False positivity can be caused by inflammation, recent BCG instillation (<12 weeks) and by a recent transurethral resection itself. The false positive rates deceases with surgeon experience. It may increase follow-up procedures but does not have any negative impact on prognosis [59].

3.1 Patient/target population

Aetiology, symptomology and prognosis

Bladder cancer is a life-long disease which has a high burden to the healthcare system. Most of the time, there is a need for lifelong treatment and surveillance due to its high risk of recurrence and progression. Haematuria (blood in the urine) is typically the primary symptom of bladder cancer, presenting in 80-90% of patients [60]. NMIBC is confined to the bladder mucosa and refers to the group of tumours staged as Ta or stage T1 (lamina propria/submucosa) [34] or carcinoma in situ. It is a heterogenous disease that can also

be classified on the basis of disease risk progression, which is clearly linked to disease recurrence, namely low, medium and high risk categories. NMIBC has a high recurrence rate (50-70% of patients), with 10-20% of NMIBCs and 54% of patients with CIS progressing to muscle-invasive disease (depending on stage and grade at diagnosis) if the flat, difficult to find CIS lesion is missed and/or no adjuvant treatment is given [61,62].

Patients with high-risk bladder cancer have a 5-year risk of recurrence and progression of up to 78% (according to EORTC risk calculator) and 44% (EAU NMIBC Guideline [47]), respectively. Notably, CIS will progress to muscle invasive disease in 54% of patients without any treatment [63] and is per definition categorised as high-risk bladder cancer. If NMIBC progresses to muscle-invasive disease, in the absence of metastases, the standard treatment is radical cystectomy [47,53]. Radical cystectomy is associated with a high morbidity and mortality rate [64] and has a major impact on patients' quality of life and well-being [65].

Table 2: Risk definitions according to the EAU guidelines [47]

Risk group	Definition
Low risk	• A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years • A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors
Intermediate risk	• Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors*: • Ta LG/G2 or T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor
Very high risk	**Stage, grade with additional clinical risk factors*:** • Ta HG/G3 and CIS with all 3 risk factors • T1G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

*age > 70; multiple papillary tumours; and tumour diameter > 3 cm

Post-TUR-BT, patients undergo regular surveillance using cystoscopy in order to spot recurrent disease in a timely fashion and ensure that patients receive the appropriate treatment. HAL may also be used in surveillance for predominantly high-risk patients to identify early recurrence, as well as an adjunct for fulguration of low to intermediate risk bladder cancer in an outpatient setting to ensure completeness of the procedure [66]. However, HAL for surveillance and/or office fulguration, is not standard practice across Europe [67], is not practiced in Denmark and is not part of the scope of this analysis. Surveillance procedures and the use of flexible cystoscopy for NMIBC are also out of scope.

Danish incidence and prevalence

The incidence of bladder cancer in Denmark is 2,100 per year [68], with a prevalence of 15,381 (2021) [68]. In 2023, 3,776 patients were registered on the National Patient Registry under code DC769, Kræft i

urinblæren/cancer in the bladder, which includes bladder cancer stages Ta and T1-T4b. The proportion of patients with metastases was reported at 18% (n=673) under codes DC77-79 (Metastaser og kræft UNS i lymfeknuder/Metastases and cancer in the lymph nodes, Metastaser i åndedrætsorganer og fordøjelsessystemer/metastases in respiratory organs and digestive system, or Metastaser i andre specificerede lokationer/Metastases in other specified locations).

In 2023, 1,230 Danish patients were recorded as having non-invasive tumours with a median age of 73 [60]. The proportion of patients in Denmark who experience a recurrence within 1 year of the date of diagnosis is 32% (95% CI: 30-35) [53], although recurrence rates did vary by region ranging from 26% in Region Zealand to 41% in the Capital Region. In 2023, progression was also recorded with 4% of patients with non-invasive disease progressing to muscle invasive cancer [53].

Current clinical practice in Denmark

Haematuria (defined as blood in the urine) is typically the primary symptom of bladder cancer, presenting in 80-90% of patients [53]. The *Pakkeforløb for kræft I urinvejene* [53] requires that patients referred to urologists with suspected bladder cancer have an initial evaluation undertaken consisting of an examination, CT urogram and cystoscopy. Where bladder cancer is suspected, a transurethral resection of the bladder (TUR-BT) is then performed. The Danish Bladder Cancer guidelines [53] cite that at the time of diagnosis, about 50% of all bladder tumours will be invasive – and half of those will be muscle invasive. This is in contrast to the 75% of invasive tumours reported in the literature [18, 42-44].

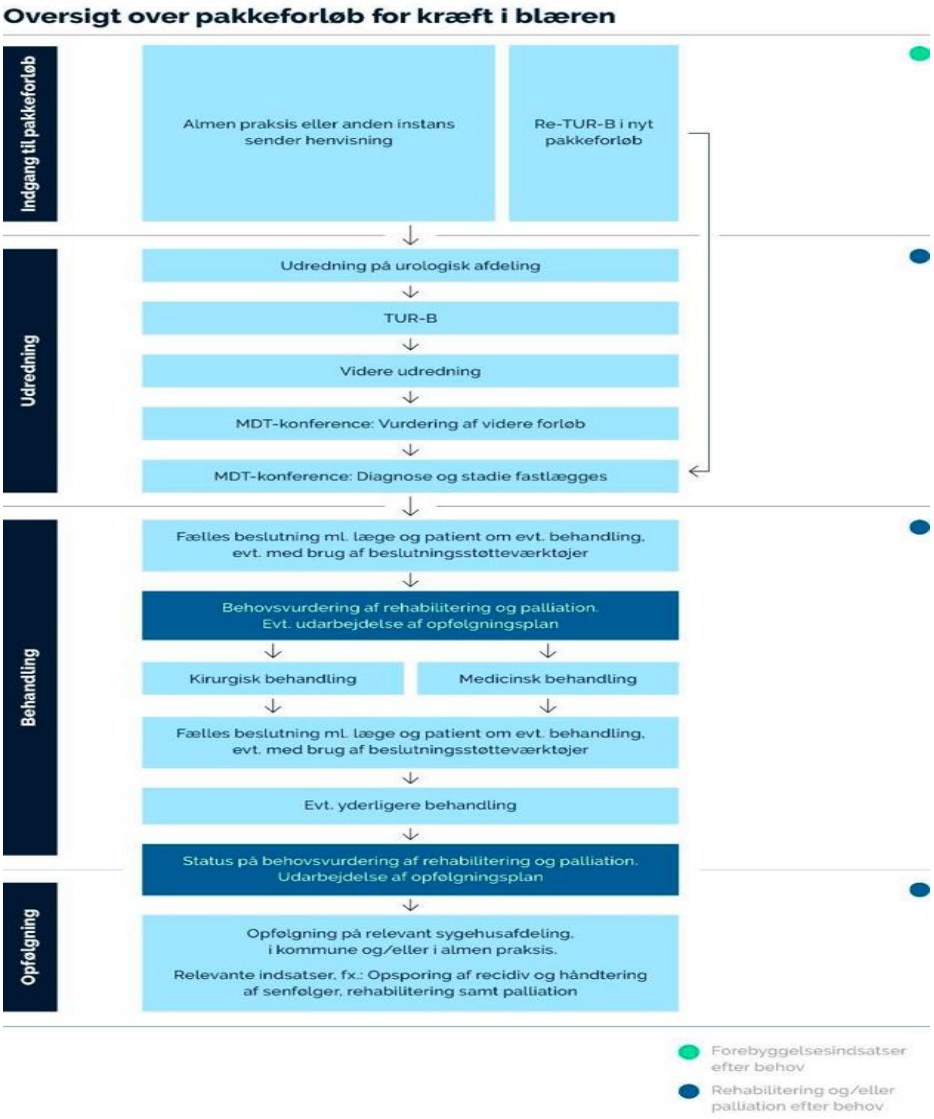
Tumours are both graded and classified, with treatment varying depending on the specific histology and staging and patient related factors (e.g. age, co-morbidities, life expectancies, etc). The guidelines state that these tumours should be treated with particular attention for early radical surgical treatment [53].

Non-invasive tumours are treated with resection of all visible tumours during the TUR-BT followed by either intravesical adjuvant agents, typically BCG or mitomycin-C (these agents are commonly referred to as single immediate intravesical chemotherapy or SIIC), and patients have follow-up cystoscopies at a frequency in line with the recommendations in the Guidelines for their risk category.

When patients are diagnosed, the tumours are described in terms of the number, size and characteristics and classified in terms of tumour type, grade of malignancy, and stage. They are treated in line with specific guidelines depending on histology, namely:

- Ta and CIS
- T1
- Muscle invasive bladder tumours
- T4b and metastatic disease

Figure 1: Current clinical practice in Denmark



The correct examination, including visual identification of the bladder tumour and complete resection and obtaining histopathology, is essential for the patient to receive adequate treatment [34]. The quality of the cystoscopy performed is therefore crucial to the correct investigation and quality of NMIBC care. Correct and early diagnosis is important for long term outcomes in NMIBC, as under-staging of the tumours is seen in 15-40% of patients, which can lead to under-treatment. The correct diagnosis, by identifying and resecting all malignant lesions in the bladder, obtaining adequate histopathology for correct risk categorisation of the patient, is crucial to receive the right treatment [53].

According to the Danish treatment guidelines mentioned above, HAL and NBI are relevant for CIS and high-risk patients, which are registered with the diagnosis codes: “DD090 Carcinoma in situ (Tis) i urinblæren”, “DD095 Non-invasive papilar tumor (Ta) i urinblæren” [53]. In total, approximately 3.900 (576+3.336) patients were registered with one of these diagnoses yearly [69].

HAL has been included in the Danish guidelines for the diagnoses of bladder cancer [53] since 2007 and was broadly used in all five regions until 2018, when there was a general switch of equipment in hospital

urology departments to using NBI (Olympus) equipment which may not have BLC/HAL capability (See Section 2.3). As a result, the number of HAL procedures has decreased drastically during the last 6 years in Denmark and currently only patients in two regions (specifically only in one hospital in each of these regions) are reported as being treated with HAL, compared to NBI in all five.

The Danish guidelines [53] (most recently revised in October 2023) do still recommend HAL, along with NBI, as follows:

- First-time bladder tumour to allow for complete resection, and as an alternative to selected site biopsies regarding the detection of CIS
- First check-up due to CIS after BCG
- Urothelial cells suspicious for high degree of malignancy (Paris Category IV) or urothelial cells with a high degree of malignancy (Paris Category V) cells in the urine at normal findings at cystoscopy and CT urography

The Danish guidelines [53] recommend HAL and NBI interchangeably regardless of diagnosis or procedure. In this regards the Danish NMIBC guidelines differ from all other international guidelines, including the recently updated European Association of Urology guidelines [47] on the use of visual enhancement like HAL and NBI. These guidelines, in contrast to Denmark, highlight the difference in level of evidence and performance between HAL and NBI, particularly with respect to high-risk, difficult-to-find small and flat lesions e.g. CIS tumours, and for targeted biopsies, where HAL alone has a strong recommendation, and its use is considered best practice. NBI is not recommended with the same strength in this patient settings which are at highest risk for recurrence and progression. The EAU guidelines recommend the use of:

- Photodynamic diagnosis (PDD or BLC or HAL-guided) – the use of BLC in patients who have received pre-treatment with an optical imaging agent. Guidance is based on level 1a evidence that BLC is more sensitive than WLC for detecting NMIBC, particularly CIS and for reducing recurrence in the short and long-term
- Narrow-band imaging (NBI) –an endoscopic visualisation-assisted (VA) technique, which makes use of two bandwidths of blue and green illumination to enhance the distinction of mucosa and microvascular structures without the prior application of dyes. Guidance is based on level 3b evidence for improved detection and level 1b evidence for a short-term improvement in recurrence rates for low grade tumours, although the overall results of the study were negative.

Patient follow-up procedures vary depending on their risk category, but subsequent to the amended Guidelines in 2023 [53], patients in Denmark are no longer followed up “for life” but rather for 5 years. However, any recurrence puts patients back to “month one” and the 5-year cycle begins again. High risk patients have surveillance cystoscopies every 4 months for 2 years reducing to every 8 months for 2 years then once in the fifth year. Low and intermediate risk patients are seen at month 4 then month 8 following TUR-BT then annually thereafter for 4 years.

Although some variations in hospital practice were identified, the patient pathway itself is clearly outlined in the “Pakkeforløb for kræft I urinvejene” with clinician interviews confirming that this pathway, alongside the Danish Guidelines, are closely followed with some minor variations in practice identified [69]:

- **The level of physician performing the TUR-BT.** In Roskilde, all TUR-BTs are done by experienced, specialist surgeons or residents under the supervision of a specialist. In most other hospitals, TUR-BTs are undertaken by junior residents.

- **Repeat TUR-BTs.** In some hospitals, TUR-BTs procedure times are limited to 1 hour in length. In patients where tumour burden or complexity of the procedure would require a procedure time of more than 1 hour, the patients are re-scheduled for a follow up TUR-BT. In most other hospitals, only one TUR-BT is performed regardless of length of time taken. In all cases, in line with the guidelines, typically each patient will only have one TUR-BT over the 5-year cycle, unless the patient has a recurrence. Each recurrent patient will again typically only have one TUR-BT. As noted, these patients go back to the beginning of the "cycle".
- **MDT involvement.** In most cases, only patients where muscle invasive disease is identified during the TUR-BT are referred to the MDT. There are some exceptions where all patients will be discussed at MDT.

Quality TUR-BTs are considered to be important to ensure detection and removal of all tumours [53]. In most cases, the aim is to perform only one TUR-BT in Denmark. The majority of monitoring/diagnosis and surveillance procedures are undertaken using flexible cystoscopy which is outside of the scope of this analysis.

In summary, although NBI and BLC are recommended interchangeably in the Danish treatment guidelines, current clinical TUR-BT practice in Denmark almost exclusively involves the use of NBI.

3.2 Comparator

Narrow Band Imaging (NBI) is an endoscopic visualisation-assisted (VA) technique, which makes use of blue and green wavelengths of light to enhance the contrast between mucosa and vascular structures without the prior application of dyes. These wavelengths of light are absorbed by haemoglobin, so blood vessels appear dark, providing contrast to surrounding tissue. Because malignant solid tumours usually demonstrate rich vascularity due to angiogenesis, the increased vascularisation is used as indirect sign to improved detection of malignant tumours by NBI technique. NBI is unique to the manufacturer Olympus.

3.3 Intervention

In malignant cells, increased vascularization and dysregulation in the activity of transport proteins leads to the accumulation of photoactive protoporphyrin IX (PPIX) in malignant cells [17,54]. After intravesical instillation of the optical imaging agent Hexvix (hexaminolevulinate), also referred to as HAL or HEX, porphyrins (including PPIX) preferentially accumulate intracellularly in malignant bladder wall lesions. The intracellular porphyrins (including PPIX) are photoactive, fluorescing compounds, which emit red light upon blue light exposure. As a result, premalignant and malignant lesions will glow red on a blue background, making them easier to visualise and remove [35,54].

HAL-guided TUR-BT with Hexvix is undertaken using blue light cystoscopy enabled equipment. Karl Storz, Olympus and Richard Wolf manufacture this equipment.

3.3.1 Advantages of HAL-guided TUR-BT compared to NBI-guided TUR-BT

- HAL more clearly visualizes tumours (including the margins of tumours) present in the bladder. NBI shows the blood vessels supplying those tumours thus only indirect signs are used (where vascularization may be less in tumour margins).
- Registrational studies for NBI reported that poor visibility in the NBI-first arm caused by bleeding during resection, which released haemoglobin. The wavelength of NBI is absorbed by the haemoglobin on the surface of the bladder wall, limiting visibility. Bleeding during surgery has no or limited impact on tumour visibility with HAL.

- HAL-guided TUR-BT demonstrates significant benefit in reduced recurrence at 12 months in low, medium and especially high-risk patients. NBI-guided TUR-BT has mainly demonstrated significant benefit in low-risk patients.
- HAL-guided TUR-BT demonstrates significant benefit in reducing recurrence at up to 5 years. NBI-guided TUR-BT has no evidence to support this.
- HAL-guided TUR-BT demonstrates benefit in reducing progression. NBI-guided TUR-BT has no evidence to support this.
- A plethora of evidence supporting benefit with BLC in reducing recurrence and progression, and emerging long-term RWE of overall survival benefit (excluded from this analysis).

3.3.2 Disadvantages of HAL-guided TUR-BT compared to NBI-guided TUR-BT

- HAL-guided TUR-BT requires instillation of Hexvix® at least 1 hour before the TUR-BT procedure. NBI requires no bladder instillation with a photosensitive agent.
- The direct fixed equipment costs of NBI and BLC are likely comparable, though NBI would be expected to have lower direct variable costs as it does not require pre-procedural catheters and drug instillation. BLC requires the instillation of HAL into the bladder approximately 1 hour prior to the procedure.
- The risk of false positive detection rates appears to be similar between the two techniques [39].

3.3.3 Brief Summary of HAL evidence

HAL has been evaluated compared with WLC in eight randomized controlled sponsor trials for regulatory approvals, including 2200 NMIBC patients, numerous independent controlled trials, and several long-term RWE registries of up to 10-years. The SLR identified a total of 28 studies including HAL, including 10 RCTs and 12 meta-analyses/ITCs.

Compared to WLC alone HAL improves the sensitivity of tumour detection, improves the ability to visualize tumour margins more clearly & enables the surgeon to make a more complete quality resection, including tumour margins, thus reducing the risk of residual tumours and tumour recurrence. In addition, HAL targeted biopsies allow for a better visualisation and identification of difficult-to-find flat lesions e.g. CIS from suspect areas which facilitates a higher 'hit-rate' and more correct staging and risk stratification during the first TUR-BT. Post-operative management is risk based e.g., using the EORTC or EAU risk tables, based on multiple clinic-pathological risk factors. The earlier one can identify a high-risk tumour, the better post-operative treatment and management decisions, and longer-term clinical outcomes. Detection, however, is not included in the scope of this assessment. For the purpose of this assessment, only studies with data that met the PICO requirements were included (recurrence at 12 months, progression, HRQoL, safety and number of TUR-BTs).

The completeness and quality of TUR-BT is increasingly considered of importance to post-operative management and clinical outcome, and a number of initiatives have been emphasized to improve the quality that specifically include the use of HAL aided TUR-BT, e.g., *Getting It Right First Time (GIRFT) (https://gettingitrightfirsttime.co.uk/),* and Mariappan P et al [61]. Consequently, the implementation of HAL can result in a change and improved staging and risk classification, which allows for a more optimal risk-based post-operative follow-up, and treatment strategy which can reduce the risk of under staging and under treatment, reduce the total number of surgical resection procedures for recurrence (re-TUR-BT) over time, prolong the time to resection of recurrent tumours, and ultimately may impact the time to progression of disease [38].

Although out of scope of this analysis, the importance of improving tumour detection, a complete resection, appropriate risk-classification, diagnosing high-risk tumours early, and the consequences for further treatment are stated as crucial for outcomes in multiple publications. In a comparative study (146 patients) the differences in recommended treatment after either HAL- or WLC-guided TUR-BT was recorded. Due to improved detection, about 20% of patients received more appropriate treatment [70]. Geavlete et al. [59] also found that in the BLC group postoperative treatment changed in 19% of the patients compared with 6.3% in the WLC group ($p<0.001$).

The majority of trials evaluating the outcomes of HAL aided TUR-BT focus on differences in detection rates for various tumours as primary outcome, with follow-up of between 3 months up to 1-3 years. The sponsor RCTs provide the basis of the SmPC and are of high, regulatory grade quality. Since approval in 2005 there have also been numerous further independent trails conducted to evaluate the benefits of BLC.

There is also substantial real-world evidence (RWE) available on the use of HAL in clinical practice, in a wide variety of patients, from different countries & regions in Denmark. The Cysview[a] BLC registry (NCT02660645) in more than 3300 NMIBC patients with up to 10 years of follow-up, since initiated in 1997 in the US, and from research collaborations with academic institutions on two Nordic registries. Follow-up 2- and 5-years BLC data from more than 8000 NMIBC patients in the Danish National population registry was recently presented at NUF, Helsinki 2021 and additional data is anticipated. The RWE on BLC brings additional validity and generalizability to the clinical trial results regarding the clinical outcomes in a broader population. There is very limited RWE with NBI.

With respect to the criteria for this analysis, only RCTs have been included.

In scope:

Comparative analysis

BLC has not been compared directly to NBI in robust prospective randomized multi-centre clinical studies.

An analysis undertaken by Ontario Health [16] to compare HAL and NBI concluded that HAL-guided TUR-BT likely reduces the rate of recurrence at 12 months when compared to using white light alone. It also concluded that NBI-guided TUR-BT likely results in little to no difference in recurrence compared to WLC alone. Their indirect treatment comparison while not statistically significant, showed a trend towards a lower rate of recurrence with HAL-guided TUR-BT than NBI-guided TUR-BT. The final recommendation from Ontario Health was to fund HAL-guided, and not NBI-guided, TUR-BT for all patients regardless of risk category.

Recurrence at 12 months

HAL: The majority of the evidence suggests that HAL-guided TUR-BT significantly reduces recurrence rate in the short term (at 12 months) in low, medium and high-risk patients [1-10].

NBI: Although the evidence suggests that NBI-guided TUR-BT significantly reduces recurrence rate in low-risk patients in the short term (at 12 months) [11-13], two of the three RCTs failed to meet their primary end-point [12,13].

The majority of the evidence suggests that NBI-guided TUR-BT is of no benefit in medium and high-risk patients at 12 months [11-13]

[a] Hexvix (HAL or HEX) is marketed under the brand name Cysview in the USA and Canada

Recurrence at up to 5 years

HAL: The majority of the evidence suggests that HAL-guided TUR-BT significantly reduces recurrence rate in the mid to long term (2-5 years) [1-3, 19].

NBI: There is no evidence that NBI-guided TUR-BT reduces recurrence rate in the long term.

Disease progression

Maisch et al, 2021 [17] undertook a meta-analysis of 5-ALA and HAL versus WLC guided cystoscopy and concluded that BLC-guided TUR-BT may reduce the risk of disease progression over time (HR 0.77, 95% CI 0.63 to 0.96) depending on baseline risk. For HAL alone, the result was:

- HAL-guided TUR-BT vs WLC-guided TUR-BT: HR 0.69 (95%CI; 0.48 – 0.98).

HAL: The impact of HAL-guided TUR-BT on progression is less well quantified since progression takes place over a longer timeframe than recurrence, numbers of people progressing are low and there are differences in the definitions of progression. Furthermore, the utilisation of different adjuvant treatments and treatment lengths are considerable confounders in the outcome. However, HAL-guided TUR-BT has shown a significant improvement in time to progression [5,8] and a trend towards a reduction in progression [8].

NBI: There is no data on the impact of NBI-guided TUR-BT on progression.

Overall survival

HAL: There is emerging data supporting overall survival benefit in HAL-guided TUR-BT [2] compared to WLC-guided TUR-BT alone.

NBI: There is no data on the impact of NBI-guided TUR-BT on overall survival.

Two robust meta-analyses [16, 17] and the Applicants meta-analysis all concluded that HAL-guided TUR-BT shows greater benefit that NBI-guided TUR-BT in reducing recurrence particularly in intermediate and high-risk patients.

Safety

HAL has been found to be safe.

Maisch et al., 2021 [17] were unable to draw conclusions regarding how HAL-guided TUR-BT affects AE of any grade but noted participants with WLC TUR-BT had 36 more (48 fewer to 131 more) AE per 1,000 participants with HAL-guided TUR-BT, which falls below their predefined threshold for MCID of 50 per 1,000.

The Ontario Health HTA 2021 review [16] also considered safety but the SLR and criteria included only one study that reported on safety outcomes for Hexvix. Reviewers concluded that Hexvix is “generally safe”.

Two HAL studies [6,10] reported on adverse events. Heer et al [6] reported no difference between WLC and HAL groups (RR 0.62;95%CI (0.24-1.60), p=0.33). O’Brien et al [10] reported that there were no adverse events related to HAL in their study. Naito et al [12] saw no significant differences between NBI and WLC.

Comprehensive information regarding the safety of Hexvix is available in the Summary of Product Characteristics [35]. Most of the reported adverse reactions were transient and mild or moderate in intensity. The adverse reactions observed were expected, based on previous experience with standard cystoscopy and TUR-BT procedures. This data is supported by an analysis of post-marketing data [36], an

RCT looking specifically at the safety of repeat HAL-guided TUR-BTs [37] and data from a large prospective registry [38].

Adverse reactions with HAL have therefore not been observed other than those associated with standard cystoscopy and TUR-BT procedures.

Due to the paucity of safety data, no further analysis was undertaken.

HRQoL

One study [6] collected self-reported HRQoL data for HAL-guided TUR-BT vs WLC-guided TUR-BT and reported similar responses using EQ-5D-3L, for both arms at all time points. At 12 months, the mean difference was -0.006 (-0.067-0.056), p=0.854. There was no evidence of a difference in QALYs gained between treatment groups at 3 years (mean difference -0.096, 95%CI, -0.342-0.151), p=0.444.

No further analysis was undertaken.

Number of TUR-BTs

The Danish guidelines [32] recommend only one primary TUR-BT in patients, with all follow-up surveillance procedures undertaken in an outpatient setting with flexible cystoscopy using either NBI or HAL. This is out of scope of this analysis. In certain circumstances, patients will undergo a second TUR-BT when the initial TUR-BT may be incomplete and there is a risk of residual tumours (NMIBC guideline recommendation).

It can be assumed, however, that a reduction in recurrence is a surrogate measure of the need to perform a TUR-BT. Studies identified concluded that in reducing recurrence, a similar reduction in the number of TUR-BTs is reduced [33,34].

No further analysis was undertaken.

3.3.4 Existing guidelines and recommendations for HAL

Note: HAL-guided procedures are referred to as BLC in The Danish Guidelines so is referred to as such in this section

The Danish guidelines [53] for bladder cancer are developed by the Danish Bladder Cancer Group, which is a part of the Danish Urological Society. The guidelines provide recommendations for the diagnosis, treatment, and follow-up of patients with bladder cancer and include the following:

1. Diagnosis: Bladder cancer is typically diagnosed through cystoscopy and urinary cytology. Imaging studies like CT scans or MRI may also be used to evaluate the extent of the disease.
2. Staging: Bladder cancer is staged using the TNM system, which considers the size and location of the tumour, the involvement of lymph nodes, and the presence of distant metastases.
3. Treatment: Treatment options for bladder cancer depend on the stage of the disease. For non-muscle invasive bladder cancer (NMIBC), transurethral resection of the bladder tumour (TUR-BT) is the standard treatment. Additional adjuvant treatments like intravesical chemotherapy or immunotherapy may be used to prevent and/or delay recurrence and progression. For muscle invasive bladder cancer (MIBC), radical cystectomy (removal of the bladder) is the standard treatment in the absence of metastases. In some cases, chemotherapy or radiation therapy may be used before or after surgery.

4. Follow-up: Patients with bladder cancer should be monitored closely after treatment to detect any recurrence or progression of the disease. Follow-up may involve cystoscopy, urinary cytology, imaging studies, and other tests.

5. Cystoscopy, TUR-BT and Cytology
   Tumour is described in terms of:
   a. Number
   b. Size
   c. Characteristics (papillary, solid, ulcerating, or necrotic).

The Danish guidelines [53] (most recently revised in October 2023) recommend BLC and NBI for:

- First-time bladder tumour to allow for complete resection, and as an alternative to selected site biopsies regarding the detection of CIS
- First check-up due to CIS after BCG
- Urothelial cells suspicious for high degree of malignancy (Paris Category IV) or urothelial cells with a high degree of malignancy (Paris Category V) cells in the urine at normal findings at cystoscopy and CT urography

The Danish guidelines [53] recommend BLC and NBI interchangeably regardless of diagnosis or procedure. In this regards the Danish NMIBC guidelines differ from the majority of other international guidelines, including EAU guidelines, on the use of visual enhancement like BLC and NBI.

The Danish guidelines [53] statement on equivalency is based on two studies comparing BLC with NBI which are out of scope for this particular research question namely one detection study using NBI-guided flexible cystoscopy (Drejer et al., DaBlaCa-7 study) [71], and another being a TUR-BT detection study (Drejer et al., DaBlaCa-8 study [72]). Although this latter study was undertaken by the DaBlaCa in the Nordics region and involved 117 patients (including Danish patients), it was a detection study with no follow up on recurrence or progression, therefore is out of scope for this comparative analysis.

Also to note, a further study in the Danish Guidelines on recurrence (Drejer et al., DaBlaCa-11 study [118]) refers to flexible-guided cystoscopy which is also out of scope for this analysis.

The difference in level of evidence and performance between BLC and NBI is highlighted in other international guidelines, particularly with respect to high-risk tumours where BLC has a strong recommendation. The EAU NMIBC [47] guidelines recommend the use of:

- "Photodynamic diagnosis (PDD or BLC) – the use of BLC in patients who have received pre-treatment with an optical imaging agent. Guidance is based on level 1a evidence that BLC is more sensitive than WLC for detecting NMIBC, particularly CIS and for reducing recurrence in the short and long-term
- Narrow-band imaging (NBI) – an endoscopic visualisation-assisted (VA) technique, which makes use of two bandwidths of blue and green illumination to enhance the distinction of mucosa and microvascular structures without the prior application of dyes. Guidance is based on level 3b evidence for improved detection and level 1b evidence for a short-term improvement in recurrence rates for low grade tumours, although the overall results of the study were negative."

The Ontario Health HTA (health technology assessment) [16] recommended the use of HAL-guided TUR-BT and not NBI-guided TUR-BT in its 2021 assessment, finding HAL to demonstrate improved recurrence benefit compared to NBI. It also found HAL to be more cost-effective than NBI.

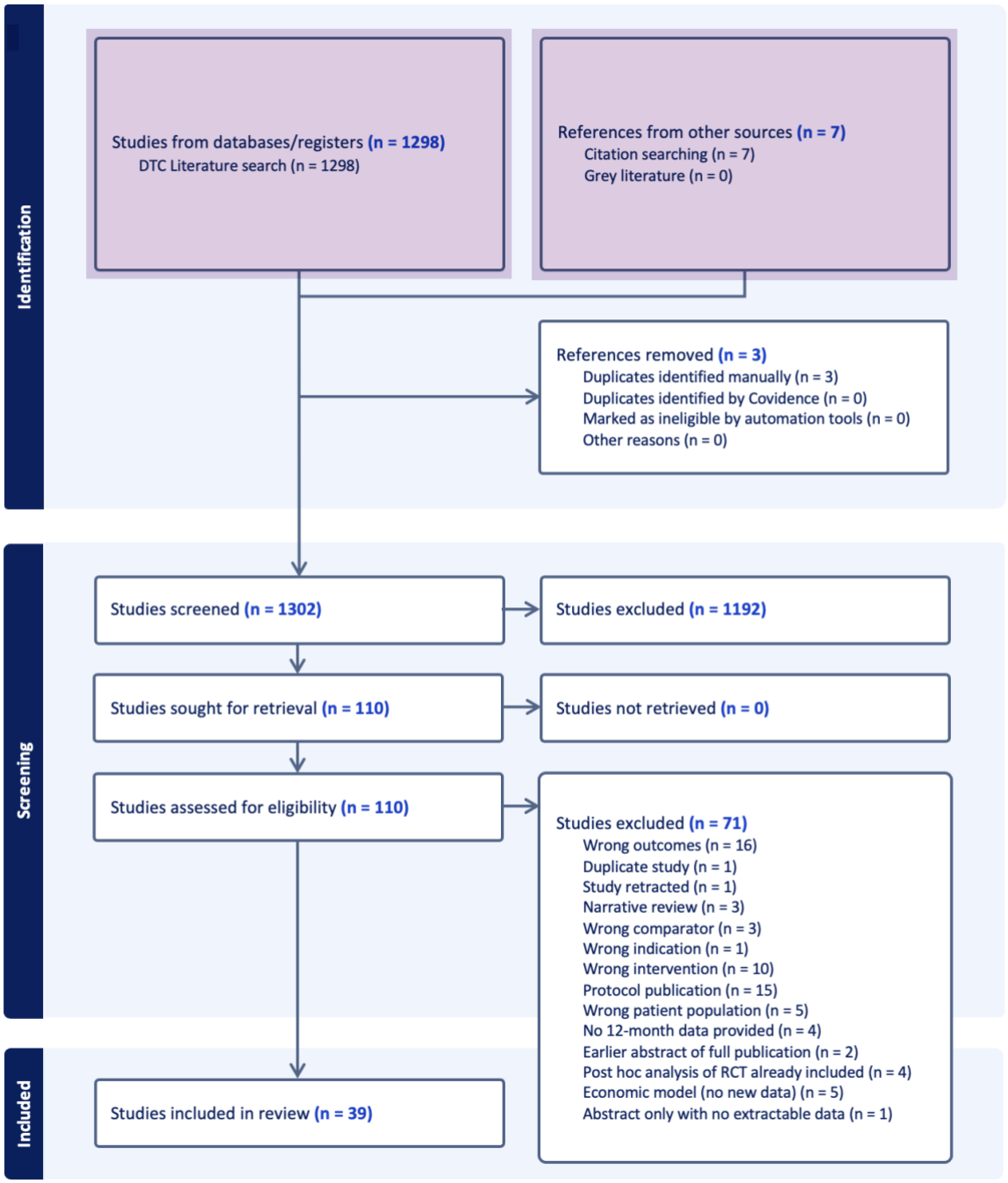
4 Evidence base

4.1 Selection of relevant studies

The Systematic Literature Review (SLR) resulted in 39 relevant studies out of the 1298 identified by the Expert Committee based on the research question and PICO criteria which assessed recurrence at 12 months, progression, HRQoL and/or safety. All other studies, including diagnostic only studies or studies not including one or more of these end-points, were eliminated. 32 summarises the eliminated studies and the rationale for exclusion.

A PRISMA diagram is attached:

Figure 2: Prisma diagram



Design	RCTs	Meta-analyses	Observational	Retrospective	Economic	TOTAL
HAL vs WLC	10	7	3	3	1	**24**
NBI vs WLC	3	4	2	-	1	**10**
HAL vs NBI	-	**5**	-	-	-	**5**
TOTAL	**13**	**16**	**5**	**3**	**2**	

As per the research question and PICO criteria, only studies assessing recurrence at 12 months, progression, HRQoL and/or safety were retained: all other studies, including diagnostic-only studies or studies not including one or more of these end-points, were eliminated. A total of 39 studies out of the 1298 identified by the Danish Treatment Council for Systematic Literature Review (SLR) were retained for inclusion in this analysis.

As per the Methods Guide and as requested by the Expert Committee, the clinical effect and safety analyses were based on randomized controlled trials. Existing meta-analyses of RCTs were considered if appropriate and relevant. Of the retained studies, 13 were RCTs, 10 of which compared HAL-guided TUR-BT with WLC-guided TUR-BT. None compared HAL with NBI.

A total of 16 meta-analyses were identified.

Recurrence data

For the clinical and safety analysis, as per the Danish Treatment Council Methods Guide and Expert Committee request, only RCTs were used. Of the 39 retained studies, 13 were RCTs, 10 of which compared HAL-guided TUR-BT with WLC-guided TUR-BT [1-4,6,7,9,10,19]. One RCT [19] involved additional follow up [5] and re-analysis [8]. None compared HAL-guided TUR-BT with NBI-guided TUR-BT. Although ultimately retained for the analyses for scenario purposes, two of the three RCTs comparing NBI-guided TUR-BT with WLC-guided TUR-BT [11-13] failed to demonstrate clinical benefit.

The SLR identified 16 publications that included meta-analyses/ITC's of the RCT data that were relevant to both the clinical question and PICO criteria, and which could be considered as appropriate to include as the comparative evidence. Seven of these [20-26] were carried out with a literature review that was more than 5 years old (range 2012 – 2016), so were not considered appropriate for this purpose. Of the remaining nine, five [15, 28-31] included at least one study with the wrong intervention, and one analysis compared NBI with WLC which included data from one RCT which only presented recurrence data for around one third of the patients [27]. The remaining three [16-18] did not include an RCT comparing HAL with WLC conducted published in 2021 [6]. Comment has been provided on these analyses for comparison purposes only in the clinical effectiveness section 5.2.2 Results at study level.

Recurrence rate was reported in four analyses [17,28,29,31]. As noted above, three of these [28,29,31] contained inappropriate studies. Only one analysis yielded robust results for HAL-guided TUR-BT vs WLC-guided TUR-BT [17] but excluded data from a large RCT published subsequently [6]. For NBI-guided TUR-BTs, none of the published meta-analyses yielded usable results.

Table 3: Recurrence data, comparison of BLC vs WLC and NBI vs WLC

Reference	Comparison	Studies pooled	Inappropriate inclusions	Studies not included	Result HR (95%CI)
Li 2021 [28]	BLC vs WLC[1]	[1-2,4,7,9-10, 19,118]	[1,118] – *note 1*	[3,6]	0.69 (0.58-0.82)
	NBI vs WLC[2]	[11-14, 73-74, 81]	[73-74, 81] - *note 2*	-	0.73 (0.60-0.69)
Maisch 2021 [17]	BLC vs WLC[3]	[2-4,7,9-10, 19,76-77]	[76,77] – *note 3*	[6]	0.60 (0.45-0.78)
Lai 2022 [29]	NBI vs WLC[4]	[11-14, 73,75]	[13-14, 73,75] – *note 4*	-	0.63 (0.45-0.89)
Zhao 2023 [31]	BLC vs WLC[5]	[1-2,4,7,9,19,72]	[1,72] – *note 5*	[3,6,10]	0.79 (0.67-0.92)

Notes

1. *Li et al's comparison for HAL-guided TUR-BT vs WLC-TUR-BT inappropriately included one study [1] that was an interim report of more complete results that were published subsequently [2], and a second study that investigated surveillance cystoscopy rather than TUR-BT [118]. They omitted one potentially relevant study [3] and undertook the analysis prior to the publication for another relevant study [6].*
2. *The comparison for NBI-guided TUR-BT vs WLC-TUR-BT in Li et al. inappropriately included three studies [73-75]. One was a randomised comparison of NBI-guided bipolar plasma vaporization vs WLC-TUR-BT [73] and therefore did not address the research question. The second was a comparison of NBI-guided flexible cystoscopy vs WLC-guided flexible cystoscopy for second look following TUR-BT, and was therefore out of scope [74]. The third study was a comparison of NBI-guided flexible cystoscopy vs WLC-guided flexible cystoscopy in a surveillance role, and was therefore also out of scope [81].*
3. *Maisch et al's inclusion of two studies with short term (3 month) recurrence outcomes [76,77] is probably appropriate, given that hazard ratio is not specific to a given duration of follow-up. However, the omission of these studies by the other authors cannot be considered a negative. The analysis was undertaken prior to the publication of another relevant study [6] and consequently the results did not include these data. Dahm et a [78] recalculated the meta-analysis including the relevant study [6]. The pooled effect size changed only to a small degree (HR 0.68; 95% CI, 0.56 to 0.82) including all studies using BLC with either 5-ALA or HAL .*
4. *Lai et al nominally identified six studies to include in their meta-analysis of NBI-guided TUR-BT vs WLC-TUR-BT. Of these, however:*
    - *One was a comparison of NBI-guided bipolar plasma vaporization vs WLC-TUR-BT [73] and was thus out of scope.*
    - *One was a comparison of NBI-guided holmium laser resection vs WLC-TUR-BT [75] and was thus out of scope.*
    - *One randomised 198 patients but only presented recurrence data on 74 of them [13]. The robustness of the results is therefore subject to significant uncertainty.*
    - *One was only ever published as an abstract [14] and thus never underwent full peer review and cannot be assessed for quality.*
    - *Concerns regarding the execution and interpretation of the results has been expressed in a letter to the editor by Roupret et al. [79].*
5. *Zhao et al, like Li et al, inappropriately included one study [1] that was an interim report of more complete results that were published subsequently [2], and a second study that investigated surveillance cystoscopy rather than TUR-BT [72]. They omitted two potentially relevant studies [3,20] and undertook the analysis prior to the publication for another relevant study [6].*

The Maisch et al, 2021 meta-analysis [17] did include a sensitivity analysis for HAL alone (the primary analysis included 5-ALA studies) however omitted a major RCT [6]. As none of the analyses were therefore fit for purpose, we consequently decided to undertake a re-analysis of Maisch et al., [17] to include data from the missing study, and to carry out a new meta-analysis for NBI-guided TUR-BT, using the same analytical method as used by both Maisch et al [17] and Lai et al [29]. Three scenarios would be examined for NBI:

- Include only Naito et al [12] and Naselli et al [11] in the analysis.
- Allow Kim et al [13] to be included.
- Allow Kim et al [13] and Lee et al [14] to be included.

To undertake the meta-analysis, the systematic literature review identified 9 randomised controlled trials of HAL-guided TUR-BT vs WLC-TUR-BT that recorded recurrence rates, with follow-up duration ranging from 12-55 months [1-4,6-7, 9-10,19]. One study [1] was an interim report of a subsequently published study [2]. Of these, comparative time to recurrence data were either recorded or could be back-calculated in 8

studies, using the methods described by Tierney et al [80], which derive estimates of hazard ratio and its variance based on information available in the published papers (Annexe 11.12 - Estimation of hazard ratios from study summary data). An additional two studies of shorter duration that were excluded from the SLR were included in the meta-analysis [76,77], as estimates of hazard ratio are not dependent on duration of follow-up.

For NBI-guided TUR-BT, only two studies clearly complied with the search criteria, each with a follow-up period of 12 months [11,12], while two further studies were potentially eligible for inclusion [13,14], although one only presented recurrence data for around one third of the patients enrolled in the study [13], and the second was only ever published as an abstract [14].

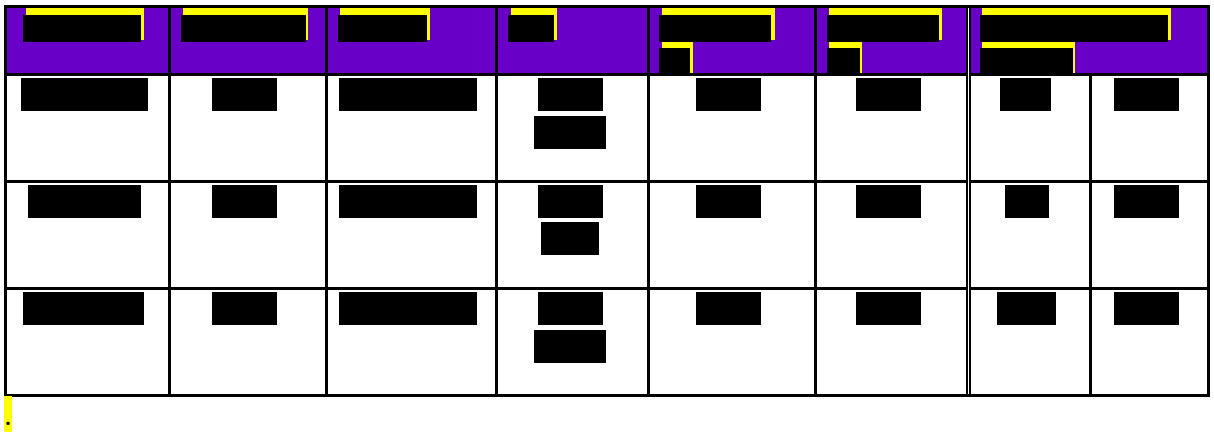
Results from an unpublished Indirect Treatment Comparison commissioned by Photocure

An unpublished indirect treatment comparison was undertaken based on the results of a systematic literature review carried out in June 2022, assessing the relative impact of WLC, HEX and NBI-guided TUR-BT on a range of disease recurrence metrics, including point-recurrence rates, recurrence-free survival and time to recurrence. The primary analytical approach was a Bayesian network meta-analysis, which yields an estimate of the median between-treatments comparison, together with a 95% credibility interval, which may be considered to be analogous to a 95% confidence interval derived from a frequentist analysis. Additionally, a series of surface under the cumulative ranking (SUCRA) analyses were carried out in order to estimate the relative probability of each treatment representing the most effective option. Full methodological details are shown in Appendix 1.

Of the outcomes considered, the 12-month recurrence-free survival outcome was considered to be the most meaningful representation of the specification in the DTC research question to demonstrate: *"Difference in proportion of patients experiencing relapse between the groups"*.

The native output of the NMA output is an odds ratio. In keeping with the requirements of the DTC, the primary results have been converted to an approximation of risk ratio and absolute risk difference, using the approach defined by the Cochrane Collaboration (table 4). For this re-analysis, the assumed comparator risk (ACR) for WLC and NBI-guided TUR-BT were derived from the largest and best quality RCT comparing the two approaches [12]

Table 4 – results for odds ratio, risk ratio, risk difference and SUCRA for recurrence-free survival, based on the results of the Photocure NMA.



Progression data

For the disease progression outcome, there were four studies yielding data for HAL-guided TUR-BT [2-3,10,19], whilst there were none for NBI-guided TUR-BT, reflecting the limited follow-up period in the RCTs. One meta-analysis was identified that compared HAL-guided TUR-BT with WLC-guided TUR-BT [17]. This was therefore used for the progression outcome.

Table 5: Progression data, comparison of BLC vs WLC and HAL vs WLC

Reference	Comparison	Studies pooled	Inappropriate inclusions	Studies not included	Result HR (95%CI)
Li 2021 [28]	BLC vs WLC	[19]	-	[2,3,10]	0.64 (0.41-1.00)
	NBI vs WLC	[81]	[81]	-	0.47 (0.22-1.03)
Maisch 2021 [17]	HAL* vs WLC	[2,3,10,19]			0.69 (0.48-0.98)

*HAL only data

Additional information and data have been included in this review including grey literature, guidelines, interviews with Danish Key Opinion Leaders and studies reporting HRQoL or safety from HAL-guided procedures out of scope for this study. Registrational studies have also been used for safety data purposes.

Table 6: List of studies and other data.

	Clinical effectiveness and safety	Patient perspective	Organisational implications	Health economics
Studies	[1 – 14] [16-19*]	[53, 69, 89, 90-92]	[16, 69]	[1-14] [19, 80, 82, 95]
	[38, 62, 76-77]			[101-104] [110, 111]
	[93]			[113-117]
				[110] – [114]
Other data**	Expert opinion		Data on file	Expert opinion
			Expert opinion	

**16-19 are included for comparative purposes only*

***For other sources (e.g. data-on-file or scientific opinions), see the subsection(s) in which the data is described.*

5 Clinical effectiveness and safety

Table 7: List of studies used in the analysis of clinical effectiveness and safety

Reference (first author, year)	Identification no. (NCT, EudraCT or similar)	Intervention	Comparator	Used for clinical question
Dragoescu 2017 [2] (Dragoescu, 2011 [1])	Exploratory Research Program (PCE-2), project number 1287/2008	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Geavlete 2010 [76]	PMID: 20627289	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Neuzillet 2014 [77]	PMID: 25023786	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Geavlete 2012 [3]	PMID: 21711438	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Gkritisios, 2014 [4]	DOI 10.1007/s11255-013-0603-z	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Heer, 2023 [6]	ISRCTN84013636	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Hermann, 2011 [7]	NCT00412971	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Karaolides, 2012 [9]	doi.org/10.1016/j.urology.2012.03.067	HAL-guided TUR-BT	WLC-guided TUR-BT	1
O'Brien, 2013 [10]	ISRCTN14275387	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Stenzl, 2010 [19] (Grossman, 2012 [5] & Kamat, 2016 [8])	NCT00233402	HAL-guided TUR-BT	WLC-guided TUR-BT	1
Naselli, 2012 [11]	PMC5305060	NBI-guided TUR-BT	WLC-guided TUR-BT	1
Naito, 2016 [12]	Doi.org. 10.1016/j.euro.2016.03.053	NBI-guided TUR-BT	WLC-guided TUR-BT	1
Kim, 2018 [13]	Doi.org.10.4.11/icu.2018.59.2.98	NBI-guided TUR-BT	WLC-guided TUR-BT	1
Lee, 2014 [14]	doi/10.1016/j.juro.2014.02.864	NBI-guided TUR-BT	WLC-guided TUR-BT	1
Palou, 2015 [62]	Observational study (safety, grey lit.)	HAL-guided TUR-BT	WLC-guided TUR-BT	
Daneshmand, 2018 [38]	Registry (safety, grey lit.)	HAL-guided TUR-BT	N/A	
Mukerjee, 2019 [93]	RCT (safety, grey lit.)	NBI-guided TUR-BT	WLC-guided TUR-BT	

Table 8: List of studies used in meta-analyses cited in the clinical section – studies used in Applicant's analysis is provided for comparative purposes.

Meta-analysis	Included studies	Intervention	Comparator	Outcome
Applicants *de novo*	[2-4, 6, 7, 9, 10, 19, 76, 77]	HAL-guided TUR-BT	WLC-guided TUR-BT	Recurrence
	[11,12]	NBI-guided TUR-BT	WLC-guided TUR-BT	Recurrence
Maisch, 2021 [17]	[2-4, 7, 9, 10, 19]	HAL-guided TUR-BT	WLC-guided TUR-BT	Recurrence
	[2, 3, 10, 19]	HAL-guided TUR-BT	WLC-guided TUR-BT	Progression
Ontario Health, 2021 [16]	[2, 9, 10, 76, 77]	HAL-guided TUR-BT	WLC-guided TUR-BT	Recurrence
	[2, 9, 10]	HAL-guided TUR-BT	WLC-guided TUR-BT	Progression
	[11,12, 93]	HAL-guided TUR-BT	NBI-guided TUR-BT	Recurrence
Veeratterpillay, 2021 [18]	[2-4,7-10]	HAL-guided TUR-BT	WLC-guided TUR-BT	Recurrence

SIIC: single immediate intravesical therapy

An additional unpublished network meta-analysis was carried out for Photocure in 2022, comparing HAL-guided TUR-BT with NBI-guided TUR-BT and WLC-TUR-BT for the disease recurrence outcome. In the absence of any published progression data for NBI, this outcome could not be analysed. The report on this analysis appears as Appendix 1.

Although the results favour HAL-guided TUR-BT over either NBI or WLC for all metrics explored, the results were restricted to a 12-month analysis and were generally associated with Bayesian 95% credibility intervals that overlapped unity, implying a lack of conventional statistical significance. The NMA also included data from one abstract that was excluded from this submission [115]. Given that the economic model design required pairwise comparisons vs WLC-TUR-BT – an analysis that would be more validly served by direct comparative meta-analyses – the unpublished NMA will not be considered further in this document.

5.1 Study and population characteristics

Studies included are stated in Table 31 (Annex 11.1).

5.2 Clinical Question: Should HAL-guided TUR-BT be used rather than NBI-guided TUR-BT for the treatment of adult patients with suspected non-muscle invasive bladder cancer?

5.2.1 Studies used

5.2.1.1 Recurrence

The systematic literature review identified 9 randomised controlled trials of HAL-guided TUR-BT vs WLC-TUR-BT that recorded recurrence data (including one study [2] which was an interim report of a subsequently published study [2]) with a follow-up duration ranging from 12-55 months [1-4, 6-7, 9,10,19[b]]. Of these, time to recurrence data were either recorded or could be back-calculated in 8 studies, using the methods described by Tierney et al [80], which derive estimates of hazard ratio and its variance based on information available in the published papers (see Appendix 1). An additional two studies of shorter duration that were excluded from the SLR were included in the meta-analysis [76,77]

For NBI-guided TUR-BT, only two studies clearly complied with the search criteria, each with a follow-up period of 12 months [11,12], while two further studies were potentially eligible for inclusion [13,14], although one only presented recurrence data for around one third of the patients enrolled in the study [13], and the second was only ever published as an abstract [14].

None of the identified meta-analyses were considered appropriate, thus a de novo analysis was undertaken.

For comparison, however, the outcomes of three meta-analyses are cited [16-18].

5.2.1.2 Progression

For the disease progression outcome, there were four studies yielding data for HAL-guided TUR-BT [2-3, 10,18] whilst there were none for NBI-guided TUR-BT, reflecting the limited follow-up period in the RCTs. One meta-analysis was identified that compared HAL-guided TUR-BT with WLC-guided TUR-BT [17]. This was therefore used for the progression outcome.

5.2.1.3 HRQoL

No data was available on HRQoL for NBI.

One study [6] did collect self-reported HRQoL data for HAL-guided TUR-BT vs WLC-guided TUR-BT and reported similar responses using EQ-5D-3L, for both arms at all time points. At 12 months, the mean difference was -0.006 (-0.067-0.056), p=0.854. There was no evidence of a difference in QALYs gained between treatment groups at 3 years (mean difference -0.096, 95%CI, -0.342-0.151), p=0.444.

No further analysis was undertaken.

5.2.1.4 Number of TUR-BTs

The Danish guidelines [32] recommend only one primary TUR-BT in patients, with all follow-up surveillance procedures undertaken in an outpatient setting with flexible cystoscopy using either NBI or HAL. This is out of scope of this analysis. In certain circumstances, patients will undergo a second TUR-BT when the initial TUR-BT may be incomplete and there is a risk of residual tumours (NMIBC guideline recommendation).

[b] One longer-term follow up study [5] and one re-analysis [8] were undertaken from study [19].

It can be assumed, however, that a reduction in recurrence is a surrogate measure of the need to perform a TUR-BT. Studies identified concluded that in reducing recurrence, a similar reduction in the number of TUR-BTs is reduced [33,34].

No further analysis was undertaken.

5.2.1.5 Safety

HAL and NBI were both found to be safe.

Maisch et al., 2021 [17] were unable to draw conclusions regarding how HAL-guided TUR-BT affects AE of any grade but noted participants with WLC TUR-BT had 36 more (48 fewer to 131 more) AE per 1,000 participants with HAL-guided TUR-BT, which falls below their predefined threshold for MCID of 50 per 1,000.

The Ontario Health HTA 2021 review [16] also considered safety, but the SLR and criteria included only one study that reported on safety outcomes for Hexvix. Reviewers concluded that Hexvix is "generally safe".

Two HAL studies [6,10] and one NBI study [12] reported on adverse events. Heer et al [6] reported no difference between WLC and HAL groups (RR 0.62;95%CI (0.24-1.60), p=0.33). O'Brien et al [10] reported that there were no adverse events related to HAL in their study. Naito et al [12] saw no significant differences between NBI and WLC.

Comprehensive information regarding the safety of Hexvix is available in the Summary of Product Characteristics [35]. Most of the reported adverse reactions were transient and mild or moderate in intensity. The adverse reactions observed were expected, based on previous experience with standard cystoscopy and TUR-BT procedures. This data is supported by an analysis of post-marketing data [36], an RCT looking specifically at the safety of repeat HAL-guided TUR-BTs [37] and data from a large prospective registry [38].

Adverse reactions with either HAL or NBI have therefore not been observed other than those associated with standard cystoscopy and TUR-BT procedures.

Due to the paucity of safety data, no further analysis was undertaken.

5.2.2 Results at study level

5.2.2.1 Recurrence

Individual studies

HAL: Recurrence at 1-year for HAL was reported for eight RCTs [1-10, 19] including an interim report [1] for one study [2], and a longer-term follow up [5] and re-analysis [8] of another study [19].

One study [3] reported a RR of 0.66 (p=0.005) with a 10.9% difference in recurrence rate in favour of HAL. Five-year RFS was reported by one HAL study [2] and was significantly higher when HAL-guided TUR-BT was used in addition to WLC-guided TUR-BT than when WLC-guided TUR-BT was used alone (HR 0.566, 95% CI 0.343-0.936; p=0.0267). Grossman et al., [5] reported a 6% improvement (p=0.04) in tumour free survival with HAL while Heer et al., [6] reported a HR of 0.94 (95% CI 0.69, 1.28) in recurrence rate in the ITT population. Herman et al., reported a 7.2% improvement in recurrence rates in favour of HAL (p=0.050, with Karioledes et al., [9] reporting a 6.6 month median improvement in time to recurrence (p=<0.001) in favour of HAL with a 34.7% improvement (p=0.0006) in recurrence free survival at 12 months. Although

not statistically significant, Gkritsios et al., [4] found a 0.8% difference in recurrence rate at 12 months and O'Brien et al., [10], a 6% improvement in recurrence at 12 months.

NBI: There was a trend to improve 12-month recurrence rates in NBI-guided versus WLC-guided TUR-BT but data from two of these studies were not statistically significant [12,13]. Naito et al., [12] reported a 1.7% difference in recurrence at 12 months (p=0.585] with a RR of 0.204 (95% CI 0.063, 0.664; p=0.02) in low risk patients. No benefit was demonstrated in medium or high risk patients. Kim et al., [13] showed a 13% improvement in 12-month recurrence-free rates however only data from 74 out of the 198 subjects were analysed. Naselli et al., [11] showed an OR of 0.62 (95% CI unadjusted 0.07, 0.81; p=0.0141) in recurrence at 1 year. Several analyses included Lee et al., [14] however this data was only ever published as an abstract. The authors reported a 1.2% difference in recurrence free rate at 24 months (p value not reported). There was no statistical difference in recurrence-free rate in high grade tumours or patients with multiple tumours, and although a 65% difference in recurrence-free rates at 12 months in patients with cis was reported (62.5% recurrence in WLC, no recurrence in NBI), no p value was reported.

Thus unlike HAL where benefit is demonstrated in all patient categories, the greatest benefits of NBI are seen in low-risk patients, with little or no advantage being seen in those with intermediate or high-risk profiles [12].

A detailed summary of data from individual RCT studies is outlined in Annex 11.3:

Recurrence at 12 months

HAL: The majority of the evidence suggests that HAL-guided TUR-BT significantly reduces recurrence rate in the short term (at 12 months) in low, medium and high-risk patients [1-10].

NBI: Although the evidence suggests that NBI-guided TUR-BT significantly reduces recurrence rate in low-risk patients in the short term (at 12 months) [11-13], results from two of the three RCTs showed no benefit in these patients when compared to WLC-guided TUR-BT [12,13].

The majority of the evidence suggests that NBI-guided TUR-BT is of no benefit in medium and high-risk patients at 12 months [11-13].

Recurrence at up to 5 years

HAL: The majority of the evidence suggests that HAL-guided TUR-BT significantly reduces recurrence rate in the mid to long term (2-5 years) [1-3, 19].

NBI: There is no evidence that NBI-guided TUR-BT reduces recurrence rate in the long term.

Recurrence-free survival

HAL: One study [2] reported a significant difference in recurrence free survival at 5 years (HR 0.566, 95%CI 0.343, 0.936; p=0.0267). Another study [9] did not report the overall difference between groups but did so for tumour characteristic at 12 and 18 months where analysis by log rank test showed that recurrence free survival was significantly better with HAL-guided TUR-BT for all tumour characteristics except solitary tumours.

NBI: There is no evidence that NBI-guided TUR-BT improves recurrence free survival.

Meta-analyses *(provided for information only, none met criteria for inclusion as a comparative analysis)*
HAL vs WLC:

Maisch et al, 2021 [17] reported a Hazard Ratio of 0.69 (95%CI; 0.48 – 0.98) from a post-hoc analysis of HAL alone. Heterogeneity was low: Tau^2 = 0.00, Chi^2 0.21, df3 (p=0.98). When all studies were included (both 5-ALA and HAL), which was the primary analysis, the HR was 0.66, 95% CI 0.54 to 0.81. The authors of Maisch et al, [17] recalculated the meta-analysis including the relevant study [6]. The pooled effect size changed only to a small degree (HR 0.68; 95% CI, 0.56 to 0.82) including all studies using HAL with either 5-ALA or HAL [79].

Ontario Health conducted a pairwise meta-analysis of HAL-guided TUR-BT significantly reduced recurrence rate at 12 months compared to WLC-guided TUR-BT (risk ratio 0.70, 95% CI 0.51-0.95). Heterogeneity between studies was low (29.9%) and not significant. The risk difference was -0.11 (955 CI -0.21 to -0.02). The number needed to treat was calculated as 9. The certainty of evidence was rated as moderate, downgrading due to risk of bias.

Based on these analyses, Ontario Health HTA [16] concluded that HAL-guided TUR-BT increases 5-year recurrence-free survival when compared to using white light alone. It also concluded that with NBI-guided TUR-BT there was no evidence of recurrence-free survival benefit. The final recommendation from Ontario Health was to fund HAL-guided, and not NBI-guided, TUR-BT for all patients regardless of risk category.

Veeratterpillay et al., 2021 [18], concluded that at 12 months, the RR for disease recurrence with HAL-guided TUR-BT was 0.73 (95% CI 0.59-0.91) and at 24 months was 0.72 (95%CI 0.57, 0.90). Recurrence free survival at 12 months for both HAL and 5-ALA showed a HR (in favour of PDD) of 1.14 (95%CI 1.05-1.23) and at 12 months, HR 1.25 (95%CI 1.15-1.35, p<0.001). 12-month RFS rates for Hal were reported to range between 66.3% and 85.4% compared to 52.7% and 81.1% for WLC, indicating that the use of HAL improved RFS. Heterogeneity between studies was not significant (I^2=0%).

NBI vs WLC:

Ontario Health conducted a meta-analysis of NBI studies [16] which did not show a significant difference between NBI-guided TUR-BT and WLC-guided TUR-BT. The risk ratio was 0.94 (95% CI 0.75 to 1.19) and the risk difference was −0.02 (95% CI -0.08 to 0.04). The certainty of evidence was rated as moderate, downgrading due to risk of bias. Heterogeneity between studies was low (41.5%) and not significant.

HAL vs NBI:

Ontario Health's indirect estimate from a network meta-analysis [16] showed a trend towards a lower rate of recurrence after HAL-guided TUR-BT than after NBI-guided TUR-BT but the difference was not statistically significant 9RR 0.76, 95% CI 0.51-1.11).

5.2.2.2 Disease progression

HAL: The impact of HAL-guided TUR-BT on progression is less well quantified since progression takes place over a longer timeframe than recurrence, numbers of people progressing are low and there are differences in the definitions of progression. Furthermore, the utilisation of different adjuvant treatments and treatment lengths are considerable confounders in the outcome. However, HAL-guided TUR-BT has shown a significant improvement in time to progression [5,8] and a trend towards a reduction in progression [8].

Dragoescu et al [2] reported tumour progression rates at 5 years in 11 of 113 patients (9.7%; 5 in the HAL group [8.7%], 6 in the white light group [10.6%]). Seven patients had tumour grade progression and four had depth progression. The investigators reported that the data were insufficient for a thorough analysis of

tumour progression rates. Two patients (3.5%) in the HAL group and three patients (5.2%) in the white light group underwent radical cystectomy, and the difference was not significant (the certainty of the evidence was rated as moderate, downgrading due to risk of bias).

Karaolides et a [9] reported that at 12-month follow-up there was no tumour progression in patients who underwent HAL-guided TUR-BT. Tumours progressed in five patients who underwent TUR-BT with white light alone, including two people who required radical cystectomy because their cancer had progressed and became muscle invasive (GRADE: Moderate).

The meta-analysis for progression results from Maisch et al, 2021 [17] for HAL only studies was as follows:

- HAL-guided TUR-BT vs WLC-guided TUR-BT: HR 0.69 (95%CI; 0.48 - 0.98)

NBI: There is no evidence that NBI-guided TUR-BT improves time to progression or reduces progression.

5.2.2.3 Overall survival

Although out of scope, there is limited data providing evidence that overall survival might be improved in patients who underwent BLC-guided TUR-BT [2]. There is no data on the impact of NBI-guided TUR-BT on overall survival.

5.2.2.4 HRQoL

No data was available on HRQoL for NBI.

One study [6] did collect self-reported HRQoL data for HAL-guided TUR-BT vs WLC-guided TUR-BT and reported similar responses using EQ-5D-3L, for both arms at all time points.

At 12 months, the mean difference was -0.006 (-0.067-0.056), p=0.854.

There was no evidence of a difference in QALYs gained between treatment groups at 3 years (mean difference -0.096, 95%CI, -0.342-0.151), p=0.444.

In terms of the HRQoL between WLC, HAL and NBI guided TUR-BTs there is no evidence suggesting there is a difference, as the procedure itself is largely identical and the HRQoL impact relates to the cystoscopy rather than the enhanced visualisation technique used.

Grey literature searches and supplementary information highlights that quality of life for NMIBC bladder cancer patients is affected both by the symptoms arising directly from the cancer and those that result from procedures incurred by intervention to address the cancer [93]. Bladder cancer diagnosis and treatment has a negative impact on both physical and psychological QOL though these effects vary by intervention and over time.

Further, the DaBlaCa guidelines [53] emphasise the following:

“Patientværdier og – præferencer En øget detektionsrate ved PDD frem for almindeligt hvidt lys skal opvejes i forhold til det øgede tidsforbrug for patienten. Dette spiller ikke samme rolle ved NBI, idet det ikke kræver tidligere fremmøde eller præoperativ installation for patienterne. Opgørelser af patienttilfredshed tyder dog på, at patienterne gerne påtager sig at bruge mere tid og de minimale ekstra gener ved installationen forud for PDD for at opnå en større sikkerhed for korrekt diagnose og behandling som man formoder PDD giver i forhold til almindeligt hvidt lys”

"Patient values and preferences an increased detection rate with PDD rather than ordinary white light must be balanced against the increased time consumption for the patient. This does not play the same role with

NBI, as it does not require previous attendance or preoperative instillation for the patients. Calculations of patient satisfaction indicate, however, that patients are happy to undertake to spend more time and the minimal extra inconvenience of the instillation prior to PDD to achieve a greater certainty of correct diagnosis and treatment, which one presumes PDD provides compared to ordinary white light."

However, a diagnosis of bladder cancer impacts patients negatively on both physical and mental QOL [82-84].

NMIBC patients have been found to have lower physical HRQOL and urinary function than non-cancer controls [85] and the general population [84,86] at the time of diagnosis. Both at diagnosis and 6 months later, mental health HRQoL has been found to be significantly lower than the general population [86]. People with high-risk NMIBC decline significantly more in physical, general health and emotional health domain scales than people at lower risk [85].

Several studies have addressed the impact of TUR-BT or cystoscopy, on QOL. In a prospective, longitudinal study of the impact of TUR-BT, the first TUR-BT appears to have a particularly negative impact on mental health QOL [87]. Physical, social and emotional functioning appeared to be lowest at the second or third TUR-BT, increasing at subsequent TUR-BTs [86,87] and intervention type influenced patient reported QOL [84].

5.2.2.5 Number of TUR-BTs

The Danish guidelines [53] recommend only one primary TUR-BT in patients, with all follow-up surveillance procedures undertaken in an outpatient setting with flexible cystoscopy using either NBI or HAL. This is out of scope of this analysis. In certain circumstances, patients will undergo a second TUR-BT when the initial TURBT may be incomplete and there is a risk of residual tumors (NMIBC guideline recommendation).

It can be assumed, however, that a reduction in recurrence is a surrogate measure of the need to perform a TUR-BT. Studies identified concluded that in reducing recurrence, a similar reduction in the number of TUR-BTs is reduced [33,34].

5.2.2.6 Safety

Two HAL studies [6,10] and one NBI study [12] reported on adverse events. Heer et al [6] reported no difference between groups (RR 0.62;95%CI (0.24-1.60), p=0.33). O'Brien et al [10] reported that there were no adverse events related to HAL in their study. Naito et al [12] reported on the frequency of intraoperative and perioperative complications in the NBI and white light study arms and saw no significant differences between the two arms with respect to intraoperative bleeding (NBI 2.1%, white light 1.7%; p=0.644) and bladder perforation (NBI 2.3%, white light 1.5%; p=0 .348).

Non-SLR sources were used to supplement safety data including the comprehensive information regarding the safety of Hexvix available in the Summary of Product Characteristics [35]. Most of the reported adverse reactions were transient and mild or moderate in intensity. The adverse reactions observed were expected, based on previous experience with standard cystoscopy and TUR-BT procedures. This data is supported by analysis of post-marketing data in over 200,000 patients and six clinical trials of Hexvix BLC-guided TUR-BT, which indicates that Hexvix BLC-guided TUR-BT is safe and poses no additional risks to standard WLC-guided TUR-BT [36]. Additional studies identified from a grey literature search reported safety data including one RCT looking specifically at the safety of repeat HAL-guided TUR-BTs [37] and data from a large US prospective registry [38] demonstrated that Hexvix, and HAL-guided TUR-BT, is safe when used more than once.

Adverse reactions with either HAL or NBI have therefore not been observed other than those associated with standard cystoscopy and TUR-BT procedures.

Although a detection study and therefore excluded from the SLR, we sourced safety data from Mukherjee et al [93] who experimentally used NBI as the first light source (followed by white light) in one of the two arms of their study, although reported 7 breaches of protocol in the NBI-first arm. Six were due to poor visibility, prompting surgeons to switch to white light, and one was due to bladder perforation. The other arm had no breach of protocol due to poor visibility (p=0.032). The investigators reported that the poor visibility in the NBI-first arm was caused by bleeding during resection, which released hemoglobin. The wavelength of NBI was absorbed by the haemoglobin on the surface of the bladder wall, limiting visibility.

5.2.3 Methodologies for comparison analysis (intervention versus comparator)

The Applicant's Indirect Treatment Comparison
A Bayesian network meta-analysis was undertaken, comparing disease recurrence outcomes for WLC-guided TUR-BT, HEX-guided TUR-BT and NBI-guided TUR-BT. Full methodology and results are presented in Appendix 1. A summary of results is shown in table 11, in section 5.2.4.1.

The Applicant's Meta-Analysis
Details of the methodology is outlined in section 11.6 with transformation outlined in 11.7 (Academic in confidence). The meta-analysis was used to answer both clinical and economic questions.

The Ontario Health Analysis [16]
A clinical literature search and critical appraisal was conducted. The Cochrane risk-of-bias tool was used to assess bias of the RCTs. An indirect treatment comparison (ITC) meta-analysis was conducted through the network of interventions to obtain an indirect estimate of the comparative effectiveness of HAL-guided versus NBI-guided TUR-BT in reducing the rate of cancer recurrence. TUR-BT using white light alone was the common comparator in the ITC analysis. A plot was generated of network of interventions as a visual representation of the available evidence and a contribution plot generated to identify the most influential head-to-head comparison for network estimates. The plot showed that 100% of information for network estimates for HAL-guided TUR-BT versus white light alone and NBI-guided TUR-BT versus white light alone came from head-to-head comparisons. The network estimate for HAL versus NBI is informed indirectly and equally (50%/50%) by HAL and NBI studies. One NBI study had a large sample size, giving more weight to the thickness of the line for studies of NBI versus white light alone with the lack of direct evidence comparing NBI and HAL therefore requiring an indirect estimate through the network.

5.2.4 Results of the comparative analysis (intervention versus comparator)
See also Tables 37-42 in Annex 11.7

Absolute recurrence benefit is based on assumed rates of recurrence using WLC of 31.1% @ 12 months and 60.2% @ 60 months.

For progression, the corresponding assumed rates on WLC are 6.2% @ 12 months and 17.7% @ 60 months.

In both cases, the assumed rates are based on data from the Netherlands documenting recurrence and progression rates over a 10-year follow-up period [102]. Risk-specific Kaplan-Meier curves from the paper were digitised to estimate the 12-month and 60-month recurrence rates using WLC. The risk-specific rates

were then aggregated based on the proportion of patients in each risk group, in order to arrive at an overall estimate.

Absolute benefit of each intervention vs WLC-TUR-BT was then estimated using the method of Tierney et al [80].

Table 9: Overview of meta-analysis of clinical trial data

Variable	Comparison	Study period	Mean value, HR (95%CI) Random effects	Absolute benefit (+95% CI) RFS/PFS (12 months)	Absolute benefit (+95% CI) RFS/PFS (60 months)	Reference
				12 months	60 months	
Disease recurrence	HAL-guided TUR-BT vs WLC-TUR-BT	Up to 55 months	HR: 0.63 (0.49 – 0.82) P = 0.001	+10.2% (+4.8%; +14.4%)	+16.2%% (+7.2%; 23.9%)	de novo meta-analysis
Disease recurrence	NBI-guided TUR-BT vs WLC-TUR-BT	1 year	HR: 0.74 (0.42 – 1.32) P = 0.308	+7.0% (-7.7%; +16.6%)	N/A	de novo meta-analysis
Disease progression	HAL-guided TUR-BT vs WLC-TUR-BT	Up to 55 months	HR: 0.69 (0.48 – 0.98) P = 0.04	+1.9% (+0.1%; +3.2%	+5.1% (+0.3%; +8.8%	[17]
Disease progression	NBI-guided TUR-BT vs WLC-TUR-BT					

5.2.4.1 Recurrence

Results from Applicant's meta-analysis

Table 10: Results from Applicant's meta-analysis (recurrence)

Variable	Comparison	Study period	Mean value, HR (95%CI) Random effects	Absolute benefit (+95% CI) RFS/PFS (12 months)	Absolute benefit (+95% CI) RFS/PFS (60 months)	Included references
				12 months	60 months	
Disease recurrence	HAL-guided TUR-BT vs WLC-TUR-BT	Up to 55 months	HR: 0.63 (0.49 – 0.82) P = 0.001 I^2 = 76.2%	+10.2% (+4.8%; +14.4%)	+16.2% (+7.2%; +23.9%)	[2-4, 6,7,9 10,19,76,77]
Disease recurrence	NBI-guided TUR-BT vs WLC-TUR-BT[1]	1 year	HR: 0.74 (0.42 – 1.32) P = 0.308 I^2 = 76.8%	+3.2% (-7.7%; +16.6%)	N/A	[11,12]

Table 11: Results from Applicant's network meta-analysis (recurrence) [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Additional information has been provided below from one other relevant, published analysis.

Ontario Health ITC analysis [16]:

An indirect treatment comparison of HAL-guided and NBI-guided TUR-BT showed a lower risk of recurrence in favour of HAL, but this difference did not reach statistical significance (risk ratio 0.76, 95% CI 0.51–1.11). The pairwise meta-analysis showed that Hexvix BLC-guided TUR-BT as an adjunct to WLC-guided TUR-BT significantly reduces recurrence rate at 12 months compared with TUR-BT using WLC alone (RR 0.70, 95% CI 0.51-0.95). Five-year RFS was reported by one BLC study and was significantly higher when Hexvix BLC-guided TUR-BT was used in addition to WLC-guided TUR-BT than when WLC-guided TUR-BT was used alone (HR 0.566, 95% CI 0.343-0.936; p=0.0267).

Two studies compared the effectiveness of TUR-BT using NBI as an adjunct to white light versus white light alone in reducing the rate of cancer recurrence at 12 months. Meta-analysis of data on recurrence rates at 12 months showed no significant difference between the two groups. The risk ratio was 0.94 (95% CI 0.75 to 1.19) and the risk difference was −0.02 (95% CI −0.08 to 0.04). The certainty of evidence was rated as moderate, downgrading due to risk of bias. Heterogeneity between studies was low (41.5%) and not significant.

5.2.4.2 Progression

From the Maisch analyses [17] for HAL only BLC:

Table 12: Progression results from the Maisch analyses [17]

Variable	Comparison	Study period	Mean value, HR (95%CI) Random effects	Absolute benefit (+95% CI) RFS/PFS (12 months)	Absolute benefit (+95% CI) RFS/PFS (60 months)	Included references
				12 months	60 months	

Disease progression	HAL-guided TUR-BT vs WLC-TUR-BT	Up to 55 months	HR: 0.69 (0.48 – 0.98) P = 0.04 I^2 = 76.2%	+1.9%% (+0.1%; +3.2%	+5.1% (+0.3%; +8.8%	[2,3,10,19]
Disease progression	NBI-guided TUR-BT vs WLC-TUR-BT	No studies with NBI-guided TUR-BT identified for this outcome				

None of the NBI studies reported on tumour progression rate.

5.2.4.3 HRQoL

No analysis was undertaken.

5.2.4.4 Number of TUR-BTs

No analysis was undertaken.

5.2.4.5 Safety

Maisch et al., 2021 [17] were unable to draw conclusions regarding how HAL-guided TUR-BT affects AE of any grade based on results from three 5-ALA studies which included AE (n=1,375) (RR 1.09, 95% CI 0.88-1.33) (5-ALA is out of scope of this analysis). Based on the assumption of 39.7% AE in WLC patients, participants with WLC TUR-BT had 36 more (48 fewer to 131 more) AE per 1,000 participants with BLC TUR-BT, which falls below their predefined threshold for MCID of 50 per 1,000.

The Ontario Health HTA 2021 review [16] also considered safety but the SLR and criteria included only one study that reported on safety outcomes for Hexvix (HAL). Reviewers concluded that Hexvix (HAL) is "generally safe".

Due to the paucity of safety data, no further analysis was undertaken.

6 Patient perspective

Given the nature of TUR-BT, from a patient perspective during the procedure there is no difference in how HAL-guided TUR-BT or WLC-guided TUR-BT is performed versus NBI-guided TUR-BT, with the exception of bladder instillation before the procedure for HAL.

Table 13: Studies and other data used to describe the patient perspective.

Reference (author, (year), country)	Objectives	Method	Population	Intervention	Comparator
SmPC [35]					n/a
Data on file [69]	Understand patient pathway in Denmark	Interviews conducted between December 2023 and April 2024	Danish patients undergoing TUR-BT	NBI-guided TUR-BT	n/a
DaBlaCa Guidelines [53]	Patient pathway	Guidelines	Danish patients diagnosed with bladder cancer	n/a	n/a
Kowalkowski, 2014 [89]	Sexual dysfunction in NMIBC	Cross-sectional mixed methods	Patients with NMIBC		

Erikson 2020 [90] Denmark	Effect of repeated TUR-BTs under general anesthesia on mortality	Cohort	Patients with non-invasive NMIBC	n/a	n/a
Jang, 2016 [91]	Impact of TUR-BT with local and general anesthesia	Cohort study	Patients undergoing TUR-BT	n/a	n/a
Jin, 2023 [92]	Impact of anesthesia	Retrospective analysis	Cardiac surgery patients	n/a	n/a

6.1 Summary of the findings concerning the patient perspective

HAL-guided TUR-BT is not a procedure used by the patient itself, but by the clinician, and with the exception of reduced recurrence or progression as a result of the procedure itself, the procedure has no impact on the patient's daily life. With respect to the specifications from the evaluation design, there is little to no difference between the procedures from the patient perspective other than the instillation of HAL itself. HAL is instilled via catheter. The insertion of the catheter may cause discomfort, although some patients will have a catheter placed regardless of which procedure is being undertaken, prior to the cystoscopy. The cystoscopy itself is an uncomfortable procedure however there is no difference between NBI and HLA in this case.

Cystoscopic interventions in general may have an impact on sexual function, with 60% of men with NMIBC reporting erectile dysfunction and 62.5% of women reporting vaginal dryness post-intervention. One quarter were concerned about contaminating their partners with treatment agents (23.2%) [88]. TUR-BT has an impact on sexual wellbeing, with patients reporting a deterioration in sexual function over time in the first year after TUR-BT (with or without adjuvant intravesical instillation treatment) [86].

Medical complications from repeated general anaesthesia during TUR-BT also warrant mention, as patients with NMIBC are older, frail, are smokers, and often suffer from serious comorbidities, including coronary, congestive heart failure and peripheral artery disease and chronic obstructive pulmonary disease - the repeated use of general anaesthesia in the elderly may predispose to cognitive decline [89].

Repetitive TUR-BTs is independently associated with an increased CV mortality risk, especially in frail elderly patients with comorbidities. The more TUR-BTs are performed, the more it imposes burden and risks on patients. The Danish national cohort study showed that repeated TUR-BTs under GA were associated with an increased risk of death in patients with NMIBC [89]. Associations between treatments and overall mortality were evaluated using multivariable regression analysis adjusted for age, gender, comorbidities and socioeconomic status. During follow-up (median 6-8), 58% of patients with low-risk tumours had 5 or more TUR-BTs under GA, and at least 25% of patients with higher risk tumours had 6 or more procedures. Compared to patients who had only the primary TUR-BT, the increased mortality risk was 14% with low-risk tumours and 48.3% with higher risk tumours for patients who had 2-4 procedures, and 27.5% for low-risk tumours and 82.6% for higher risk tumours who had 8 or more procedures.

Age, tumour characteristics, smoking, obesity and comorbidities such as heart disease and diabetes can all increase the risk of complications from repeat TUR-BT procedures.

Although regional anaesthesia can be performed in TURB procedures which may mitigate some risks, there is conflicting evidence on the impact on morbidity and mortality [90,91].

However, although the reduction of the number of TUR-TB procedures may have significant impact on the patient's morbidity and mortality by reducing the risk of anaesthesia exposure, in line with the Danish guidelines, typically each patient will only have one TUR-BT over a 5-year cycle, unless the patient has a recurrence. Each recurrent patient will again typically only have one TUR-BT. As noted, these patients go back to the beginning of the "cycle". In theory, given HAL reduces recurrence compared to NBI and therefore one would expect less procedures, in practice these patients return to "day 1" making quantification challenging.

For Primary Tumours:

Table 14: Patient pathway

Step in pathway with comparator	Change required in pathway with intervention
Patient referred to urologist by GP, typically as a result of haematuria	No change
Urologist books CT urography and performs flexible cystoscopy as outpatient procedure (within 7 days)	No change
If bladder tumours are detected, patient is booked in for a TUR-BT (within 7 days)	No change
Urine tests are performed for UTIs the day of TUR-BT	In addition to this, HAL would be instilled by nurse
TUR-BT is performed by urologist	No change
If muscle invasive disease is detected, patient will be discussed at Multidisciplinary Team and future care plan agreed	No change
Majority of patients are discharged same day	No change

6.2 Considerations regarding user requirements and accessibility

Patient with known hypersensitivity to the active substance or any excipients should not have HAL (Hexvix) instilled. It should not be used in patients at high risk of bladder inflammation such as after BCG therapy and so prior to use widespread inflammation of the bladder should be excluded by cystoscopy before the product is administered. Inflammation may lead to increased porphyrin build-up and increased risk of local toxicity upon illumination causing false fluorescence [35].

Elements for this topic (and the topics highlighted on the table) is not considered to be relevant as the intervention and comparator are unlikely to differ significantly from one another in relation to this topic. Furthermore, the patient is not the active user and does not interact with the health technology as it is used by healthcare staff.

7 Organisational implications

Table 15: Studies and other data used in the organisational perspective.

Reference	Type of study/ type of data	Purpose of the study/ data collection	Context (Year, location, who)	Respondents (number, characteristics)	Comparator
Danish Registry [69]	Report/grey literature (abstract)	Examination of referral patterns within the treatment area	2024	Not applicable. Registry data.	Current practice
Data on file [69]	Interviews with JL Vasquez conducted via Video Conference. Interviews took place in	Examine operational impact of implementing HAL-guided TUR-BT	2024	Urologist that has used the intervention and the comparator in clinical practice in Denmark	Current practice
OHTAC [16]	Health Technology Assessment	Examine operational impact of implementing enhanced visualisation methods during TUR-BT and determining benefit between BLC and NBI	2021	Not applicable. HTA report.	Current practice

7.1 Summary of findings regarding the organisational perspective

Historically, HAL-guided TUR-BT was widely adopted and so a re-introduction would not be expected to cause major organisational changes.

Physical framework

The equipment required for this procedure involves a tower housing the hardware, light cable and light source for the cystoscopes. Towers are portable but do require some space. In some instances, operating rooms will be able to house an additional tower in addition to existing NBI equipment unless replaced completely.

Instillation is required which may require use of an additional room for physicians to complete their list on the day unless this procedure occurs in parallel with UTI screening.

Interaction with technology

The equipment required for this procedure - regardless of whether HAL or NBI is used - involves a processor, a light source, a camera head, a light cable and a cystoscope. A button on the camera head allows to switch between BLC and WLC or NBI and WLC. For HAL/BLC there are three manufacturers of this equipment: Karl Storz, Olympus and Richard Wolf.

A switch on the camera head allows for urologists to visualise the bladder under WL with BL enabled via a switch. Although some centres report that equipment is interchangeable and is used as such, the Manufacturers do not recommend nor guarantee equipment when used in this way. Some hospitals in Denmark are already equipped with HAL-enabled equipment but most are not.

These challenges can be met by re-introducing HAL-enabled equipment.

Autoclaves are already used to clean cystoscopes and some light cables. Fluid filled light cables cannot be autoclaved but instead are sterilised using other methods including ethylene oxide solutions. As this is already the case with NBI equipment, we do not anticipate any changes to this process if HAL is re-introduced. Furthermore, the latest HAL-enabled equipment are not based on fluid filled light cables anymore, and common sterilisation methods can be used according to WLC-light cables.

Expected lifetime of hardware
All enhanced visualisation methods require a processor housing the light source. Software for this is provided and updated by the manufacturer. In the case of NBI, most hospitals are already equipped with an Olympus processor. The documentation available on the manufacturers' websites do not contain details of the lifespan of the equipment.

Light cables and optics do have a limited lifespan regardless of whether these are for WLC, HAL or NBI. Anecdotal information suggests cables can be used for 2+ years - the optics even longer - however this would need to be validated with the manufacturer. In the case of the light source, this is the same light source whether used for WLC or HAL/BLC, so there is no difference.

The equipment is re-usable, with autoclaves used to clean cystoscopes and some light cables. Fluid-filled light cables cannot be autoclaved, instead they are soaked for short periods in sterilising solutions. Novel BL-equipment do not use fluid-filled light cables anymore.

Staff and time consumption
HAL is instilled into the bladder before the procedure. Nursing staff or nursing assistants will perform this, which takes place at least one hour before the TUR-BT. The instillation itself is a straightforward procedure performed by single-use catheterisation of the bladder and instillation of Hexvix into the bladder and is typically undertaken at the same time as urine tests are performed for Urinary Tract Infections.

Qualifications
NBI requires special training (typically provided by the manufacturer) in order for it to be used correctly. HAL-guided TUR-BT also requires training (typically provided by Photocure, the applicant). As with most procedures, there is a learning curve which again like NBI, is considered to be in the region of 20 procedures [94]. Anecdotal information obtained from physicians suggest this is the same with NBI.

7.2 Organisational description

HAL-guided TUR-BT has been recommended in the Danish guidelines [53] for the diagnosis and treatment of bladder cancer since 2007 and was broadly used in all five regions until 2018 following the widespread introduction of NBI enabled Olympus equipment in urology departments. The number of HAL procedures in Denmark has drastically decreased since and the current status is that only patients in two regions (specifically 2 hospitals) are still receiving HAL while the others have mostly converted to NBI.

Despite this, Danish guidelines [53] do still recommend the use of HAL/BLC (see section 3.3).

Table 16: Organisational description

Topic	Description of
Physical environment	
1. Interaction with technology	The use of HAL-guided TUR-BT in adjunct to WLC would replace NBI-guided TUR-BT. No other technology would need to be phased out. Both procedures require the use of equipment. HAL-guided TUR-BT is performed with either Olympus, Karl Storz or Richard Wolf equipment that consist of a processor, a light source, a camera, a light cable and a cystoscope. The units have different modes of operation including, but not limited to, white light mode and blue light mode. A button on the camera head allows to switch between white-light and blue-light mode. NBI-guided TUR-BT can only be performed with Olympus equipment using an optical filter technique. It is also used in adjunct to WLC. NBI technology does not require instillation of an agent into the bladder. As with BLC, a switch on the camera head allows the surgeon to switch between white light and NBI during the TUR-BT procedure. Adoption of HAL-guided TUR-BT may therefore require acquisition of compatible equipment. Also to note, in some regions, and in some cases, laser ablation is performed at the time of the diagnostic (flexible) cystoscopy. Such patients are not typically booked in for a TUR-BT. If this practice increases, there may be a subsequent decrease in the number of BLC-guided TUR-BTs or NBI-guided TUR-BTs. All enhanced visualisation methods require a processor housing the light source. Software for this is provided and updated by the manufacturer. In the case of NBI, most hospitals are already equipped with an Olympus processor. The documentation available on the manufacturers' websites do not contain details of the lifespan of the equipment. Light cables and optics do have a limited lifespan regardless of whether these are for WLC, HAL or NBI. Anecdotal information suggests cables can be used for 2+ years, the optics even longer, however this would need to be validated with the manufacturer. In the case of the light source, this is the same light source whether used for WLC or HAL/BLC, so there is no difference. The equipment is re-usable, with autoclaves used to clean cystoscopes and some light cables. Fluid-filled light cables cannot be autoclaved, instead they are soaked for short periods in sterilising solutions.
2. Compatibility	HAL/BLC requires specialized equipment and, in some hospitals, or clinics, this may not be compatible with existing systems currently in use.
interaction with staff	
3. Task shifting	No task shifting is anticipated.
4. Function creep	No function creep is anticipated.
5. Training in use	TUR-BTs are currently undertaken by urologists, varying from junior residents to specialist surgeons depending on the hospital. The quality of TUR-BT is increasingly considered of importance to the oncological outcome, and a number of initiatives have been emphasized to improve the quality, including the use of BLC-guided TUR-BT, e.g., Getting It Right First Time (GIRFT), and Mariappan et al [61].

	Consequently, the implementation of BLC can result in a change and improved staging and risk classification, which allows for a more optimal risk-based post-operative follow-up, and treatment strategy which can reduce the risk of under staging and under treatment, reduce the total number of surgical resection procedures for recurrence (re-TUR-BT) over time, prolong the time to resection of recurrence, and ultimately may impact the time to progression of disease [18]. Training in the use of BLC is important. There is a learning curve when using HAL/BLC, with studies reporting as many as 20 procedures [94]. Equipment manufacturers and Photocure field teams are able to support with this in addition to peer-supported procedure training as required.
6. Treatment levels	The health technology will be used in hospitals by physicians. Nurses will be involved in the instillation of Hexvix prior to the procedure taking place. This is the only change to current practice that would be required as the comparator does not involve this step.
7. Level of establishment	The procedure is extremely well established and has been recommended in the guidelines since 2007 [53]
8. Qualifications	Whether the technology requires special qualifications (knowledge or skills) in the personnel who will use it; special qualifications that would likely not to be there if the health technology were not to be used.
The surrounding world	
9. Technical environment	The health technology will not be used in other treatment areas than those specified in the expert committee's evaluation design.
10. Minimal level of use	The effect, safety and/or cost-effectiveness of the health technology is not contingent on a minimal level of use of the technology. The technology will not be used in other situations than the one described for the studied population and intervention, as economies of scale might be achievable.
Development of the health technology	
11. Expected product modifications	No future product modifications will be undertaken.

7.3 Applicant's summary of the transferability of the research setting

Transferability from research to practice is absolute as the patient populations, use of enhanced visualisation methods and general practice are the same in Denmark as in the studies cited. Also to note, historically, urologists in Denmark fully utilised BLC-guided TUR-BT and its use in practice reflected data generated from the clinical trials. The Danish registry continues to monitor use.

Other registries have also confirmed that outcomes in patients reflects data generated in clinical trials. As such, the organisational description included in the studies in section 4 can be scaled up to include the anticipated Danish patient population. Further, given patients in Denmark are diagnosed by flexible cystoscopy and ultrasound before being scheduled for a TUR-BT, Danish patients will typically undergo only one TUR-BT procedure (see section 3.3). This reflects the research criteria performed by Ontario Health [16] suggesting that patients would benefit from BLC than NBI, and that cost advantages existed, further suggesting applicability to the Danish population.

8 Health economics

8.1 Existing (health) economic analyses

Literature searches identified seven potentially relevant published economic analyses assessing the impact of different imaging strategies used alongside TUR-BT [6, 79, 96-100]. Three were cost-utility analyses, one was a cost-benefit analysis and three were pure cost analyses. All of the identified models compared the use of BLC-assisted TUR-BT vs standard WLC-assisted TUR-BT – none included an assessment of NBI-assisted TUR-BT. Equally, there were no analyses carried out from a Danish perspective. The model structure that we used was developed de novo, without reference to previously published models, as none of the published structures met the requirements of the DTC's evaluation design. For these reasons, all were excluded from further consideration. For the sake of transparency, a summary of the excluded studies is included in Table 35 (Annex 11.5).

8.2 Health economic analysis

Table 17: Analysis elements included in the health economic analysis as stated in the expert committee's evaluation design and the analysis elements used in the health economic analysis completed in this application.

Item	Analysis element	Expert committee specifications	Element applied in the analysis	Elaborated in section
1	**Time horizon**	Lifetime	Lifetime (50 years)	8.2.3
2	**Intervention**	HAL-guided TUR-BT	HAL-guided TUR-BT (BLC)	8.2.2
3	**Comparator(s)**	NBI-guided TUR-BT	NBI-guided TUR-BT (NBI)	8.2.2
4	**Analysis method**	CUA	CUA	8.2.6
5	**Outcome measure**	QALYs	QALYs	8.2.6
6	**Method of data extrapolation, if relevant**	Carried out to the relevant extent based on DTC Technical Appendix	Based on estimated hazard function for each outcome	8.2.5.6 Annex 11.8
7	**Analysis perspective**	Limited societal perspective	Limited societal perspective	8.2.7.3
8	**Minimum cost components to be estimated**	Costs should include but are not limited to: • TUR-BT related costs • Instillation of Hexvix • Costs for Hexvix incl. the necessary additional equipment in the form of optics, light cables and bulbs. (excl. cystoscope and column) • Personnel costs related to the instillation of Hexvix and costs for bed space. • The patient's transport and time	Patient transport costs excluded, as this component will be the same for both NBI and BLC	8.2.7.3
9	**Sensitivity analyses that should be carried out as a minimum***	The applicant is expected to carry out sensitivity analyzes to test uncertainties in the input parameters, which include both deterministic and probabilistic sensitivity analyses.	Univariate deterministic analysis Probabilistic analysis Targeted scenario analyses	8.2.8.2

8.2.1 Patient population

Patient population as described in section 0.

8.2.2 Intervention and comparator(s)

Data used is relevant to Danish clinical practice and evaluation design.

8.2.3 Time horizon

Lifetime horizon applied. Based on typical age of NMIBC patients, this has been set at 50 years.

Danish Ministry of Finance specified discount rate of 3.5% applied to both costs and benefits.

8.2.4 Analysis structure

The economic analysis is carried out using an economic model. Transition probabilities are based on meta-analyses of results from published randomised controlled trials. The design was created de novo for the submission to the Danish Treatment Council and was not derived from or inspired by any previously published health economic model, as listed in Table 35 in Annex 11.50.

8.2.4.1 Data from a single trial

Not applicable

8.2.4.2 Health economic model

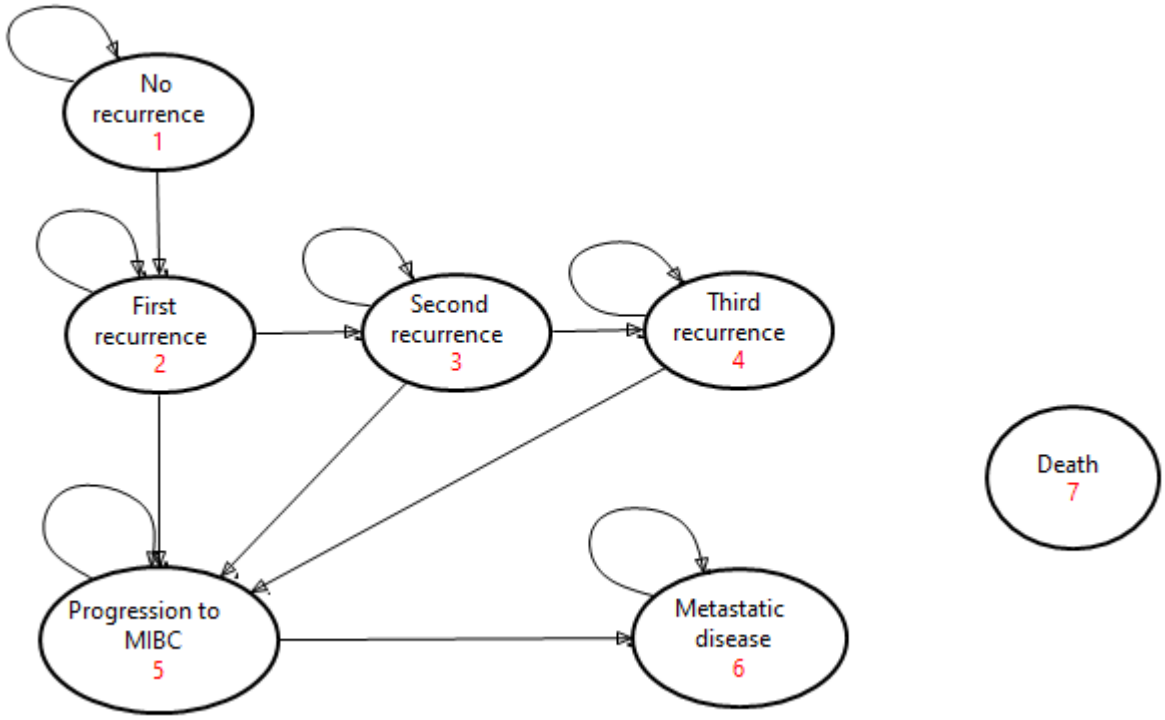
The analysis was carried out using a semi-Markov health state transition model. Six mutually exclusive health states were defined, with an additional absorbing death state (Figure 3). The first five health states ("No recurrence", "First recurrence", "Second recurrence", "Third recurrence" and "Progression to MIBC") directly reflect the outcomes of interest detailed in the DTC health economics specification. The remaining two states – "Metastatic disease" and "Death" - are not expected to display a difference between the two intervention arms but are included reasons of structural and clinical integrity within the model. The full rationale for the approach adopted is described in Annex 11.60.

In the absence of direct comparative data for the outcomes of interest, transitions between the health states are based on a two-stage process. The core transition structure is based on time to event analyses for patients managed with conventional WLC-guided TUR-BT, using long term epidemiological data to reflect transitions over time for each health state (see section 8.2.5.1). The relative impact of both HAL-guided TUR-BT and NBI-guided TUR-BTs then imposed on this core transition structure, based on hazard ratios derived from meta-analyses of clinical trials for the respective technologies (see section 8.2.5.2). All transitions are based on variable probabilities over time, with the transition matrices being based on transformed data from the published survival curves (see section 8.2.5.4).

Cycle length was 1 month, in order to capture the granularity of the varying follow-up and monitoring protocols defined in the clinical guidelines issued by Danske Multidisciplinære Cancer Grupper [95]. Because the cycle length is so short, it was not felt to be necessary to apply half-cycle correction to the costs and utilities accrued.

All modelling was carried out using TreeAge Pro 2024 (TreeAge Software LLC, Williamstown MA, USA).

Figure 3: Health state transition diagram for semi-Markov model used to assess cost effectiveness of HAL-guided TUR-BT vs NBI-GUIDED TUR-BT in patients diagnosed with NMIBC.



Notes:

1. *All patients enter the model in health state 1 ("No recurrence").*
2. *Once transition to a subsequent state has occurred, no reversion to an earlier health state is possible.*
3. *Transition to "Death" is possible form any of the other health states. For the sake of clarity, these transition arrows have been omitted from the diagram.*

8.2.4.2.1 Model validation

The model was developed by a single health economist, working in the context of the DTC specification and the care pathway defined in the relevant Danish clinical guidelines [95]. Guidance was provided by an independent Danish urologist, who assisted in both refining the model structure and informing the input parameters [*Professor Juan Luis Vásquez. Dept of Clinical Medicine, University of Copenhagen,* 70]. Periodically through the development process the model structure and assumptions were tested in workshops with an expert working group from within Photocure.

Internal validation:

1. Descriptive validity. "…*The model should provide a simplified, but adequate picture of reality. A model should consider all relevant aspects and omit only those aspects that do not alter its results and conclusions significantly..."* [101]. The available clinical evidence suggest that the choice of imaging technology is likely to influence the time to first recurrence and possibly the time to disease progression. Health states 1, 2 and 5 are therefore essential. Our clinical advisor pointed out that multiple recurrences can have a significant resource use impact: the model was consequently expanded to include this component. One could argue that health state 6 is unnecessary, as it will not be influenced by the original TUR-BT technology. It is, however, a potential driver of total treatment cost and, as it does not detract from the function of the model in

any way, it was felt reasonable to retain it. The death state was required to allow for patients to be withdrawn from the cohort over the lifetime horizon.

As highlighted in section 5, there is no specific documented safety signal associated with either HAL-guided TUR-BT or NBI-guided TUR-BT. Adverse events that occur tend to relate to the TUR-BT procedure, rather than the imaging technology used. Consequently, as these events are not relevant to the decision problem, adverse events have not been separately captured within the model.

2. Technical validation. Once complete, the model was reviewed from a technical standpoint by an independent health economist, in order to ensure that the structure, transitions and rewards were appropriately coded and reflected the intended strategy. We undertook extreme-case stress testing, to ensure that the model was robust to a range of different scenarios. The data transformation involved transforming Kaplan-Meier survival curves into hazard tables. This made use of a newly developed module in the analytical software (TreeAge Pro 2024). In order to assess whether this had been implemented correctly in the model, the software developer responsible for the hazard module reviewed our approach and confirmed its validity [*Wojciech Chrosny, Chief Scientific Officer, TreeAge Software LLC*].

3. Face validity. The available evidence in the field suggested that the use of both HAL-guided TUR-BT and NBI-guided TUR-BT were associated with improved time to first recurrence compared to conventional WLC TUR-BT. NBI uses an optical enhancing technique by filtering wavelengths in order to enhance the contrast of vessels and mucosal structure. In contrast, HAL is an agent which is metabolised, and fluorescent metabolites accumulate preferentially in tumour cells which glow red on blue background [35,54]. Although good quality RCT evidence relating to NBI is very sparse, it appears that the impact of HAL-guided TUR-BT on this outcome is superior to NBI. It is also possible that use of HAL-guided TUR-BT is associated with delayed time to progression to MIBC. This is considered due to a more complete resection, improved tissue sampling (including tumour margins and targeted biopsies) for histo-pathological evaluation during TUR-BT, leading to improved staging, grading and risk stratification. More early and accurate diagnosis of especially lesion with high-risk of recurrence and progression (e.g. of difficult to detect CIS lesions) allows for better post-operative management and adjuvant treatment decisions (see Sections 3 and 6.1). Patient costs of HAL-guided TUR-BT are somewhat higher than for NBI-guided TUR-BT, as the patient requires pre-operative intravesical instillation of a fluorescent agent, although this premium is likely to be offset to some extent by a reduced need for downstream repeat procedures to manage recurrent disease.

   The prior expectation for the model, therefore, was that it should show a modest increase in incremental costs incurred, with a corresponding increase in incremental utility. This is indeed the result that was seen – a result that was robust to a range of plausible inputs – confirming the face validity of the analysis.

External validation:

1. Convergent validity. Ideally one would check the results generated against previously published health economic analyses but, as stated before, no such published models exist – so far as we are aware, this is the first cost-utility comparison of HAL-guided TUR-BT vs NBI-guided TUR-BT. Three previous models comparing HAL-guided TUR-BT with conventional WLC TUR-BT have

been published [6,96,99, of which only one [99] had a lifetime horizon and considered disease progression as well as recurrence. This suggested that HAL dominated WLC, although the incremental cost saving was modest (~3.5%). The incremental utility was 0.1 QALYs, which is comparable in magnitude to the results seen in our model base case (0.115 QALYs).

2. Predictive validity. Once again, we would have liked to externally validate the conclusions of our study, but we have been unable to identify any publicly accessible source of data, whether within Denmark or elsewhere in the world, that would allow us to explore and validate the legitimacy of clinical outcome curves and costs predicted by our model. We were therefore unable to undertake this step.

8.2.5 Probability data

The model as specified above requires the following inputs:

1. For the WLC-guided TUR-BT backbone, the following long-term data are required:
    a. Recurrence-free survival
    b. Progression-free survival
    c. Metastasis-free survival
    d. Overall survival (all-cause mortality)
2. In order to estimate the impact of HAL-guided TUR-BT and NBI-guided TUR-BT on the WLC time-to-event backbone, the following further data are required:
    a. Hazard ratio for HAL-guided TUR-BT: impact on recurrence-free survival
    b. Hazard ratio for NBI-guided TUR-BT: impact on recurrence-free survival
    c. Hazard ratio for HAL-guided TUR-BT: impact on progression-free survival
    d. Hazard ratio for NBI-guided TUR-BT: impact on progression-free survival
    e. No published data relating to the impact of imaging technology on later stage outcomes (metastases and mortality) exist

The sections below detail the sources used and the data transformations required to incorporate it into the model.

8.2.5.1 Use of epidemiological data

There are relatively few real-world data sources that document long term time to event survival curves for the critical outcomes of interest in NMIBC. Given the requirement to provide a lifetime horizon for the cost utility analysis and the uncertainties inherent in extrapolating survival curves, we sought to identify sources that minimised our need to estimate outcomes in the early years of the model, when relatively low cumulated discounting was in effect. On this basis, we selected three studies that provided survival data for 10-15 years following initial diagnosis (Table 18).

For the recurrence and progression outcomes, Kaplan-Meier survival curves extending to 10 years follow-up were extracted from a 2014 paper that assessed outcomes in a retrospective analysis of 1,892 patients treated in three European countries – Denmark, Netherlands and Spain [102]. Although our original intention was to use the data from the Danish centre, it emerged that these were a specially selected group of high-risk patients. Given that we wanted to identify a more representative sample, we elected instead to use the data for Netherlands, which was based on 639 sequentially treated patients with NMIBC. Because the patients were diagnosed between 1990 and 2012, exposure to HAL or NBI assisted TUR-BT was not a problem – all were managed with conventional WLC-guided TUR-BT. As such, this data represents a fair baseline characterisation of unenhanced treatment interventions.

The primary objective of the study was a comparison of different risk stratification algorithms, so the data were presented as separate Kaplan-Meier curves, one for each of three risk levels (see Annex 11.7). There were insufficient data for HAL and NBI to allow the subdivision of model along these lines, so we had to undertake data transformation to hazard tables, to allow an aggregated assessment of all risks survival probabilities. This approach is described further in section 8.2.5.4 and Annex 11.7.

For the metastasis-free survival assessment, we found very few data in the published literature. Almost all available studies related to patients with MIBC – we were only able to find a single study based on a retrospective review of 434 NMIBC patients diagnosed in two hospitals in Japan [103]. Although this was not ideal, there was no prior expectation that progression to metastatic disease would be a major determinant of outcome – an expectation that was confirmed by sensitivity analysis of the final results. For this reason, we were willing to accept the Japanese data for this outcome. As for the previous study, the survival curves were split by risk – in this case the presence or absence of chronic kidney disease – so the same hazard table extraction was performed to allow merging of the curves (see section 8.2.5.4).

Finally, the overall mortality data were sourced from a large US claims database analysis, that drew data from around 98,000 patients diagnosed with NMIBC between 2004 and 2014 [104]. Although not a European source, the sheer number of patients involved and the fact that all-cause mortality was documented – most published papers present only cancer-specific mortality – meant that this was clearly the best resource to use. OS curves were presented for a wide range of different tumour subtypes. We selected the curve for patients with high grade Ta or low grade T1 tumours at the time of diagnosis, as these represented the mid-point of the available survival curves (see Annex 11.7.).

Table 18 Overview of epidemiological data used in the health economic analysis.

Variable	Study period (Maximum follow-up)	Median value (IQR); % with outcome at 10 years	Reference	Probability distribution
Cumulative recurrence probability[1]	120 months	Low risk: 51 months; (16-NR) 58.3% at 10 years Intermediate risk: 30 months (9-NR) 67.5% at 10 years High risk: 28 months (9-NR) 71.2% at 10 years	[102]	PERT[2]
Cumulative progression probability[3]	120 months	Low risk: median NR. 11.1% at 10 years Intermediate risk: median NR 20.4% at 10 years High risk: median NR 45.6% at 10 years	[102]	PERT[2]
Metastasis-free survival	140 months	Low risk (no CKD) NR 2.5% at 10 years High risk (CKD) 24.6% at 10 years	[103]	PERT[2]
Overall survival	190 months	Median: 108 months (57-NR) 53% at 10 years Both data points for Ta high grade/T1 low grade	[104]	PERT[2]

Notes:

1. *These data were not presented in the source paper – the median + IQR estimates are based on digitised cumulative event curves. Full details of these study outputs, together with the approach to integrating them in the model are shown in Annex 11.7.*

2. *The data were transformed into a hazard table before use in the model (see 8.2.5.4). In line with advice from TreeAge Software, the appropriate distribution to use was consequently a β-PERT continuous probability distribution.*
3. *These data were not presented in the source paper and fewer than 50% of patients progressed in each risk group, so the median could not be estimated. Full details of these study outputs, together with the approach to integrating them in the model are shown in Annex 11.7.*

8.2.5.2 Use of data from clinical trials

The approach adopted for the model required that hazard ratios should be calculated for both HAL-guided TUR-BT and NBI-guided TUR-BT. These would be applied to the WLC-TUR-BT survival curves in order to estimate the effect of each imaging technology on the outcomes of interest. The systematic literature review identified 9 randomised controlled trials of HAL-guided TUR-BT vs WLC-guided TUR-BT that recorded recurrence data, with a follow-up duration ranging from 12-55 months [1-4,6,7,9,10,19]. Of these, time to recurrence data were either recorded or could be back-calculated in 8 studies [80] (see also Annexe). One study [1] was an interim report of another study [2].

For NBI-guided TUR-BT, only two studies clearly complied with the search criteria, each with a follow-up period of 12 months [11,12], while two further studies were potentially eligible for inclusion [13,14], although one only presented recurrence data for around one third of the patients enrolled in the study [13], and the second was only ever published as an abstract [14].

For the disease progression outcome, there were four studies yielding data for HAL-guided TUR-BT [2,3,10,19], whilst there were none for NBI-guided TUR-BT, reflecting the limited follow-up period in the RCTs.

The arbitrary selection of single studies to represent the competing technologies would have significantly biased the conclusions of the model. For this reason we made the decision to use the results of paired meta-analyses to drive the efficacy outcomes. The results of our content and quality assessment of the 16 published meta-analyses are detailed in Annex 11.7. On completion of this exercise, it was apparent that none of the available analyses met our requirements for the time to recurrence outcome, while one analysis met the requirement for the progression outcome. To address the lack of recurrence estimate, a de novo meta-analysis was carried out (this meta-analysis also served as the Clinical Effectiveness and Safety Meta-Analysis and is the same as in section 5.2.3 the results of which are presented in Table 19 below. Full details are provided in Annex 11.7. This is the same method and analysis used for the Clinical Effectiveness and Safety section 5.2.3.

For the purposes of the economic model, all relative efficacy estimates (recurrence and progression) were derived from the de novo meta-analysis. Individual study data were only used insofar as they contributed to the meta-analysis.

Table 19: Overview of meta-analysis of clinical trial data used in the health economic analysis.

Variable	Comparison	Study period	Mean value, HR (95%CI) Random effects	Reference	Probability distribution
Disease recurrence	HAL-guided TUR-BT vs WLC-TUR-BT	Up to 55 months	HR: 0.63 (0.49 – 0.82) P = 0.001	[2-4,6,7,9,10,19,76,77]	Log normal
Disease recurrence	NBI-GUIDED TUR-BT vs WLC-TUR-BT[1]	1 year	HR: 0.74 (0.42 – 1.32) P = 0.308	[11,12]	Log normal
	NBI-GUIDED TUR-BT vs WLC-TUR-BT[2]	1 year	HR: 0.77 (0.0.51 – 1.18) P = 0.235	[11-13]	Log normal
	NBI-GUIDED TUR-BT vs WLC-TUR-BT[3]	1 year	HR: 0.67 (0.42 – 1.06) P = 0.084	[11-14]	Log normal
Disease progression	HAL-guided TUR-BT vs WLC-TUR-BT	Up to 55 months	HR: 0.69 (0.48 – 0.98) P = 0.04	[2,3,10,19]	Log normal
Disease progression	NBI-GUIDED TUR-BT vs WLC-TUR-BT	No studies with NBI-GUIDED TUR-BT identified for this outcome			

Notes:

1. *Analysis based on two high quality studies [11,12]*
2. *Analysis as for option 1 but including study with recurrence analysis for 37% of randomised patients [13]*
3. *Analysis as for option 2 but including study only published as abstract [14]*

It is apparent that none of the three meta-analyses for NBI-guided TUR-BT vs WLC-guided TUR-BT demonstrated a statistically significant difference between groups. For the purposes of this submission, however, we elected to ignore this finding and assume that NBI-guided TUR-BT was indeed associated with a recurrence benefit vs WLC-guided TUR-BT. However, it was unclear which of the results should be used. A robust approach to the analysis would suggest that only the two high quality studies should be used (HR=0.74) or potentially allow for the third study with the subgroup analysis to be included (HR=0.77). A more liberal approach might also allow the inclusion of the abstract-only data (HR=0.67), although the result of this individual study are significantly at odds with the other three studies (see Annex 11.7). In the interest of equipoise, we chose to use the median estimate (HR=0.74) for the base case, with the other two estimates being explored in scenario analyses.

With regard to disease progression, the issue is more complex. Clearly, in absence of evidence, it was assumed for the model that NBI-guided TUR-BT exerted no effect on future disease progression risk. For HAL-guided TUR-BT, the analysis shows that there was a significant improvement in progression-free survival (HR = 0.69), which is of potential clinical relevance. However, it is impossible to say from the available evidence whether the progression benefit is independent of the well documented delay in time to recurrence. It can be shown that progression from documented NMIBC to MIBC rarely, if ever, takes place in the absence at least one episode of recurrent disease [105]. Consequently, it is reasonable to expect that, if one, through more complete resection, improved histo-pathology sampling leading to improved, e.g. intensified adjuvant treatment management, can delay the time to first recurrence, as a direct

consequence the time to progression will similarly be delayed (See Sections 3 and 6). This event linkage is explicitly captured in our Markov model. Thus, although we cannot exclude the possibility that there is a direct and independent effect of HAL-guided TUR-BT, it is possible that the indirect dependent effect is what we are seeing in the meta-analysis results. As a conservative strategy, therefore, we have assumed for the base case that there is no independent effect of HAL-guided TUR-BT on progression to MIBC, with a scenario analysis being carried out to explore the contrary assumption.

8.2.5.3 Use of proxy outcome measures

Proxy outcome measures were not used in the model

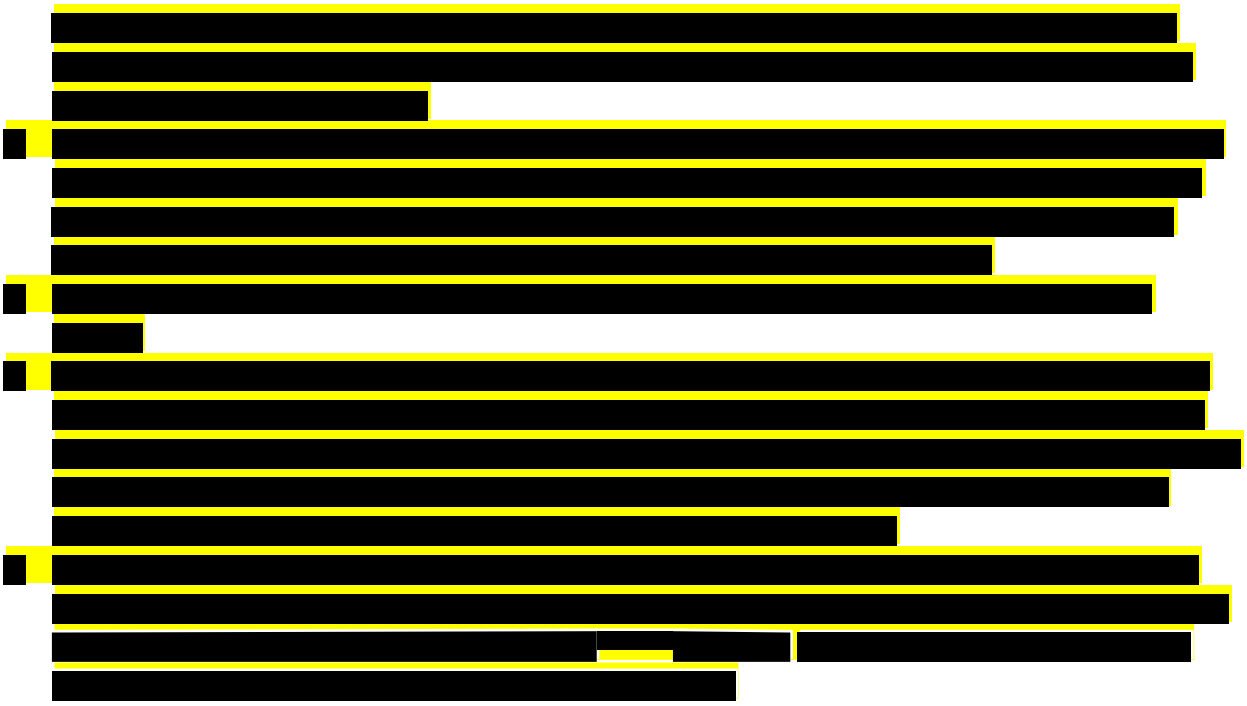
8.2.5.4 Transformation of data

In order to incorporate the available time to event data in this model, transformation was required. This section summarises the approach. Full details and illustrations of the process are provided in Annex 11.7.

As described above, the basis of this model was an indirect comparison. A core structure based on long term survival data for patients managed with WLC-TUR-BT was created, against which hazard ratios calculated for the technologies of interest were applied in order to assess their impact. Although this approach maximises the use of the available information, it presents certain problems from a practical point of view:

- The survival data for the outcomes of interest were only available as Kaplan-Meier curves from the literature. No individual patient data were accessible for the analysis. There was therefore a need to digitally extract information from the published graphics.
- For the outcomes of interest, the published K-M curves were split according to a range of risk stratification factors. Evidence of risk-specific efficacy was either sparse or absent for the two technologies under evaluation. There was consequently a need to aggregate the different curves into a single "weighted mean" survival curve. This task cannot be achieved simply using native survival curves – instead, the curves need to be deconstructed into their underlying hazard tables.
- Similarly, in order to apply a hazard ratio to a K-M curve and arrive at an adjusted curve that reflects an alternative management strategy, the survival data needs to be transformed into hazard data.
- In order to incorporate the final adjusted hazard tables into the model, a further transformation is required to convert the information into a transition probability.
- Finally, there is a need to explore the parameter uncertainty as part of the deterministic and probabilistic sensitivity analyses. Although this is straightforward for the hazard ratio component, consideration must also be given to the underlying WLC-TUR-BT survival functions that form the core of the model. K-M survival data are not readily amenable to this process, although it is straightforward to apply to a hazard table.

Consequently, the following sequential process was undertaken to yield the necessary outputs:



8.2.5.5 Changes in probabilities over time

This is inherent to the function of this model. The approach adopted has been described in brief above and is detailed in Annexes 11.6 and 11.7

8.2.5.6 Extrapolation of data

Core data for all four health states of interest are based on long term survival data that extend out over a 120-190 month period. In order to capture the specified lifetime horizon, these survival data were extrapolated out to 600 months. The hazard module within TreeAge Pro allows this process to be carried out across a non-constrained range, using a graphical interface, rather than being restricted to the 10 or so parameterisation distributions that are traditionally used for this purpose. Details of the process, together with screen-shots, are shown in Annex 11.8.

Given the relatively long period covered by the primary data, a scenario analysis was carried out exploring the model results without extrapolation.

8.2.6 Measurement of outcomes

8.2.6.1 Cost-consequence and cost-effectiveness analyses

Not applicable

8.2.6.2 Cost-utility analysis

8.2.6.2.1 Health-related quality of life for NMIBC

NMIBC, when in the pre-progressed state, has an impact on quality of life attributable to various aspects of the disease and its management [82]:

- Psychological impact of a cancer diagnosis
- Physical and psychological impact of recurrent interventions related to surveillance, intravesical treatments and repeat TUR-BT when recurrences occur
- Impact of treatment on sexual health

In patients whose disease progresses to MIBC or metastatic disease, the effect is substantially greater, given the more physically and psychologically impactful nature of the management strategies (cystectomy, radiotherapy, chemotherapy). There is a clear trend towards deterioration in quality of life as patients advance through the stages of the disease, over and above any impact purely associated with ageing [106].

Given that the primary drivers of deteriorating quality of life are treatment-related, any approach that can delay transition from a less severely to a more severely affected health state may be expected to yield quality of life gains.

8.2.6.2.2 Data basis for the impact on health-related quality of life

None of the randomised controlled trials of HAL-guided TUR-BT or NBI-guided TUR-BT evaluated quality of life in a way that was usable within the model. We therefore looked to the literature to identify health-state specific utility estimates from the literature. Our list of ideal criteria to apply when identifying sources of utility data for use in the model were as follows:

- Documentation of utility data for all health states of interest from a single study population
- Direct elicitation using a generic tool (eg EQ-5D) rather than mapping from an HRQoL tool (eg EORTC QLC-C30)
- Elicitation or validation against a Danish population

Although several Danish quality of life studies were identified [107-109], these focussed exclusively on sub-populations of patients with advanced disease and did not use a generic tool for elicitation of utilities. In this regard, the studies were not unusual – a broader review of the literature identified that most studies used HRQoL tools, with most failing to map the results to generic utilities.

One UK study [6] elicited generic quality of life scores using EQ-5D-3R at 6-monthly intervals, as part of a randomised controlled trial comparing WLC-guided TUR-BT with HAL-guided TUR-BT. Mean domain scores for each treatment group at each time point were presented in the published paper, but extraction of results to define individual health state utility was not undertaken. We were consequently unable to use the data within the economic model.

We identified one study that met with our first two criteria, in that it used a generic TTO methodology to elicit utilities, with all aspects of the pathway of disease being documented within the same elicitation study [113 (suppl table 1)]. Unfortunately, it was a UK rather than Danish perspective. Additionally, it was based on a high risk NMIBC population undergoing treatment with BCG, rather than an all-risks population. However, despite these limitations it offered the most reliable set of utility estimates that we could identify from the literature and in consequence we chose it to populate all stages of the model. We chose to use median rather than mean values as the point estimate within the model, as the results were significantly skewed, resulting in potentially unrepresentatively low values for the mean utilities.

Table 20: List of preference weights ascribed to health states

Health state/event	Preference weight, median. (IQR)	Instrument and value set	Probability distribution	Mapping used? yes/no	Comment	Ref.
No recurrence	0.825 (0.675-0.925)	EQ-5D-5L, UK TTO	beta	no	High risk population receiving BCG	[113]
First recurrence	0.625 (0.475-0.775)	EQ-5D-5L, UK TTO	beta	no	High grade recurrence	[113]
Second recurrence	0.625 (0.475-0.775)	EQ-5D-5L, UK TTO	beta	no	Assumed same as first recurrence	[113]

Third recurrence	0.625 (0.475-0.775)	EQ-5D-5L, UK TTO	beta	no	Assumed same as first recurrence	[113]
Progression to MIBC (first year)	Male: 0.375 (-0.042-0.625) Female: 0.458 (0.104-0.708)	EQ-5D-5L, UK TTO	PERT	no	Assumes treated with cystectomy. Estimates integrated as a table keyed in to progression tracker in model. Hence PERT distribution used.	[113]
Progression to MIBC (year 2+)	0.675 (0.425-0.825)	EQ-5D-5L, UK TTO	PERT	no		[113]
Metastatic disease	0.375 (0.125-0.600)	EQ-5D-5L, UK TTO	beta	no	Assumes no cystectomy	[113]

8.2.7 Cost statement

Treatment and investigation costs have been calculated based on 2023 DRG tariffs [110]. Resource use associated with bladder cancer monitoring is based on the Danish Multidisciplinary Cancer Group guidelines [53].

8.2.7.1 Costs of using the health technology and comparator(s)

Both HAL-guided TUR-BT and NBI-guided TUR-BT have an associated DRG code (11MP17 and 11MP24 respectively. As we understand it, this DRG covers the following components:

- The department's actual gross operating expenses associated with the procedure
- Joint actual gross operating expenses at hospital level
- General common actual gross operating expenses, healthcare
- All staff costs
- Depreciation on capital and lease purchases of associated equipment
- Drug costs incurred as part of the procedure

We understand that the cost of 1 additional hour of patient time required for the pre-operative Hexvix instillation procedure is not captured within the DRG and is consequently separately documented in Table 21.

Table 21: Costs of using the HAL-guided TUR-BT and NBI-guided TUR-BT

Cost component	Cost per patient*, DKK (95%CI)	Probability distribution**	Annuitized	Allocated	Ref.
HAL-guided TUR-BT					
Procedure	DKK 20,385 per patient DRG 11MP17	gamma			[110]
Patient time	DKK 347 per procedure	gamma			[111]
NBI-guided TUR-BT					
Procedure	DKK 12,480 per patient DRG 11MP24	gamma			[110]

8.2.7.2 Costs associated with health conditions and events

Note that in Table 22 below, the resource use described is specific to the health state, not the imaging technology used. Consequently, only a single value is given to each component. Estimates are based on the

state-specific guidelines issued by the Danish Multidisciplinary Cancer Group. As these treatment and follow-up strategies are protocol-driven, no confidence intervals are given, although nominal estimates of spread for the resource x cost product are assigned for the purposes of deterministic and probabilistic sensitivity analyses.

Table 22: Identification and quantification of cost components associated with different health states and events included in the health economic model.

Health state/ event	Cost component	HAL-guided TUR-BT + NBI-guided TUR-BT Ave. quantity consumed	Probability distribution (applied to resource x cost product)	Ref.
Pre-progression (low/intermediate risk – BCG not given)	Surveillance cystoscopy	2 in year 1 1 per year in year 2-5	gamma	[95]
Pre-progression (intermediate/high risk – BCG given)	BCG (TICE strain) 12.5mg	15 in year 1	gamma	[95]
	Instillation of BCG	15 in year 1	gamma	[95]
	Surveillance cystoscopy	4 in year 1 3 in year 2 1 per year in year 3-7	gamma	[95]
Progression to MIBC (cystectomy)	Cystectomy	Single procedure	gamma	[95]
	CT scan	2 in year 1 1 in year 2	gamma	[95]
Progression to MIBC (bladder conserving)	TUR-BT	Single procedure	gamma	[95]
	Radiotherapy	32 fractions over 6 weeks	gamma	[95]
	Cystoscopy	3 in year 1-2 1 per year in year 3-5	gamma	[95]
	CT scan	2 in year 1 1 in year 2	gamma	[95]
Metastatic disease	Chemotherapy	Assumed monthly cycles – see table 23,24	gamma	[95]

Table 23: Valuation of the cost components associated with different health states and events included in the health economic model

Health state / event	Cost component	Valuation, DKK 95% (CI)	Probability distribution*	Ref.
Pre-progression (low/intermediate risk – BCG not given)	Surveillance cystoscopy DRG 11PRO2	4,187	gamma	[110]
Pre-progression (intermediate/high risk – BCG given)	BCG (TICE strain) 12.5mg	700	gamma	Hospital
	Instillation of BCG DRG 11PRO4	1,233	gamma	[110]
	Surveillance cystoscopy DRG 11PRO2	4,187	gamma	[110]
Progression to MIBC (cystectomy)	Cystectomy DRG 11MP04	234,681	gamma	[110]

	CT scan DRG 30PRO07	2,023	gamma	[110]
Progression to MIBC (bladder conserving)	TUR-BT DRG 11MP24	12,480	gamma	[110]
	Radiotherapy DRG 27MP05	40,193	gamma	[110]
	Surveillance cystoscopy DRG 11PRO2	4,187	gamma	[110]
	CT scan DRG 30PRO07	2,023	gamma	[110]
Metastatic disease	Chemotherapy (see note below table 24)	10,000 – 100,000 per month	gamma	Clinician opinion

Table 24: Total costs associated with health states and events, estimated as the quantity of the individual cost components associated with the health state/event multiplied by the valuation of the cost component.

Health state/ event	**Cost component**	**HAL-guided TUR-BT + NBI-guided TUR-BT Ave. quantity consumed**	
		Cost of the component, DKK per health state/event	**Total cost, health state /event, DKK**
Pre-progression (low/intermediate risk – BCG not given)	Surveillance cystoscopy	Year 1: 8,374 Year 2-5: 4,187	Year 1: 8,374 Year 2-5: 4,187
Pre-progression (intermediate/high risk – BCG given)	BCG (TICE strain) 12.5mg	Year 1: 10,500	Year 1: 45,743 Year 2: 12,561 Year 3-7: 4,187
	Instillation of BCG	Year 1: 18,495	
	Surveillance cystoscopy	Year 1: 16,748 Year 2: 12,561 Year 3-7: 4,187	
Progression to MIBC (cystectomy)	Cystectomy	Year 1: 234,681	Year 1: 284,470 Year 2: 2,023
	CT scan	Year 1: 4,046 Year 2|: 2,023	
Progression to MIBC (bladder conserving)	TUR-BT	Year 1: 12,480	Year 1: 69,280 Year 2: 14,584 Year 3-5: 4,187
	Radiotherapy	Year 1: 40,193	
	Cystoscopy	Year 1-2: 12,561 Year 3-5: 4,187	
	CT scan	Year 1: 4,046 Year 2: 2,023	
Metastatic disease	Chemotherapy	Estimated 240,000 per year*	240,000

**Note: For patients in the metastatic state, there are a wide range of options, including radiotherapy, conventional chemotherapy (cisplatin + gemcitabine), checkpoint inhibitor (pembrolizumab) or palliative treatment, with little evidence to document the relative proportion of patients receiving each option, nor the duration of treatment. Depending on the category, costs can range from a few thousand DKK per month up to 100,000 DKK. This component is not a point of distinction between HAL-guided TUR-BT and NBI-guided TUR-BT, and as such is not a driver of the ICER (see tornado diagram below). It is only included in the model for the sake of completeness and therefore an arbitrary cost assumption of DKK 20,000 per month has been made.*

8.2.7.3 Limitations of the cost statement

The impact of the technologies under examination relates purely to the probability that a patient will rest in one health state or another at a given time. The costs per health state remain constant across both treatment groups.

8.2.8 Result of the health economic analysis

8.2.8.1 Base case results

The base case results of the cost-utility analysis are presented in Table 25. Note that, because the model uses individual patient trackers to determine changes in resource use over time, these cost and QALY estimates are based on 10,000 microsimulations, rather than a single Expected Value. For this reason, if the simulations are re-run, marginally different results for the ICER will be obtained.

Table 25: Results of the health economic analysis.

Intervention	Total cost, DKK	Total benefit QALY	ΔC, DKK	ΔE	ICER	Statement of dominance
			vs. relevant comparator			
HAL-guided TUR-BT	57,764	6.579	-	-		
NBI-guided TUR-BT	50,562	6.484	7,202	0.095	75,811 DKK/QALY	No dominance

8.2.8.2 Sensitivity analyses

We present below the results of:

a) Deterministic sensitivity analysis

All independent input variables used in the model were tested across plausible ranges. Depending on the variables, this range was defined as:

- +/- 95% confidence interval (Hazard ratios for recurrence; health state utility estimates)
- +/- 20% (Probability of a patient being high risk; probability of cystectomy on progression)
- +25%/-10% (All cost estimates, to capture the skewed nature of healthcare costs)
- Max/min (parameters that varied over time, such as transition probabilities)

Analyses were run and tornado diagrams generated for both ICER and INMB, with full tabulated results being presented for all parameters where the ICER spread covers >5% of the base case ICER estimate. For the purposes of these analysis, a willingness to pay threshold of DKK 500,000/QALY was assumed.

b) Probabilistic sensitivity analysis

All input variables used in the model were included in the PSA. Distribution types and parameters were selected to mimic the expected distribution of values. Types used were:

- Beta distribution (probabilities; utilities)
- Gamma distribution (costs)
- LogNormal distribution (Hazard ratios)

- PERT distribution (Variables referenced in time-specific tables)

Results were used to generate an ICER scatterplot with 95% confidence ellipse.

c) Scenario analyses

Five scenarios were evaluated:

- *Allow HAL-guided TUR-BT to exert an independent effect on time to progression*. The rationale for this scenario is discussed in paragraph 8.2.5.2. For this analysis we have applied the hazard ratio for time to progression for HAL-guided TUR-BT from the meta-analysis (HR = 0.69), while simultaneously retaining the HR for time to recurrence. For NBI-guided TUR-BT the HR was retained at 1.0. All other parameters were held at base case levels.
- *Use HAL-guided TUR-BT for treatment of tumour recurrences.* This analysis was requested in the DTC specification. Although no study has explicitly explored the use of HAL-guided TUR-BT for subsequent TUR-BT, a several of the RCTs included in the meta-analysis included these patients alongside newly diagnosed cases [4,9,19]. This scenario therefore accrued costs and benefits for both HAL-guided TUR-BT and NBI-guided TUR-BT arms for the subsequent recurrence health states. All other parameters were held at base case levels.
- *Explore impact of alternative estimates for effect of NBI-guided TUR-BT on time to recurrence*. As discussed in section 8.2.5.2, it is uncertain which of the studies comparing NBI-guided TUR-BT to WLC-guided TUR-BT should legitimately be included in the meta-analysis assessing the HR for time to recurrence. Given that this is a key driver of the outcome (see 8.2.8.2.1 below), it is important to explore this uncertainty further. The base case uses a central estimate (HR=0.74) – for the scenario analysis both high and low estimates were explored: (HR=0.77 and HR=0.67)
- *Repeat base case analysis using 10 year time horizon*. Extrapolation of data beyond the point at which real data exist is an inevitable weak point of any cost utility model. The purpose of this scenario analysis is to re-run the base-case using a time horizon that is within the follow-up duration of the source survival curves, in order to assess whether any qualitative difference in conclusions is observed.
- *Evaluate the base-case outcome using curve-fitting extrapolations for RFS, PFS and MFS outcomes*. The base case was evaluated based extrapolations of clinical outcomes from 10 years to lifetime modelled using an unconstrained extension of the survival curve hazard table (Section 11.8.1). Traditionally this process is carried out by fitting a parametric distribution to the available Kaplan-Meier survival curve and extending this simulated survival curve beyond the period documented in evidence. This process was undertaken for the clinical outcomes evaluated in this model (Section 11.8.2) and the resulting extrapolations were used to re-run the base-case analysis.

8.2.8.2.1 Deterministic sensitivity analysis

All variables used in the model were included in a deterministic sensitivity analysis, with parameter estimates being varied across the range shown in Table 26. Note that for variables that varied over time and were thus referenced by the model using a table, the range chosen varied from the lowest to the highest value per cycle used in the table – the same parameters being used to define the PERT distribution in the probabilistic sensitivity analysis.

Results are displayed in Table 26and Figures 4 and 5.

Interpretation

The deterministic analysis shows that the parameters that are the most sensitive drivers of outcome are the hazard ratios capturing the time to first recurrence for both HAL-guided TUR-BT and NBI-guided TURBT, with extreme values for these two variables potentially resulting in ICERs that exceed an acceptable willingness to pay.

The most intuitively informative column for these two metrics are the low and high estimates for the incremental net monetary benefit (INMB). The NMB combines the difference between the monetary value of total expected quality-adjusted life years (QALYs) and the total expected costs, with the difference between the two technologies under consideration being the INMB. If the INMB has a negative value, this means that the technology under consideration is not cost effective at the defined WTP threshold, while a positive value means that the intervention would be considered to be cost effective. The magnitude of the NMB (positive or negative) gives an indication of how far below or above the WTP threshold the technology lies.

It can be seen that, at the lower estimate for treatment benefit for each technology (highest hazard ratio versus WLC) the INMBC is negative, whilst at the higher estimates, the results comfortable falls into the cost-effective category. Given that the confidence intervals for both estimates are relatively wide – particularly for NBI, where the confidence interval straddles unity – the range of INMB is correspondingly wide. Threshold analysis suggests that a HR of >0.73 for HAL-guided TUR-BT vs WLC-guided TUR-BT or a HR of <0.65 for NBI-guided TUR-BT vs WLC-guided TUR-BT would yield results that would exceed a WTP threshold of 500,000 DKK/QALY and generate a positive INMB. The base case HR for HAL-guided vs WLC-guided TUR-BT is 0.63. In order to reach the threshold of no longer being cost-effective, the HR would need to be increased to 0.73 - implying that the technology would need to be significantly less effective than the current central estimate, while the NBI estimate remained at its base case level. For NBI, by contrast, the HR would need to decrease from 0.74 to 0.65 - an improvement in efficacy while the HAL value remained the same, in order to drive the overall estimate of cost effectiveness for HAL below the acceptable threshold.

Considering the other parameters, utility estimates, costs of TUR-BT and the time-to-event curves for the underlying WLC-TUR-BT, whilst all exert a significant independent effect on both ICER and INMB, in no case does the plausible range of parameter values tested result in a result outside the acceptable WTP threshold. All other metrics exert an effect on the ICER that is insignificant (spread <5% of central ICER estimate).

In reality, of course, few of the parameters within the model will exert an effect independently of the other. In order to fully understand the variability around the central estimate of cost-effectiveness, an analysis allowing for all these parameters to vary simultaneously is required. The results of this analysis are shown in paragraph 8.2.8.2.2.

Table 26: Results of deterministic sensitivity analyses

Variable Description	Low value	Base case	High value	Inc cost (Low)	Inc cost (High)	Inc QALY (Low)	Inc QALY (High)	ICER (Low)	ICER (High)	INMB (Low)	INMB (High)
HR vs WLC for time to first recurrence using BLC	0.487	0.632	0.819	5,606	9,133	-0.057	0.250	-159,684	761,060	-37,731	119,263
HR vs WLC for time to recurrence using NBI	0.415	0.74	1.32	2,839	11,583	-0.226	0.485	-51,261	759,879	-124,565	239,703
Utility in pre-recurrence state	0.675	0.825	0.925	7,493	7,493	0.032	0.142	52,827	237,783	8,263	63,425
Utility in post-recurrence state	0.475	0.625	0.775	7,493	7,493	0.046	0.157	47,740	162,195	15,605	70,982
Cost of TUR-BT using BLC	18,347	20,385	25,481	5,455	12,590	0.103	0.103	52,858	121,995	39,009	46,144
Cost of TUR-BT using WLC	11,232	12,480	15,600	4,350	8,718	0.103	0.103	42,157	84,483	42,880	47,248
Time to death (WLC)	Variable over time – lowest to highest values in tables used for range			6,322	7,843	0	0	0.092	0.126	38,385	56,624
Utility in post-progression state	Variable over time – lowest to highest values in tables used for range			7,493	7,493	0	0	0.084	0.113	34,482	49,074
Time to recurrence (WLC)	Variable over time – lowest to highest values in tables used for range			7,083	7,905	0	0	0.094	0.110	38,907	48,075
Time to progression to MIBC (WLC)	Variable over time – lowest to highest values in tables used for range			7,079	7,585	0	0	0.102	0.105	43,348	45,034
Time to progression to metastatic disease (WLC)	Variable over time – lowest to highest values in tables used for range			7,228	7,693	0	0	0.103	0.103	43,726	44,463
Monitoring and follow-up costs (post recurrence)	Variable over time – lowest to highest values in tables used for range			7,174	7,546	0	0	0.103	0.103	44,053	44,425

Figure 4: Tornado diagram ICER

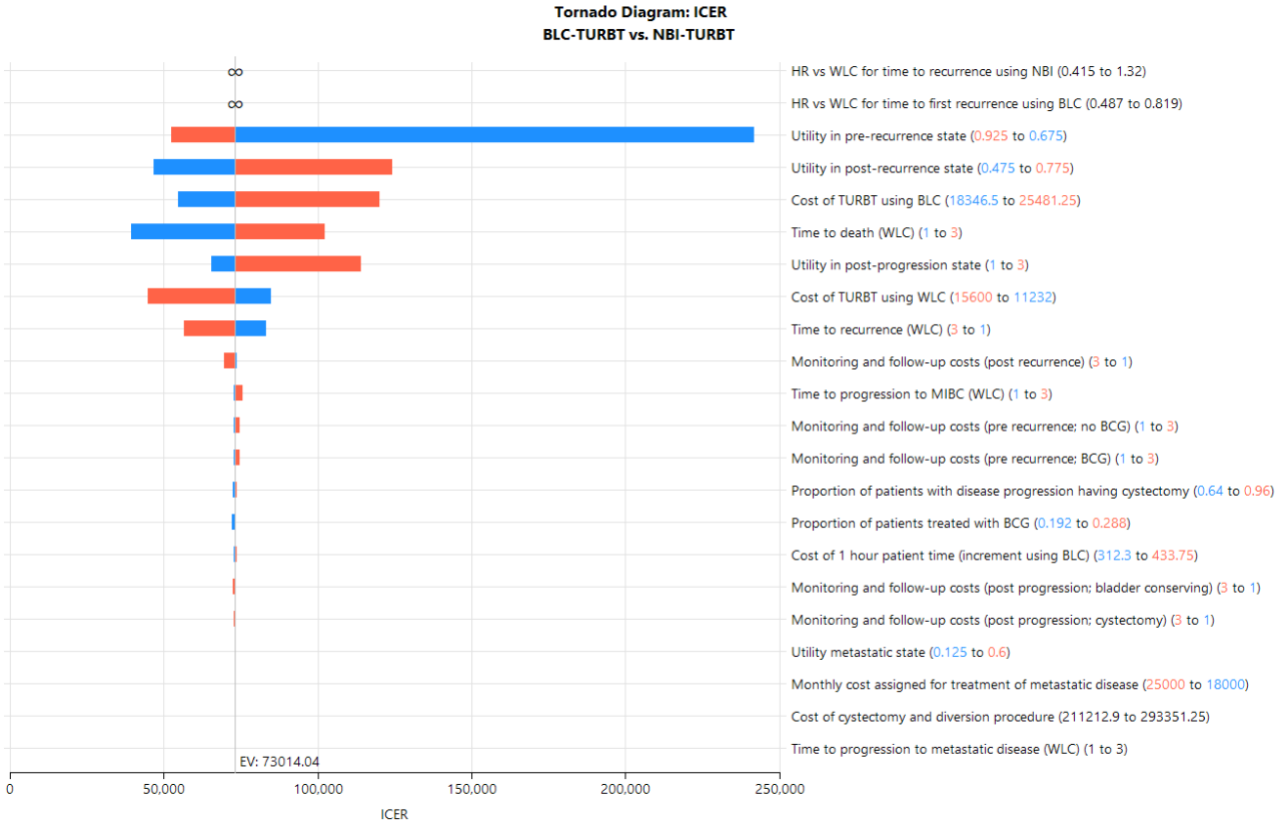
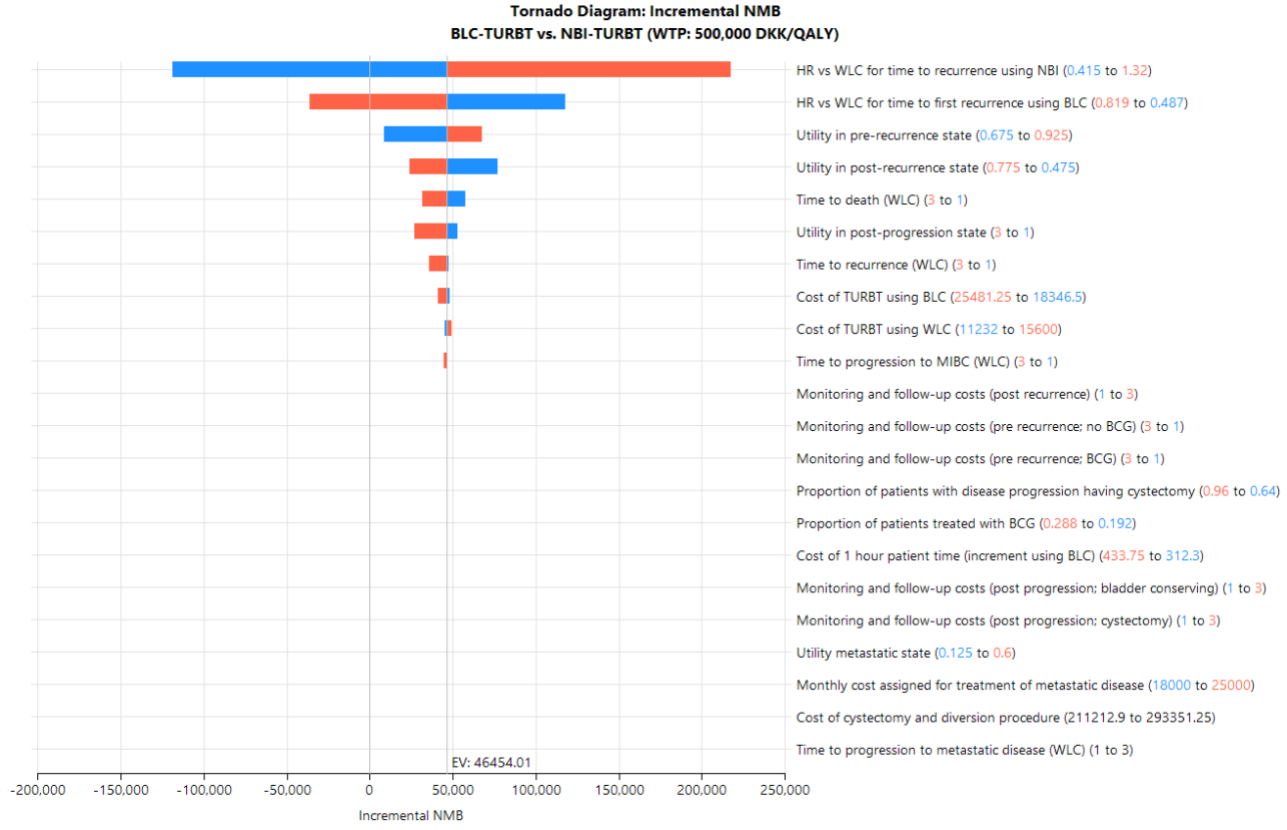


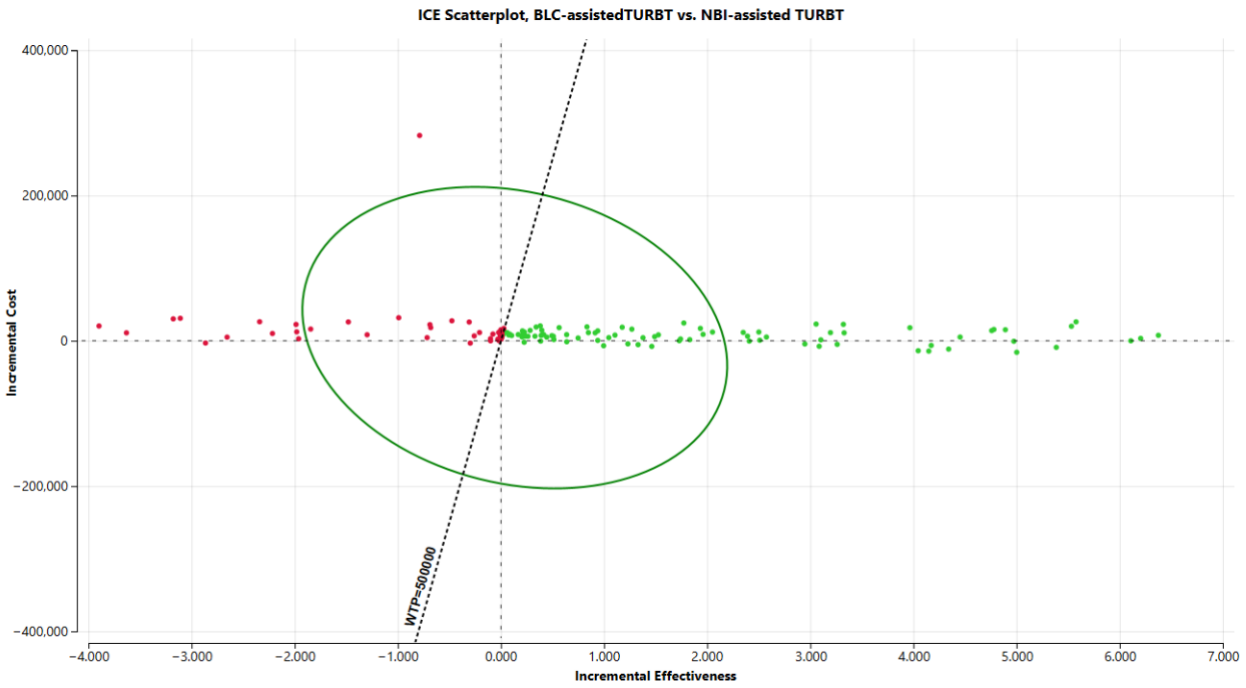
Figure 5: Tornado diagram INMB



8.2.8.2.2 Probabilistic sensitivity analysis

Figure 6 shows the incremental cost effectiveness scatter plot for the probabilistic sensitivity analysis, with 95% confidence ellipse.

Figure 6: Probabilistic sensitivity analysis ICER scatter plot



Interpretation

The results of the probabilistic sensitivity analysis are consistent with the deterministic result, in that it shows a trend to simulations yielding a moderate QALY gain for a modest additional cost. The deterministic ICER result (approximately 0.1 QALY gain for a DKK 7,000 incremental cost) falls comfortably within the centre of the 95% confidence ellipse.

It is worth noting that, in line with expectations based on the data, a large majority of simulations yield minimal incremental QALY gain, reflecting the small differences in the major downstream clinical outcomes that have significant utility impact. There is, however a fairly consistent small incremental cost, reflecting the additional fixed cost for Hexvix infusion in the HAL-guided TUR-BT arm. However, the simulations where outcomes differ between the two technologies utilities accrued in the HAL-guided arm tend to exceed those seen in the NBI-guided arm, yielding a sufficiently large benefit to push the net ICER impact into the North East (cost-effective) quadrant.

8.2.8.2.3 Scenario analyses

Table 27 shows the results of the scenario analyses described in paragraph 8.2.8.2 above. As for the base case analysis, the use of patient trackers within the model requires that microsimulation rather than EV is used to estimate the results. This may result in small variations if the analyses are re-run, although the qualitative conclusions will remain robust.

Table 27: Results of scenario analyses

Intervention	Total cost, DKK	Total benefit QALY	ΔC, DKK	ΔE	ICER	Statement of dominance
			vs. relevant comparator			
Scenario 1: Allow HAL-guided TUR-BT to exert an independent effect on time to progression						
HAL-guided TUR-BT	59,090	6.746				
NBI-guided TUR-BT	54,337	6.617	4,752	0.129	36,775 DKK/QALY	No dominance
Scenario 2: Use HAL-guided TUR-BT for treatment of tumour recurrences						
HAL-guided TUR-BT	62,230	6.772				
NBI-guided TUR-BT	55,492	6.671	6,738	0.102	66,351 DKK/QALY	No dominance
Scenario 3a: Explore impact of alternative estimates for effect of NBI-guided TUR-BT on time to recurrence (HR = 0.77)						
HAL-guided TUR-BT	56,434	6.564				
NBI-guided TUR-BT	50,283	6.453	6,151	0.111	55,414 DKK/QALY	No dominance
Scenario 3b: Explore impact of alternative estimates for effect of NBI-guided TUR-BT on time to recurrence (HR = 0.67)						
HAL-guided TUR-BT	57,407	6.764				
NBI-guided TUR-BT	49,676	6.728	7,731	0.036	215,965 DKK/QALY	No dominance
Scenario 4: Repeat base case analysis using 10 year time horizon						

HAL-guided TUR-BT	54,180	4.534				
NBI-guided TUR-BT	46,408	4.471	7,772	0.063	123,927 DKK/QALY	No dominance
Scenario 5: Repeat base case analysis using parametric extrapolations of RFS, PFS and MFS						
HAL-guided TUR-BT	63,127	6.360				
NBI-guided TUR-BT	55,822	6.276	7,245	0.084	86,250 DKK/QALY	No dominance

Interpretation

All scenarios explored yield ICERs within the range of acceptable cost effectiveness (36,775 DKK/QALY – 215,965 DKK/QALY). Consistent with the results of the deterministic analysis, varying the hazard ratio for time to recurrence with NBI has the greatest impact on the result, although the results seen within the range tested do not approach any plausible willingness to pay threshold. There is no evidence that the approach used to extrapolate the clinical outcome survival curves to a lifetime time horizon has any significant effect on the results (86,250 DKK/QALY using parametric extrapolation vs 75,811 DKK/QALY using hazard table extension)

8.2.9 Applicant's interpretation of the health economic analysis

So far as we are aware, this is the published first cost-utility analysis that has investigated the relative performance of HAL-guided TUR-BT vs NBI-guided TUR-BT.

Strengths

- The model has been designed de novo to meet the needs of the DTC and as such is built around Danish clinical practice, management and costing guidelines.
- There is a substantial evidence base of long duration relating to standard management with WLC-guided TUR-BT, which forms the core reference structure of the model.
- There are multiple randomised controlled trials that have been carried out using HAL-guided TUR-BT (vs WLC-guided TUR-BT), providing confidence in the robustness of the efficacy estimates used in the model.
- The results of the cost-utility analysis fall well within the range of ICERs that would normally be considered cost-effective (<100,000 DKK/QALY for most simulations). This gives considerable confidence that, even allowing for structural and parameter uncertainty, HAL-guided TUR-BT is highly likely to represent a cost-effective option in the management of NMIBC.
- The use of HAL-guided TUR-BT is familiar to Danish clinicians, having been extensively used in Denmark in the past. This ensures that the clinical and validation input to the model comes from an informed standpoint.

Weaknesses

- In the absence of direct comparative clinical trials for HAL-guided TUR-BT vs NBI-guided TUR-BT, calculation of the transition probabilities within the model is driven by an indirect methodology.
- The evidence base for NBI-guided TUR-BT is sparse and of short follow-up duration. In order to provide a meaningful comparator for HAL-guided TUR-BT within the model, this has required acceptance of efficacy estimates for NBI-guided TUR-BT that are not statistically significant. Given that the estimate of hazard ratio for the two technologies is the most important driver of ICER outcome, the uncertainty around NBI-guided TUR-BT is an important potential limitation.
- For one of the primary scenario analyses requested by DTC (use of HAL-guided TUR-BT in recurrent disease), an absence of clear-cut RCT-evidence has meant that conclusions have been based on assumptions.
- Clinical practice elsewhere in Europe has been to target use of HAL-guided TUR-BT at individuals at higher risk of recurrence/progression. Whilst it may have been useful to have explored that strategy within this model, the available data was insufficient to support this:
    - RCTs comparing HAL-guided TUR-BT to WLC-guided TUR-BT have recruited populations of mixed risk profile. Outcome results have not been published separately for the different risk groups.
    - One large RCT for NBI-guided TUR-BT to WLC-guided TUR-BT broke down results by risk group [22], but unfortunately only showed benefit for those at lowest risk.

8.3 Budget impact analysis

See also Annex 11.11

8.3.1 Patient population

Table 28: The size of the patient population WITH recommendation to use the health technology and the distribution across the different health technologies.

	Year 1	Year 2	Year 3	Year 4	Year 5
HAL-guided TUR-BT (%)	10%	15%	20%	25%	30%
NBI-guided TUR-BT (%)	90%	85%	80%	75%	70%
Total patient population	1,213	1,229	1,249	1,268	1,284

Table 29: The size of the patient population WITHOUT recommendation to use the health technology and the -distribution across the different health technologies.

	Year 1	Year 2	Year 3	Year 4	Year 5
HAL-guided TUR-BT (%)	5%	5%	5%	5%	5%
NBI-guided TUR-BT (%)	95%	95%	95%	95%	95%
Total patient population	1,213	1,229	1,249	1,268	1,284

8.3.2 Results of the budget impact analysis

Table 30. Overview of budget impact of a recommendation to use the health technology, over the five-year time horizon.

Budget impacts of recommendation	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs if the health technology is recommended for use	16,597,117	17,295,207	18,062,189	18,830,525	19,569,326
Of which: Disease management	16,097,117	16,795,207	17,562,189	18,330,525	19,069,326
Of which: Equipment upgrade	500,000	500,000	500,000	500,000	500,000
Total costs if the health technology is not recommended for use	15,617,678	15,823,682	16,081,187	16,325,817	16,531,821
Of which: Disease management	15,617,678	15,823,682	16,081,187	16,325,817	16,531,821
Budget impact of recommendation to use	**979,439**	**1,471,525**	**1,981,002**	**2,504,708**	**3,037,505**

9 Discussion on the documentation submitted

Strengths

- There is a substantial evidence base of long duration relating to standard management with WLC-TUR-BT, which forms the core reference structure of the clinical analysis and health economic model.
- There are multiple randomised controlled trials that have been carried out using HAL-guided TUR-BT (vs WLC-guided TUR-BT), providing confidence in the robustness of the efficacy estimates used in the analysis and in the model.
- The results of the cost-utility analysis fall well within the range of ICERs that would normally be considered cost-effective (<100,000 DKK/QALY for most simulations). This gives considerable confidence that, even allowing for structural and parameter uncertainty, HAL-guided TUR-BT is highly likely to represent a cost-effective option in the management of NMIBC.
- The use of HAL-guided TUR-BT is familiar to Danish clinicians, having been extensively used in Denmark in the past. This ensures that the clinical and validation input to the analysis and cost-utility model comes from an informed standpoint. Likewise, it gives confidence to the statements and discussion on organisational implications.

Weaknesses

- There is a paucity of data for NBI-guided TUR-BT and no direct comparative clinical trials for HAL-guided TUR-BT vs NBI-guided TUR-BT. As a result, calculation of the transition probabilities for the clinical analysis and within the cost-utility model, is driven by an indirect methodology.
- The evidence base for NBI-guided TUR-BT is not only sparse, follow-up duration is limited. In order to provide a meaningful comparator for HAL-guided TUR-BT within the economic model, this has required acceptance of efficacy estimates for NBI-guided TUR-BT that are not statistically significant. Given that the estimate of hazard ratio for the two technologies is the most important driver of ICER outcome, the uncertainty around NBI-guided TUR-BT is an important potential limitation.
- For one of the primary scenario analyses requested by DTC (use of HAL-guided TUR-BT in recurrent disease), an absence of clear-cut RCT-evidence has meant that conclusions have been based on assumptions.
- Equipment for undertaking TUR-BT, regardless of whether this is guided by WL, HAL or NBI, is not manufactured by the Applicant. Further, a number of models exists for each component of the equipment, some of which may have been retired or superseded over the years. As such, many assumptions were made with regards to the equipment and the DTC is recommended to consult with the manufacturers for up to date and accurate information with regards to the equipment components.
- In Denmark, clinical guidelines for NMIBC with respect to the use of visualisation enhancement, are informed by data which is out of scope of this analysis such as studies using flexible cystoscopy in a surveillance setting. As such, conclusions may differ with respect to HAL vs NBI.
- Clinical practice elsewhere in Europe has been to target use of HAL-guided TUR-BT at individuals at higher risk of recurrence/progression. Whilst it may have been useful to have explored that strategy within this model, the available data was insufficient to support this:

- RCTs comparing HAL-guided TUR-BT to WLC-guided TUR-BT have recruited populations of mixed risk profile. Outcome results have not been published separately for the different risk groups.
- One large RCT for NBI-guided TUR-BT to WLC-guided TUR-BT broke down results by risk group [12], but unfortunately only showed benefit for those at lowest risk.

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11 List of Annexes

11.1 Selection of the literature

The Prisma diagram is outlined in Section 4.1.

11.2 Table for description of the characteristics of the studies and populations included

Table 31: List of included studies

Study identification no.	Exploratory Research Program (PCE-2), project number 1287/2008
Link to abstract	Link
Reference (first author, year)	Drăgoescu, 2011
Overall objective of the study	Impact of using HAL-guided TUR-BT in diagnosis and treatment of non-muscle invasive bladder cancer
Study type and design	Prospective RCT (Single Hospital, Romania)
Follow-up period	12 months
Inclusion and exclusion criteria	Inclusion: • Patients with primary NMIBC Exclusion: • None stated
Intervention	HAL-guided TUR-BT subsequent to WLC-guided cystoscopy
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n=22 (M/F ratio 2.66) • Age: 62.09 ± 12.46 • # Tumors: 1.48 ± 0.73 • Primary tumour size: 2.02 ± 0.84 • Tumour stage: Ta, 6; T1, 16 • Tumour grade: G1, 7; G2, 12; G3, 3 Intervention arm (BLC): • n=22 (M/F ratio 4.5) • Age: 58.7 ± 14.31 • # Tumors: 1.66 ± 0.94 • Primary tumour size: 1.95 ± 0.58 • Tumour stage: Ta, 4; T1, 18 • Tumour grade: G1, 6; G2, 14; G3, 2
Primary and secondary outcome measures	Primary: • Impact of using BLC-guided TUR-BT on the diagnosis and treatment of NMIBC (detection and recurrence at 3,6, 9 and 12 months)
Analysis method	• Not stated. Deduced to be complete case. • MS Excel and MedCalc 10.2 software (no further details provided) • Kaplan-Meier for recurrence-free survival analysis.

Relevant sub-group analyses	NA
Supplementary articles based on the same study	Drăgoescu 2017 [2] was the full report of this study

Study identification no.	Exploratory Research Program (PCE-2), project number 1287/2008
Link to abstract	Link
Reference (first author, year)	Drăgoescu 2017
Overall objective of the study	To evaluate the diagnostic efficiency and long-term influence upon the tumour recurrence rate for patients with NMIBC undergoing hexaminolevulinate PDD compared to standard white-light cystoscopy (WLC)
Study type and design	Prospective randomized study
Follow-up period	5 years (72.3±5.8 months for the WLC group and 71.8±6.2 months for the PDD group, with no significant differences between the two groups (p=0.64))
Inclusion and exclusion criteria	Inclusion criteria: primary Ta/T1 CIS NMIBC, over 18 years old, good life expectancy, no significant bladder outlet obstruction [postvoid residual urine volume (PVR)
Intervention	HAL-guided TUR-BT subsequent to WLC-guided cystoscopy
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n=56 (M/F ratio 3.38) • Age: 60.3 ± 10.2 • # Tumours: 1.64 ± 0.86 • Primary tumour size: 1.63 ± 0.7 • Tumour stage: Ta, 17; T1, 39 • Tumour grade: G1, 19; G2, 30; G3, 7 • CIS: 6 (10.5%) Intervention arm (BLC): • n=59 (M/F ratio 3.67) • Age: 59.4 ± 9.9 • # Tumours: 1.74 ± 0.99 (WLC), 2.19 ± 1.26 (BLC) • Primary tumour size: 1.69 ± 0.75 • Tumour stage: Ta, 16; T1, 41 • Tumour grade: G1, 22; G2, 29; G3, 6 • CIS: 3 (5.2%)
Primary and secondary outcome measures	Primary: • Diagnostic performance • Recurrence rate
Analysis method	• Tumour detection rate (inpatient comparison in the PDD group) analysis as well as tumour recurrence rate comparison as a parallel intent to treat (ITT)

	analysis were performed. Statistical data analysis was performed using the MedCalc software. • Kaplan–Meier survival curves (were used to analyse RFS rates)
Relevant sub-group analyses	NA
Supplementary articles based on the same study	Drăgoescu 2011 [1] was an interim report of this study

Study identification no.	PMID: 21711438
Link to abstract	Link
Reference (first author, year)	Geavlete, 2012
Overall objective of the study	To evaluate the impact of HAL-guided TUR-BT on diagnostic accuracy, treatment changes and assess long-term recurrence rates in patients with non-muscle-invasive bladder cancer (NMIBC)
Study type and design	Prospective RCT (individual cohort). Non-blinded, randomized, long-term trial. Single postoperative mitomycin-C instillation was given during the first 6 h after surgery in all cases undergoing TUR-BT. The follow-up protocol consisted of urinary cytology and WLC every 3 months for 2 years. Only first-time recurrences after the initial diagnosis were considered. Resected specimens were subjected to central pathology review.
Follow-up period	2 years
Inclusion and exclusion criteria	Inclusion: • Positive urine cytology and/or US • Suspicion of bladder tumours Follow up protocol: • First time recurrences after the initial diagnosis Exclusion: • Massive haematuria • Moderate to severe leukocyturia • Prior intravesical instillations earlier than ≤ 3 months • Imaging aspects suggestive of upper urinary tract malignancies • Patients with cystoscopically detected bladder tumours before inclusion were not enrolled
Intervention	BLC-guided TUR-BT
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n=181 (M/F ratio unknown) • # Tumours: 237 • Primary tumour size: 1.63 ± 0.7 • Tumour stage: Ta, 74; T1, 33 • CIS: 15 Intervention arm (BLC): • n=181 (M/F ratio unknown) • # Tumours: 272

	• Primary tumour size: 1.69 ± 0.75 • Tumour stage: Ta, 81; T1, 35 • CIS: 20 Data extracted from detection part of study
Primary and secondary outcome measures	Primary: detection rates Secondary: treatment changes and recurrence rates
Analysis method	• Chi-square test and binomial test (latter used for recurrence rates and progression rates) • P < 0.05 considered to indicate statistical significance and a confidence level of at least 95%. With a sample size of 181 patients per arm at this confidence level, the trial was determined to have a power of 82.6% to detect a significant difference between the analysed characteristics of the study groups.
Relevant sub-group analyses	• Treatment changes as a result of risk category changes (progression) were also analysed • Recurrence rate at 2 years in patients with multiple tumours • Recurrence rate at 2 years regardless of patient's history of bladder cancer • Progression rates
Supplementary articles based on the same study	

Study identification no.	DOI 10.1007/s11255-013-0603-z
Link to abstract	Link
Reference (first author, year)	Gkritsios, 2013
Overall objective of the study	Assess impact of HAL on long-term recurrence rate of NMIBC
Study type and design	Prospective, Randomized Controlled Trial
Follow-up period	40 months
Inclusion and exclusion criteria	Inclusion criteria: suspected or confirmed NMIBC, patient with recurrent disease at least 3 months after initial TUR-BT Exclusion: patients scheduled for a second TUR-BT
Intervention	BLC-guided TUR-BT following WLC
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n=50 (M/F ratio 44:6) • Age: 68.24 • # Tumours: none, 7; 1 or more, 42 • Tumour stage: Ta, 21; T1 & CIS, 9 • Tumour grade: low, 22; High & CIS, 8 Intervention arm (BLC): • n=54 (M/F ratio 43:11) • Age: 66 • # Tumours: none, 10; 1 or more, 44

	• Tumour stage: Ta, 26; T1 & CIS, 8 • Tumour grade: low, 29; High & CIS, 5
Primary and secondary outcome measures	Primary: detection Secondary: recurrence rate
Analysis method	Recurrence-free period: Kaplan-Meier Recurrence rates: Chi squared test Comparison of cancer characteristics: Fisher's exact test and Mann-Whitney test
Relevant sub-group analyses	NA
Supplementary articles based on the same study	

Study identification no.	DOI: 10.1056/EVIDoa2200092 ISRCTN84013636
Link to abstract	Link
Reference (first author, year)	Heer, 2022
Overall objective of the study	Long term clinical effectiveness and cost-effectiveness of HAL-guided TUR-BT
Study type and design	Pragmatic, open-label, parallel-group randomized trial
Follow-up period	3 years
Inclusion and exclusion criteria	Inclusion: patients over 16 years with suspected first diagnosis of intermediate or high risk NMIBC Exclusion: patients with suspected low risk NMIBC, imaging evidence of MINC. Upper-tract involvement, other life-threatening malignancy in the past 2 years. Evidence of metastases, porphyria/known porphyrin hypersensitivity, pregnancy, contraindications to PDD or WLC syrgery
Intervention	HAL-guided TUR-BT
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n=217 (M/F ratio not reported) • Age: 70 (10) • # Tumours: single, 81 (37.3%); 2-7, 113 (52.1%); ≥8, 21 (9.7%) • Tumour stage: Ta, 160 (73.7%); T1, 66 (30.4%) • CIS, 24 (11.1%) • EORTC risk group: Low, 2 (0.9%); I/mediate, 190 (87.6%); High 15 (6.9%) • Tumour size: <3cm, 81 (37.3%); ≥3cm, 129 (59.4%) • Tumour grade: G1, 16 (7.4%); G2, 112 (51.6%); G3, 68 (39.6%) Intervention arm (HAL): • n=209 (M/F ratio not reported) • Age: 71 (11)

	• # Tumours: single, 66 (31.6%); 2-7, 122 (58.4%); ≥8, 17 (8.1%) • Tumour stage: Ta, 150(70.8%); T1, 64 (30.6%) • CIS, 27 (12.9%) • EORTC risk group: Low, 0 (0%); I/mediate, 184 (88.0%); High 17 (8.1%) • Tumour size: <3cm, 69 (37.3%); ≥3cm, 133 (63.6%) • Tumour grade: G1, 17 (8.1%); G2, 116 (55.5%); G3, 72 (34.4%)
Primary and secondary outcome measures	Primary: time to recurrence, progression, cystectomy, or bladder cancer death. Secondary outcomes: self-reported HRQoL resulting from surgery and any consequent cancer treatment. AEs, complications, disease progression and overall & bladder-cancer specific survival.
Analysis method	• Modified ITT • Primary: Cox proportional hazards models adjusted for a number of prognostic factors including grade of surgeon. • Time to recurrence, time to progression & overall survival; Kaplan-Meier
Relevant sub-group analyses	• Economic analysis
Supplementary articles based on the same study	Heer et al HTA, NIHR Vol 26, Issue 40, October 2022

Study identification no.	NCT00412971
Link to abstract	Link
Reference (first author, year)	Hermann, 2011
Overall objective of the study	Recurrence rate in Ta/T1 tumours at 12 months
Study type and design	Prospective, open-label RCT (two centres)
Follow-up period	1 year
Inclusion and exclusion criteria	Inclusion: • Adult patients with suspected Ta/T1 tumours (consecutive enrolment) based on flexible cystoscopy performed in outpatient department Exclusion: • Patients with porphyria, gross haematuria or known allergy to HEX
Intervention	HAL-guided TUR-BT using Hexvix®
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n= 77 (gender split unknown) • Age: Not known • Tumour Grade: Ta low grade, 69; Ta high grade, 5; T1 low grade, 0; T1 high grade, 3; low grade, 69 high grade, 8; N/A, 0 • Tumour #: single, 48; 2-7, 29; >7, 0 • Tumour size: <3cm, 57; ≥3cm, 20 Intervention arm (BLC): • n= 68 (gender split unknown)

	• Age: Not known • Tumour Grade: Ta low grade, 57; Ta high grade, 8; T1 low grade, 0; T1 high grade, 2; low grade, 57; high grade, 10; N/A, 1 • Tumour #: single, 44; 2-7, 24; >7, 0 • Tumour size: <3cm, 54; ≥3cm, 14
Primary and secondary outcome measures	Primary: Recurrence rate during 12 months of follow up Secondary: Relate recurrence rate to fluorescence detected residual tumour after WLC; assess false positive rate
Analysis method	• Per Protocol (PP) • Primary outcome measure: Cochran-Mantel Haenszei chi-squared test with a two sided significance level of 5%. Recurrence-free analyses using Kaplan-Meier method & regression analyses of grouped survival data. • Secondary: descriptive stats at patient and lesion level, homogeneity of data between 2 centres assessed using Breslow-Day test
Relevant sub-group analyses	• Note: reported incorrect units on the horizontal axis of the TTR figure making TTR and RFS data uninterpretable.
Supplementary articles based on the same study	-

Study identification no.	doi.org/10.1016/j.urology.2012.03.067
Link to abstract	https://doi.org/10.1016/j.urology.2012.03.067
Reference (first author, year)	Karaolides T, 2012
Overall objective of the study	To evaluate the effect of hexaminolevulinate (HAL)-induced fluorescence during resection of non-invasive bladder cancer on tumour recurrence compared with resection under white light.
Study type and design	Prospective randomized control trial
Follow-up period	Median follow-up: 14 months (range 4.5-25) in the white light group and 17.5 months (range 6-25) in the BLC group.
Inclusion and exclusion criteria	Suspicion of bladder cancer was the only inclusion criterion
Intervention	BLC-guided TUR-BT using Hexvix®
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n= 45 (F/M, 5/40) • Age: 63.82 (39-88) • Tumour Grade: CIS, 3; High Grade, 14; Low Grade, 27, PUNLMP*, 1 • Tumour #: single, 26; multifocal, 19 • Risk group: High, 13; low, 12; moderate, 20 • Recurrence, 18; no recurrence, 27 Intervention arm (BLC): • n= 41 (F/M, 8/33) • Age: 66.29 (37-82)

	• Tumour Grade: CIS, 5; High Grade, 9; Low Grade, 26, PUNLMP*, 1 • Tumour #: single, 18; multifocal, 23 • Risk group: High, 11; low, 7; moderate, 23 • Recurrence, 7; no recurrence, 34 *papillary urothelial neoplasm of low malignant potential
Primary and secondary outcome measures	Differences in tumour recurrence rate and recurrence-free survival (RFS) between the 2 groups were the study's primary endpoints.
Analysis method	• The chi-square test, the Mann-Whitney U test, and the Kaplan-Meier method with log-rank tests were used for data analysis. • Differences were considered significant at a level of P 0.05.
Relevant sub-group analyses	• Subgroup analysis on RFS was performed for solitary vs multifocal tumours, primary vs recurrent tumours, and aggressive (high-grade tumours and CIS) vs nonaggressive tumours (papillary urothelial neoplasm of low malignant potential and low-grade tumours)
Supplementary articles based on the same study	

Study identification no.	ISRCTN Register (number: 14275387).
Link to abstract	https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.12355
Reference (first author, year)	O'Brien, 2013
Overall objective of the study	To determine if photodynamic 'blue-light'-assisted resection leads to lower recurrence rates in newly presenting non-muscle-invasive bladder cancer (NMIBC).
Study type and design	Prospective randomized non-blinded clinical trial
Follow-up period	Patients with low grade tumours: check cystoscopies at 3 and 12 months Patients with high grade tumours: additional cystoscopy at 6 months.
Inclusion and exclusion criteria	Inclusion criteria: • Patients presenting with a suspected new NMIBC • The suspicion of NMIBC was based on the appearance of the bladder at a diagnostic flexible cystoscopy performed under local anaesthetic. Exclusion criteria: • Patients with suspected carcinoma invading the bladder muscle or • a history of bladder cancer were excluded, as well as • patients with porphyria, pregnancy and sensitivity to 5-aminolevulinate-acid-based intravesical photosensitizers.
Intervention	BLC-guided TUR-BT using Hexvix®
Comparator	WLC-guided TUR-BT
Baseline characteristics	A total of 249 patients were randomized between March 2005 and April 2010. 97 eligible patients with NMIBC in the HAL-PDD arm and 88 with NMIBC in the white-light arm available • A total of 129 patients were allocated to the PDD arm and all those patients received the HAL. Of these patients, 32 patients were excluded; 16 because no cancer was identified on final histological analysis and 16 because the

	tumour proved to be carcinoma invading the bladder muscle, e.g. ≥T2 stage. Age (median, interval) • A total of 120 patients were allocated to the conventional white-light arm. Of these, 32 were excluded; 24 because no cancer was identified on histology and eight because the tumour proved to be carcinoma invading the bladder muscle. • Did not complete 3- or 12 month follow-up: 11 (9%) vs. 6 (5%) for HAL and WLC respectively • Analysed 86 (67%) vs. 82 (68%) for HAL and WLC respectively • Male gender: 95 (74%) vs. 88 (73%) for HAL and WLC respectively • Multifocal tumour: 70 (54%) vs. 79 (66%) for HAL and WLC respectively • Unifocal tumour: 55 (43%) vs. 36 (30%) and not stated 4 (3%) vs. 5 (4%) for HAL and WLC respectively • Mean (range) age: 68 (31-95) vs. 68 (29-90) for HAL and WLC respectively
Primary and secondary outcome measures	Primary: recurrence within 3 months and, in those free of tumour at 3 months, recurrence up to 12 months after the initial TUR-BT.
Analysis method	• Fisher's exact test (two-tailed). • Cox regression was used for multivariate analysis.
Relevant sub-group analyses	NA
Supplementary articles based on the same study	

Study identification no.	PMC5305060
Link to abstract	https://dx.doi.org/10.1016/j.eururo.2012.01.018
Reference (first author, year)	Naselli, 2012
Overall objective of the study	A randomized prospective trial to assess the impact of transurethral resection in narrow band imaging modality on non-muscle-invasive bladder cancer recurrence
Study type and design	Randomised prospective trial
Follow-up period	1 year
Inclusion and exclusion criteria	Inclusion: • Consecutive adult patients with known or suspected bladder cancer Exclusion: • Pregnant or breastfeeding women or women not on adequate contraceptive measures • Patients with invasive BCa • Absence of urothelial cancer after pathologic examination or those without follow up
Intervention	NBI-guided TUR-BT (no use of standards WLC in NBI arm)
Comparator	WLC-TURBT
Baseline characteristics	Control arm (WLC):

	• n= 72 (55 females, 17 male) • Age: 71.6 ± 12.4 • Clinical status: recurrent, 28; newly diagnosed, 44 • Multifocal tumours: No,39; Yes, 33 • Tumour Grade: Low, 41; High*, 31 • Tumour Stage: Ta**, 52; T1, 20 • CIS: Pure, 4; Associated, 6 • Tumour size: ≤3cm, 53; >3cm, 19 • Adjuvant topical therapy: no therapy, 44; BCG 19; MMC, 4 Intervention arm (NBI): • n= 72 (64 females, 12 male) • Age: 70.8 ± 10.3 • Clinical status: recurrent, 37; newly diagnosed, 39 • Multifocal tumours: No, 37; Yes, 39 • Tumour Grade: Low, 39; High*, 37 • Tumour Stage: Ta**, 58; T1, 18 • CIS: Pure, 8; Associated, 6 • Tumour size: ≤3cm, 55 >3cm, 21 • Adjuvant topical therapy: no therapy, 42; BCG 24; MMC,10 *Includes patients with pure or associated CIS **Includes patients with pure CIS
Primary and secondary outcome measures	Primary: 1 year intravesical recurrence risk Secondary: 3 month recurrence risk. Detection rate.
Analysis method	• Cohen formula, Chi-square test, Fisher exact test where useful (no details) • Logistic regression analysis
Relevant sub-group analyses	N/A
Supplementary articles based on the same study	

Study identification no.	doi.org/10.1016/j. eururo.2016.03.053.
Link to abstract	http://dx.doi.org/10.1016/j. eururo.2016.03.053.
Reference (first author, year)	Naito, 2016
Overall objective of the study	Compare 12 month recurrence rates following TUR-BT using NBI vs WLC guidance in primary NMIBC
Study type and design	Prospective RCT (multinational, multicentre)
Follow-up period	1 year
Inclusion and exclusion criteria	Inclusion: • Adult patients scheduled for primary (first) TUR-BT following detection by imaging or cystoscopy, or scheduled for random biopsies and/or TUR-BT due to positive cytology Exclusion: • presence of tumours in the upper urinary tract;

	• muscle-invasive bladder tumour; • previous irradiation of the pelvis; • gross haematuria (defined as heavy bladder bleeding resulting in marked amounts of blood in the urine) that might interfere with cystoscopy at the time of TURBT; • participation in other clinical studies with investigational drugs, either concurrently or within the previous 30 days; • pregnancy; and a • any condition associated with a risk of poor protocol compliance
Intervention	NBI-guided TUR-BT
Comparator	WLC- guided TUR-BT
Baseline characteristics	SUMMARY ONLY **ITT Population** Control arm (WLC): • n= 481 (98 females, 383 male) • Age: 65.8 (mean) • Tumour Grade: 1, 144; 2, 145; 3, 137; • Tumour Stage: pTx, 27; pT0, 40; pTa, 214; pTIS, 7; pT1, 144; pT2 or higher, 42 • Tumour size,mm (mean): 21.5 Intervention arm (NBI): • n= 484 (94 females, 390 male) • Age: 66.7 (mean) • Tumour Grade: 1, 155; 2, 149; 3, 133; • Tumour Stage: pTx, 24; pT0, 38; pTa, 218; pTIS, 12; pT1, 149; pT2 or higher, 35 • Tumour size,mm (mean): 20.4 **PP Population** Control arm (WLC): • n= 365 (72females, 293 male) • Age: 66.5 (mean) • Tumour Grade: 1, 135; 2, 123; 3, 101; • Tumour Stage: pTx, 0; pT0, 00; pTa, 214; pTIS, 7; pT1, 144; pT2 or higher, 0 • Tumour size,mm (mean): 21.1 Intervention arm (NBI): • n= 379 (79 females, 300 male) • Age: 67.3 (mean) • Tumour Grade: 1, 146; 2, 125; 3, 99; • Tumour Stage: pTx, 0; pT0, 0; pTa, 218; pTIS, 12; pT1, 149; pT2 or higher, 0 • Tumour size,mm (mean): 20.0
Primary and secondary outcome measures	Primary: Recurrence rate at 1 year Secondary: Tumour recurrence at 1st follow up (3 months)

Analysis method	• ITT & PP • Pearson chi-test or Fisher. Survival analysis with log-rank test and shown as Kaplan-Meier curves. LCOF was applied.
Relevant sub-group analyses	Sub-analyses conducted according to disease status including low, intermediate and high risk as classified by EORTC:
Supplementary articles based on the same study	

Study identification no.	doi.org/10.4111/icu.2018.59.2.98
Link to abstract	https://dx.doi.org/10.4111/icu.2018.59.2.98
Reference (first author, year)	Kim, 2018
Overall objective of the study	Detection and recurrence rate of TUR-BT by NBI-guidance
Study type and design	Prospective, RCT (single centre)
Follow-up period	1 year
Inclusion and exclusion criteria	Inclusion: • Adult patients undergoing TUR-BT as a result of a suspicion of bladder tumour following detection by imaging or cystoscopy Exclusion: • muscle-invasive bladder tumour; • patients undergoing radical cystectomy; • patients receiving chemotherapy or radiotherapy • patients with non-urethral carcinoma • patients not hisologically diagnosed with cancer • patients lost to follow up or who died for other reasons
Intervention	NBI-guided TUR-BT
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n= 67 (13 females, 54 male) • Age: 66.96 • Tumour Grade: No tumour or CIS, 14; low, 24; high, 29 • Tumour size: 1 (<1cm), 40; 2 (1-3cm), 19; 3 (>3cm), 8 Intervention arm (NBI): • n= 85 (23 females, 62male) • Age: 64.54 • Tumour Grade: No tumour or CIS, 17; low, 33; high, 35 • Tumour size: 1 (<1cm), 42; 2 (1-3cm), 35; 3 (>3cm), 8
Primary and secondary outcome measures	Primary: identification of tumours in each group and number of additional tumours diagnosed using NBI Secondary: Recurrence rate at 1 year

Analysis method	• Student t-test and Mann-Whitney test • Recurrence free estimates: log-rank analysis & Kaplan- Meier curves
Relevant sub-group analyses	• 1 year recurrence-free rate
Supplementary articles based on the same study	

Study identification no.	doi/epdf/10.1016/j.juro.2014.02.864
Link to abstract	https://www.auajournals.org/doi/epdf/10.1016/j.juro.2014.02.864
Reference (first author, year)	Lee, 2014 ABSTRACT
Overall objective of the study	Recurrence rate using NBI-guided TUR-BT
Study type and design	RCT, Pilot Study
Follow-up period	24 months
Inclusion and exclusion criteria	Inclusion: • Consecutive adult patients with overt or suspected NMIBC Exclusion: • Patients with MIBC • Patients with negative pathologic examination or without follow up
Intervention	NBI-guided TUR-BT
Comparator	WLC-guided TUR-BT
Baseline characteristics	Mean age: 63.13. No other baseline data reported. Control arm • Mean age, 63.13 Intervention arm • Mean age, 63.03
Primary and secondary outcome measures	Primary: recurrence rate Secondary: no details provided
Analysis method	• Not reported, assumed case • Kaplan-Meier curve for recurrence-free rate analysis
Relevant sub-group analyses	• High grade tumours • Multiple mass • Recurrence in patients under 65 • Recurrence free rate in patients with cis
Supplementary articles based on the same study	No additional publication was made beyond the abstract

Study identification no.	NCT00233402
Link to abstract	Link
Reference (first author, year)	Stenzl [19]
Overall objective of the study	Assess impact of improved detection of NMIBC with HAL on recurrence rates
Study type and design	RCT
Follow-up period	9 months
Inclusion and exclusion criteria	Inclusion criteria: • Exclusion criteria: • From ITT – no study drug, no cystoscopy, no pathology, no Ta/Tz • From PPS – no follow up data, equipment failure, CT within 24 hours, BCG outside protocol, incomplete follow up, Hexvix installation to TURB <45mins
Intervention	BLC-guided TUR-BT using Hexvix®
Comparator	WLC-guided TUR-BT
Baseline characteristics	ITT Recurrence Group Control arm (WLC): • n= 280 (20 females, 57 male) • Age: 69.6 (mean) • Tumour Stage: TaG1 or G2, 204; TaG3 or cis, 83 Intervention arm (HAL): • n= 271 (21 females, 59 male) • Age: 68 (mean) • Tumour Stage: TaG1 or G2, 218; TaG3 or cis, 73
Primary and secondary outcome measures	Primary: • Proportion of patients with histologically confirmed Ta or T1 tumours with at least one additional Ta or T1 tumour detected with blue but not with white light • Comparison of proportion of patients with recurrent tumours within 9 months Secondary: proportion patients with additional cis detected
Analysis method	CMH Chi-square test
Relevant sub-group analyses	Adverse events
Supplementary articles based on the same study	Grossman [5], Kamat [8]

Study identification no.	doi:10.1016/j.juro.2012.03.007
Link to abstract	https://www.auajournals.org/doi/10.1016/j.juro.2012.03.007

Reference (first author, year)	Grossman, 2012
Overall objective of the study	Study extension protocol from Stenzl et al, 2010 Impact of HAL-guided cystoscopic detection (PDD) on long-term recurrence rates.
Study type and design	Prospective, randomized controlled study
Follow-up period	Median follow-up: WLC 53.0 and for HAL 55.1 months
Inclusion and exclusion criteria	Inclusion: suspected Ta and/or T1 urothelial bladder cancer. Presence of more than one initial or recurrent papillary bladder tumour or a recurrence within 12 months of a previous bladder cancer.
Intervention	HAL-guided TUR-BT following WLC
Comparator	WLC-guided TUR-BT
Baseline characteristics	Control arm (WLC): • n=261 (ITT 280) Intervention arm (BLC): • n=255 (ITT 271) Both: Male 78%, female 22%, Median age 68, Mean weight 82 kg, 62,7% had recurrent tumors, Tumor characteristics: 72% had Ta, 17% had T1 and 11% CIS tumors. BCG was administered to 55 (20%) of the participants in the white light group and 50 (19%) of those in the fluorescence group.
Primary and secondary outcome measures	Time to first recurrence
Analysis method	• PP and ITT • Database integration • All time-to-event models were analyzed using Kaplan-Meier methods. • The 25th, 50th, and 75th percentiles for survival times and the 95% confidence interval of the median were calculated for each treatment group (PP, ITT) using Kaplan-Meier product-limit estimation. • The time to events were compared between procedure groups using the log-rank test. The Wilcoxon test was added for recurrence time-to-event analyses.
Relevant sub-group analyses	NA
Supplementary articles based on the same study	Original study: Stenzl et al. J Urol. 2010 November ; 184(5): 1907–1913. doi:10.1016/j.juro.2010.06.148

Study identification no.	NCT00233402
Link to abstract	https://pubmed.ncbi.nlm.nih.gov/27376146/
Reference (first author, year)	Kamat, 2016

Overall objective of the study	Re-analysis of Stenzl/Grossman with new definition of disease progression in NMIBC. Objective was to establish whether blue light cystoscopy with hexaminolevulinate (HAL) impacts the rate of progression and time to progression using the revised definition
Study type and design	An earlier long-term follow-up of 4.5 years (Grossmann et al. 2012) of a randomized controlled Phase III study (Stenzl et al. 2010) reported outcomes following blue light cystoscopy with HAL (255 patients) or white light (WL) cystoscopy (261 patients) in NMIBC patients. The extension study collected data retrospectively and time from inclusion to follow-up was not pre-specified. The data was re-analysed according to the new IBCG definition of progression. The new definition proposed by the IBCG includes any one of: an increase in T stage from Ta to CIS or T1, CIS to T1 (indicating invasion of the lamina propria), development of T2 or greater, lymph node disease (N+), distant metastasis (M1) or an increase in grade from low to high.
Follow-up period	Median follow-up was for WL 53.0 and for HAL 55.1 months
Inclusion and exclusion criteria	Suspected Ta and/or T1 urothelial bladder cancer. Presence of more than one initial or recurrent papillary bladder tumor or a recurrence within 12 months of a previous bladder cancer.
Intervention	HAL-guided TUR-BT using Hexvix®
Comparator	WLC-guided TUR-BT
Baseline characteristics	Male 78%, female 22%, Median age 68, Mean weight 82 kg, 62,7% had recurrent tumors, Tumor characteristics: 72% had Ta, 17% had T1 and 11% CIS tumors. BCG was administered to 55 (20%) of the participants in the white light group and 50 (19%) of those in the fluorescence group.
Primary and secondary outcome measures	The data from the extension study were re-analysed at time points of 1, 3 and 4.5 years using the new definition for progression proposed by the IBCG. Definition: The new definition proposed by the IBCG includes any one of: an increase in T stage from Ta to CIS or T1, CIS to T1 (indicating invasion of the lamina propria), development of T2 or greater, lymph node disease (N+), distant metastasis (M1) or an increase in grade from low to high
Analysis method	• ITT population • Fischer's exact test was used to test differences in rate of progression • Kaplan Meier estimates to test differences in time to progression.
Relevant sub-group analyses	NA
Supplementary articles based on the same study	Reanalysis of : Stenzl et al. J Urol. 2010 November ; 184(5): 1907–1913. doi:10.1016/j.juro.2010.06.148 and Grossman HB, et al. J Urol. 2012 Jul;188(1):58-62. doi: 10.1016/j.juro.2012.03.007.

Study identification no.	DOI 10.3233/blc-160060
Link to abstract	Link

Reference (first author, year)	Gakis, 2016
Overall objective of the study	Impact of HAL=guided TUR-BT on progression in NMIBC
Study type and design	Systematic review and meta-analysis
Follow-up period	Up to 55.1 months
Inclusion and exclusion criteria	Studies reporting progression
Intervention	HAL-guided TUR-BT
Comparator	WLC-guided TUR-BT
Baseline characteristics	-
Primary and secondary outcome measures	Primary: rate of progression Secondary: progression-free survival (insufficient data to complete)
Analysis method	Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) was utilized for this meta-analysis. Fixed and random effect models were used according to the n2 value of heterogeneity; for I squared ≤50%, a fixed effect model was applied, whereas for I^2 >50% a random model was used. A *p*-value <0.05 was considered as level of significant difference.
Relevant sub-group analyses	-
Supplementary articles based on the same study	

Meta-analyses

Study identification no.	DOI: 10.1002/14651858.CD013776.pub2.
Link to abstract	Link
Reference (first author, year)	Maisch, 2021
Overall objective of the study	Assess BLC-guided TUR-BT versus WLC-guided TUR-BT
Study type and design	Meta-analysis
Follow-up period	RCTs were included with a follow up period of 12 months
Inclusion and exclusion criteria	Included studies: • RCTs with participants over 18 with suspected primary bladder cancer or recurrent bladder cancer Excluded: • Studies including patients with metastatic disease • Surveillance
Intervention	BLC guided TUR-BT
Comparator	WLC guided TUR-BT
Baseline characteristics	-

Primary and secondary outcome measures	• Time to disease recurrence • Time to disease progression • Surgical complications, serious • Time to death from bladder cancer • Any adverse events • Surgical complications, non-serious
Analysis method	Unless there was good evidence for homogeneous effects across studies, data was summarized using a random-effects model. Random-effects meta-analyses were interpreted with due consideration of the whole distribution of effects. Statistical analyses were undertaken according to the statistical guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions.* Mantel- Haenszel method was used for dichotomous outcomes and the generic inverse-variance method for time-to-event outcomes. Review Manager 5 software was used to perform the analyses.
Relevant sub-group analyses	Subgroup analyses: • Primary vs recurrent bladder cancer • multifocality: solitary versus multiple lesions of bladder cancer; • tumor size: tumor size 3 cm or less versus greater than 3 cm; • stage: positive cytology and/or history of CIS (in the case of recurrent disease). Post-hoc sub-group analysis • use of 5-ALA vs HAL as the photodynamic agent
Supplementary articles based on the same study	

Study identification no.	NA
Link to abstract	Link
Reference (first author, year)	Ontario Health Technology Assessment Series
Overall objective of the study	Assess the safety, effectiveness, and cost-effectiveness of HAL and NBI during first TUR-BT, and budget impact of publicly funding HAL & NBI.
Study type and design	Meta-analysis and cost-effectiveness analysis
Follow-up period	Up to 10 years
Inclusion and exclusion criteria	Studies Included: • RCTs or observational studies for specific outcomes where no RCT was published • Studies with patients over 18 undergoing first TUR-BT for suspected NMIBC • Studies with HAL-guided TUR-BT, NBI-guided TUR-BT or WLC-guided TUR-BT alone • Studies with cancer survival rate at 3,6,9,12 months and p to 10 years • Studies with: RFD, OS, TPR, diagnostic outcomes, adverse events Excluded: • Studies where proportion of patients with recurrent tumour was more than 30% of sample size • Editorials, commentaries, case reports, conference abstracts, letters • Surveillance • Studies with 5-ALA-guided TUR-BT

	•
Intervention	HAL and NBI
Comparator	WLC
Baseline characteristics	NA
Primary and secondary outcome measures	Analysis of safety, effectiveness, and cost-effectiveness
Analysis method	• Pairwise meta-analysis using fix effects model. Indirect treatment comparison between HAL and NBI in absence of Hal vs NBI comparative data • Cost-utility analysis with 15-year time horizon from pubic payer perspective • Budget impact analysis
Relevant sub-group analyses	• Cancer recurrence rate stratified by risk categories • Cancer recurrence rate stratified by tumour grade • Recurrence-free survival • Overall survival • Tumour progression rate • Diagnostic outcomes • Adverse events
Supplementary articles based on the same study	-

Study identification no.	N/A
Link to abstract	https://doi.org/10.1016/j.euros.2021.06.011
Reference (first author, year)	Veeratterpillay, 2021
Overall objective of the study	To assess the effect of PDD-guided TURBT, comparing PDD (using either intravesical HAL or 5-ALA) compared with WL on long-term recurrence rates (RRs) in non–muscle-invasive bladder cancer (NMIBC)
Study type and design	A systematic review of the literature from inception to April 2020 using Medline, EMBASE, and CENTRAL
Follow-up period	Study follow-up between 12 and 72.3 months. Recurrence rates at 12 and 24 months were extracted from 12 RCTs (2288 patients) selected according to Cochrane handbook. One RCT incl 60 months recurrence rate.
Inclusion and exclusion criteria	Patient characteristics were adults (>18 yr) with suspected new NMIBC (any size), or those with a prior history of NMIBC and a minimum of 3 months of recurrence-free interval, that is, not residual tumours from an incomplete resection.
Intervention	PDD using admin of either intravesical HAL or 5-ALA prior to TURBT
Comparator	White light is used as standard with cystoscopy / TURBT
Baseline characteristics	Describe the baseline characteristics of the trial participants, e.g. • 66-71 (interval) • CIS present in 0-14% • Multifocal 35-68%

Primary and secondary outcome measures	Recurrence rates and RFS at 12 and 24 months
Analysis method	• An analysis was performed using a random effect model, and heterogeneity was calculated using Higgin's and Thompson's I2 value to assess percentage of variability between studies.
Relevant sub-group analyses	-
Supplementary articles based on the same study	-

11.2.1 Excluded studies

71 studies were excluded at full text review level. These are listed below with the reason for exclusion.

Table 32: List of excluded studies

Study	Reason for exclusion
Almassi 2018	Wrong intervention
Bach 2017	Wrong outcomes
Buaban 2018	Wrong outcomes
Burger 2013	Post hoc analysis of RCT already included
Chan 2023	Wrong comparator
Chappidi 2022	Wrong outcomes
Creswell 2023	Economic model based on previously published data
DiStasi 2015	Wrong outcomes
Drejer 2017	Wrong intervention
Euctr 2004	Protocol publication
Euctr 2005	Protocol publication
Euctr 2010	Protocol publication
Euctr 2013	Protocol publication
Fukuhara 2023	Wrong intervention
Gakis 2015	Wrong patient population
Garfield 2013	Economic model based on previously published data
Geavlete 2021	Wrong intervention
Herr 2015	Study retracted
Isrctn 2005	Protocol publication
Isrctn 2014	Protocol publication
Jablonowski 2015	Abstract only with no relevant extractable information
Klaassen 2017	Duplicate study
Klaassen 2017	Economic model based on previously published data
Lane 2017	Wrong outcomes
Longo 2013	Wrong outcomes
Malik 2019	Wrong outcomes
Mariappan 2015	No 12-month data provided;
Mariappan 2021	No 12-month data provided

Morelli 2021	Wrong patient population
Mostafid 2009	No 12-month data provided;
Mowatt 2009	Earlier abstract of full publication
Mowatt 2011	Wrong intervention
Mukherjee 2016	Wrong outcomes
Mukherjee 2017	Wrong outcomes
Mukherjee 2019	Wrong outcomes
Nakagawa 2023	Wrong intervention
Nct 2005	Protocol publication
Nct 2006	Protocol publication
Nct 2008	Protocol publication
Nct 2009	Protocol publication
Nct 2010	Protocol publication
Nishimura 2023	Economic model based on previously published data
Nishimura 2023	Exclusion reason: No 12-month data provided;
Nohara 2022	Wrong outcomes
Ntr 2012	Protocol publication
Otto 2009	Wrong comparator
Palou 2015	Wrong outcomes
Pohar 2022	Wrong intervention
Ragonese 2018	Wrong patient population
Renninger 2020	Wrong patient population
Richards 2014	Narrative review
Rink 2013	Narrative review
Rose 2016	Post hoc analysis of RCT already included
Russo 2021	Wrong outcomes
Shadpour 2016	Wrong outcomes
Shore 2023	Post hoc analysis of RCT already included
Skolarikos 2012	Earlier abstract of full publication
Smith 2019	Wrong intervention
Soorojebally 2023	Narrative review
Study	Notes
Sun 2021	Wrong comparator
Svatek 2014	Wrong intervention
Tandogdu 2019	Protocol publication
Todenhfer 2021	Economic model based on previously published data
Tschirdewahn 2020	Wrong intervention
Umin 2010	Protocol publication
Umin 2012	Protocol publication
Williams 2022	Wrong indication
Witjes 2014	Wrong outcomes
Ye 2015	Wrong outcomes
Yu 2023	Post hoc analysis of RCT already included

11.3 Results per study included in the analysis of clinical effectiveness and safety

Table 33: Results per study included in the analysis of clinical effectiveness and safety.

Many of the studies did not report Confidence Interval data, p values, absolute effects and/or relative effects. Data which was reported or could be calculated has been included in the tables below. Where gaps remain, this was either not reported or could not be calculated.

Reference and NCT/EudraCT no: Drăgoescu et al., 2011 [1], PCE-2 1287/2008								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence rate at 12 months	WLC-guided TUR-BT	22	45.45%	27.3% difference in recurrence rate in favour of HAL (CI not reported)	Not reported	-	-	-
	HAL-guided TUR-BT	22	18.8%					
Recurrence-free survival rate	HAL-guided TUR-BT	22	-	-	-	HR= 0.3271 [0.1091-0.9809]	0.0461	Kaplan-Meier
Progression rates	Unable to calculate due to insufficient data							

Reference and NCT/EudraCT no: Drăgoescu et al., 2017 [2], PCE-2 1287/2008								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
12 month recurrence rate	WLC-guided TUR-BT	56	15 (27%)	9%	<0.01	-	-	-

	HAL-guided TUR-BT	57	10 (18%)					
5-year recurrence rate	WLC-guided TUR-BT	56	28 (49.1%)	18.8% recurrence rate reduction between the groups in favour of HAL (CI not reported)	<0.01	RFS HR 0.566 (0.343-0.936) in favour of HAL	0.0267	Kaplan Meier
	HAL-guided TUR-BT	57	38 (67.9%)					
Progression	WLC-guided TUR-BT	56	6 (10.7%)	2% difference in favour of HAL	ns	Not reported (unable to calculate due to insufficient data)	-	-
	HAL-guided TUR-BT	57	5 (8.7%)					

Reference and NCT/EudraCT no: Geavlete, 2012 et al. [3], doi:10.1111/j.1464-410X.2011.10374.x								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence at 1 year	WLC-guided TUR-BT	114	37 (32.5%)	10.9% recurrence rate reduction between groups in favour of HAL (CI not reported)	0.005	RR 0.66		Chi squared, Binominal
	HAL-guided TUR-BT	125	27 (21.6%)					
Recurrence at 2 years	WLC-guided TUR-BT	114	45.6%	14.4% recurrence rate reduction between groups in favour of HAL (CI not reported)	0.001	RR 0.68		Chi squared, Binominal
	HAL-guided TUR-BT	125	31.2%					
Progression at year 1	WLC-guided TUR-BT	114	4.4%	2% progression rate reduction (CI not reported)	0.195	RR 0.54		Binominal
	HAL-guided TUR-BT	125	2.4%					

Progression rate at year 2	WLC-guided TUR-BT	114	7%	3% progression rate reduction (CI not reported)	0.123	RR 0.57		Binominal
	HAL-guided TUR-BT	125	4%					
Recurrence rate at 2 years in patients with multiple tumours	WLC-guided TUR-BT	63	34 (54%)	12% recurrence rate reduction in favour of HAL (CI not reported)	0.001			Binominal
	HAL-guided TUR-BT	82	29 (35.4%)					
Recurrence rate at 2 years in single tumour cases	WLC-guided TUR-BT	51	18 (35.3%)	12% recurrence rate reduction in favour of HAL (CI not reported)	0.064			Binominal
	HAL-guided TUR-BT	43	10 (23.3%)					
Recurrence rate at 2 years in Primary NMIBC	WLC-guided TUR-BT	70	26 (37.1%)	12.8% recurrence rate reduction in favour of HAL (CI not reported)	0.014			Binominal
	HAL-guided TUR-BT	74	18 (24.3%)					
Recurrence rate at 2 years in recurrent NMIBC	WLC-guided TUR-BT	44	26 (59.1%)	17.9% recurrence rate reduction in favour of HAL (CI not reported)	0.007			Binominal
	HAL-guided TUR-BT	51	21 (41.2%)					
Recurrence at months 3, 6 and 9	Out of scope: excluded from this analysis							

Reference and NCT/EudraCT no: Gkritsios, 2012 et al. [4], DOI 10.1007/s11255-013-0603-z								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence rate at 12 months	WLC-guided TUR-BT	31	3.2% (-3.0 – 9.4%)	0.8% No benefit	0.202			Kaplan-Meier
	HAL-guided TUR-BT	42	RR 2.4% (-2.2 – 7.0%)					
Recurrence rate at 24 months	WLC-guided TUR-BT	30	RR 23.3% (8.2 – 38.5%)	11.1% No benefit	0.507			Chi squared test
	HAL-guided TUR-BT	41	RR 12.2% (2.2 – 22.2%)					

Reference and NCT/EudraCT no: Heer* et al., 2022 [6], ISRCTN84013636								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence rate (mITT)	WLC-guided TUR-BT	269	84			HR 0.94 (0.69 to 1.28)	0.7	Cox proportional hazards Kaplan-Meier
	HAL-guided TUR-BT	269	86					
3 year recurrence free rate	WLC-guided TUR-BT	269	61.6% (54.7 – 67.8)	-3.8 percentage points		0.94 HR (0.69 to 1.28)	0.7	Kaplan-Meier

	HAL-guided TUR-BT	269	57.8% (50.7 – 64.2)	Favouring HAL				
Adverse events (related to TUR-BT)	WLC-guided TUR-BT	51	2 (3.9%)			1.41 (0.67 to 2.96)	Not reported	Poisson regression
	HAL-guided TUR-BT	56	3 (5.4%)					
QALY at 3 years	WLC-guided TUR-BT	269	2.087	-	-	-	-	-
	HAL-guided TUR-BT	269	2.094					

*known issues with Heer et al,2022 reported to the editor included: reported evidence of issues with blinding at randomisation, reporting results not consistent with the ITT analysis & a clear violation of the proportional hazards assumption at 22 months.

Reference and NCT/EudraCT no: Hermann et al., 2011 [7] NCT00412971								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence rate at 12 months	WLC-guided TUR-BT	77	23.5% [20.8-42.9%]	7.2%	0.05			Chi squared
	HAL-guided TUR-BT	68	16.3% [7.3-29.7%]					
Total recurrence rate	WLC-guided TUR-BT	77	47.3% [35.6-59.3]	16.8%				Chi squared
	HAL-guided TUR-BT	68	30.5% [19.2-43.9%]					
Recurrence-free survival within 12 months	WLC-guided TUR-BT	77				35.5% RR	0.02	NOTE: taken from text. Table reports incorrect units on horizontal axis making TTR and RFS data uninterpretable
	HAL-guided TUR-BT	68						

Detection	Not included: not relevant to research question							
False positives	Not included: not relevant to research question							
Reference and NCT/EudraCT no: Stenzl et al., 2010 [19]								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence rate (patients with initial cancer at baseline)	HAL-guided TUR-BT	101	42 (41.6%)	7.2% (in favour of HAL)	0.31			CMH Chi-square test with center as stratification factor
	WLC-guided TUR-BT	123	60 (48.8%)					
Recurrence rate (patients with recurrent cancer at baseline)	HAL-guided TUR-BT	170	86 (50.6%)	11.2% (in favour of HAL)	0.04			CMH Chi-square test with center as stratification factor
	WLC-guided TUR-BT	157	97 (61.8%)					
Recurrence rate (patients with TaG1 or TaG2 at baseline)	HAL-guided TUR-BT	218	99 (45.4%)	10% (in favour of HAL)	0.02			CMH Chi-square test with center as stratification factor
	WLC-guided TUR-BT	204	113 (55.4%)					
Recurrence rate (patients with TaG3, Ta ad CIS, T1, T1 and CIS at baseline)	HAL-guided TUR-BT	73	40 (54.8%)	1.8% (in favour of HAL)	0.48			CMH Chi-square test with center as stratification factor
	WLC-guided TUR-BT	83	47 (56.6%)					

Reference and NCT/EudraCT no: Grossman et al., 2012 [5] - extension of [19], doi:10.1016/j.juro.2012.03.007								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence free survival	WLC-guided TUR-BT	261/280	16.4 months	absolute improvement in tumour free survival of more than 6%	0.04			Kaplan-Meier CI – Kaplan-Meier product-limit estimation. Log-rank test. Wilcoxon.
	HAL-guided TUR-BT	255/271	9.6 months					
Progression to T2-4	WLC-guided TUR-BT	261	16 (6.1%)	3% difference in progression	0.066			
	HAL-guided TUR-BT	255	8 (3.1%)					

Reference and NCT/EudraCT no: Kamat et al., 2016 [8] re-analysis of [5,19], NCT00233402								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Progression rate at 12 months	WLC-guided TUR-BT	261	23 (8.8%)	2.9% difference in favour of HAL (CI not reported)	0.239			Fischer's exact test
	HAL-guided TUR-BT	255	15 (5.9%)					
Progression rate at 4.5 years	WLC-guided TUR-BT	261	46 (17.6%	5.4% in favour of HAL (CI not reported)	0.066			Fischer's exact test
	HAL-guided TUR-BT	255	31 (12.2%)					
Progression rate at 3 years	WLC-guided TUR-BT	261	38 (14.6%)	4.4% in favour of HAL (CI not reported)	0.143			Fischer's exact test
	HAL-guided TUR-BT	255	26 (10.2%)					

Reference and NCT/EudraCT no: Karioledes et al., 2012 [9], doi.org/10.1016/j.urology.2012.03.067								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Median time to first recurrence	WLC-guided TUR-BT	41	13.6 months	6.6 months in favour of HAL	<0.001			chi-square test
	HAL-guided TUR-BT	45	7.0 months					
Recurrence free survival at 12 months	WLC-guided TUR-BT	41	91%	34.7% in favour of HAL	0.0006			chi-square test
	HAL-guided TUR-BT	45	56.3%					
Recurrence free survival at 18 months	WLC-guided TUR-BT	41	82.5%	31.9% in favour of HAL	0.0006			chi-square test
	HAL-guided TUR-BT	45	50.6%					
Recurrence free survival with single tumours at 12 months	WLC-guided TUR-BT	41	79.7%	Not significant	0.3525			chi-square test
	HAL-guided TUR-BT	45	93.3%					
Recurrence free survival with single tumours at 18 months	WLC-guided TUR-BT	41	74.2%	Not significant	0.3525			chi-square test
	HAL-guided TUR-BT	45	76.7%					
Recurrence free survival with multifocal tumours at 12 months	WLC-guided TUR-BT	41	27.1%	62.6% in favour of HAL	<0.001			chi-square test
	HAL-guided TUR-BT	45	89.7%					
Recurrence free survival with	WLC-guided TUR-BT	41	13.6%	76.1% in favour of HAL	<0.001			chi-square test

multifocal tumours at 18 months	HAL-guided TUR-BT	45	89.7%					
Recurrence free survival with non-aggressive tumours at 12 months	WLC-guided TUR-BT	41	63%	30.6% in favour of HAL	0.0204			chi-square test
	HAL-guided TUR-BT	45	93.6%					
Recurrence free survival with non-aggressive tumours at 18 months	WLC-guided TUR-BT	41	63%	25.9% in favour of HAL	0.0204			chi-square test
	HAL-guided TUR-BT	45	88.9%					
Recurrence free survival with aggressive tumours at 12 months	WLC-guided TUR-BT	41	42.6%	41.3% in favour of HAL	0.0134			chi-square test
	HAL-guided TUR-BT	45	83.9%					
Recurrence free survival with aggressive tumours at 18 months	WLC-guided TUR-BT	41	34.0%	39.4% in favour of HAL	0.0134			chi-square test
	HAL-guided TUR-BT	45	73.4%					
Recurrence free survival with primary tumours at 12 months	WLC-guided TUR-BT	41	62%	28.4% in favour of HAL	0.0237			chi-square test
	HAL-guided TUR-BT	45	90.4%					
Recurrence free survival with primary tumours at 18 months	WLC-guided TUR-BT	41	55.1%	22.3% in favour of HAL	0.0237			chi-square test
	HAL-guided TUR-BT	45	77.4%					

Recurrence free survival with recurrent tumours at 12 months	WLC-guided TUR-BT	41	41.6%	50.1% in favour of HAL	0.0189			chi-square test
	HAL-guided TUR-BT	45	91.7%					
Recurrence free survival with recurrent tumours at 18 months	WLC-guided TUR-BT	41	41.6%	50.1% in favour of HAL	0.0189			chi-square test
	HAL-guided TUR-BT	45	91.7%					
Progression	WLC-guided TUR-BT	41	0%	4.4% in favour of HAL	Not reported			
	HAL-guided TUR-BT	45	4.4%					

Reference and NCT/EudraCT no: O'Brien, et al., 2013. [10], ISRCTN: 14275387								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence at 12 months	WLC-guided TUR-BT	67	15 (22%)	6% in favour of HAL	0.38			Fisher's exact test
	HAL-guided TUR-BT	63	10 (16%)					

NBI Studies

Reference and NCT/EudraCT no: Naselli et al., 2012 [11], NCT01004211								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence at 1 year	WLC-guided TUR-BT	72	51.4%	19.8% (-34.4 to -4.2%)	0.0141	OR 0.62 (0.07 – 0.81) unadjusted	0.0141	Pearson's Chi-square. Logistic regression analysis using Odds Ratio as index of Relative Risk of recurrence.
	NBI-guided TUR-BT	76	31.6%					

Reference and NCT/EudraCT no: Naito et al ., 2016 [12], dx.doi.org/10.1016/j. eururo.2016.03.053.								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence at 1 year (ITT)*	WLC-guided TUR-BT	481 (ITT)	27.1%	1.7%	0.585			Pearson's Chi-Square Test or Fisher's exact test. Survival analyses using log-rank test.
	NBI-guided TUR-BT	484 (ITT)	25.4%					
Recurrence at 1 year (PP)	WLC-guided TUR-BT	365 (PP)	28.4%	0.4%	Not reported			Student's t-test. Absolute difference calculated as the mean difference.
	NBI-guided TUR-BT	379 (PP)	28%					
Recurrence at 1 year (PP),	WLC-guided TUR-BT	58 (PP)	27.3%	ARR -0.217 (-0.350, -0.085)	0.002	RR 0.204 [0.063, 0.664]	0.002	Student's t-test. Absolute difference

Low risk patients	NBI-guided TUR-BT	57 (PP)	5.6%			OR 0.157 (0.040, 0.620)		calculated as the mean difference.
Recurrence at 1 year (PP), Intermediate risk patients	WLC-guided TUR-BT	121 (PP)	16.8%	-0.8% (No benefit)	-	-	-	Student's t-test. Absolute difference calculated as the mean difference.
	NBI-guided TUR-BT	124 (PP)	17.6%					
Recurrence at 1 year (PP), High risk patients	WLC-guided TUR-BT	186 (PP)	36.8%	-12% (No benefit)	-	-	-	Student's t-test. Absolute difference calculated as the mean difference.
	NBI-guided TUR-BT	198 (PP)	41.4%					
3 month recurrence data	Not included: out of scope							
Detection	Not included: out of scope							

**Contained missing values but author states percentages are valid.*

Reference and NCT/EudraCT no: Kim et al., 2018 [13], doi 10.4111_icu2018.59.2.98								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
1 year recurrence-free rate	WLC-guided TUR-BT	35	72.2%	13% in favour of NBI	0.3			Student's test and Mann-Whitney test Kaplan-Meier
	NBI-guided TUR-BT	39	85.2%					
Detection	Not included: not relevant to research question							

Reference and NCT/EudraCT no: Lee, 2014 et al. [14] ABSTRACT								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence free rate at 24 months	WLC-guided TUR-BT	Not reported	73.0% [61.1-97.7]	1.2%	Not reported			
	NBI-guided TUR-BT	Not reported	77.2% [57.2-93.3]					
Recurrence-free rate in high grade tumours	WLC-guided TUR-BT	Not reported	Not reported	No statistical difference				
	NBI-guided TUR-BT	Not reported	Not reported					
Recurrence-free rate in multiple tumours	WLC-guided TUR-BT	Not reported	Not reported	No statistical difference				
	NBI-guided TUR-BT	Not reported	Not reported					
Recurrence-free rate in patients with cis at 12 months	WLC-guided TUR-BT	Not reported	62.5% [36.5-100]	62.5%	Not reported			
	NBI-guided TUR-BT	Not reported	Reported as zero					
Recurrence-free rate in patients with cis at 24 months	WLC-guided TUR-BT	Not reported	25.0% [7.5-83.0]	25%	Not reported			
	NBI-guided TUR-BT	Not reported	Reported as zero					

Note: all data taken from abstract, no full text publication available.

Meta-analyses

Reference and NCT/EudraCT no: Ontario Health, 2021 [16]								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
12 month recurrence rate	WLC-guided TUR-BT	183	68	RD -0.11 (-0.21, -0.02)		RR 0.70 (0.51,0.95)	p=0.240	Cochran Q test; I^2
	HAL-guided TUR-BT	184	48					
12 month recurrence rate	WLC-guided TUR-BT	380	107	RD -0.02 (-0.08,0.04)		RR 0.94 (0.75, 1.19)	p=0.191	Cochran Q test; I^2
	NBI-guided TUR-BT	393	104					
12 month recurrence rate (ITC)	HAL-guided TUR-BT	1,140		Indirect RD -0.09 (-0.21, 0.02)		Indirect RR 0.76 (0.51, 1.11)		Cochran Q test; I^2
	NBI-guided TUR-BT							

Reference and NCT/EudraCT no: Maisch, 2021 [17]								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Time to disease recurrence	WLC-guided TUR-BT	2994 (15 RCTs)				HR 0.66 (0.54, 0.81)	<0.00001	I^2 Chi^2
	BLC-guided TUR-BT*							
12 month recurrence rate	WLC-guided TUR-BT	1512 (9 RCTs)				HR 0.60 (0.45, 0.78)	0.0002	I^2 Chi^2
	HAL-guided TUR-BT	1482 (9 RCTs)						
Progression	HAL-guided TUR-BT	1107 (9 RCTs)				HR 0.77 (0.63,0.96)	0.04	I^2 Chi^2
	BLC-guided TUR-BT*	1093 (9 RCTs)						
Progression	WLC-guided TUR-BT	477 (4RCTs)				HR 0.69 (0.48,0.98)	0.02	I^2 Chi^2
	HAL-guided TUR-BT	484 (4 RCTs)						

*5-ALA and HAL

Reference and NCT/EudraCT no: Veertaterpillay, 2021 [18]								
Outcome measure	**Group**	***N***	**Result per group [95 % CI]**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
12 month recurrence rate	WLC-guided TUR-BT	183	68	RD -0.11 (-0.21, -0.02)		RR 0.70 (0.51,0.95)	p=0.240	Cochran Q test; I^2
	HAL-guided TUR-BT	184	48					
12 month recurrence rate	WLC-guided TUR-BT	380	107	RD -0.02 (-0.08,0.04)		RR 0.94 (0.75, 1.19)	p=0.191	Cochran Q test; I^2
	NBI-guided TUR-BT	393	104					
12 month recurrence rate (ITC)	HAL-guided TUR-BT	1,140		Indirect RD -0.09 (-0.21, 0.02)		Indirect RR 0.76 (0.51, 1.11)		Cochran Q test; I^2
	NBI-guided TUR-BT							

11.4 Results per clinical question

Table 34: Results per clinical question.

Clinical question <1>								
Results per outcome measure	**Studies used in the analysis (insert references)**	**Groups**	**Total *N* per group**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95 % CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Recurrence	[2-4, 6,7,9 10,19,76,77]	HAL	994	Change in recurrence-free survival: +10.2 (+4.8% to +14.4%) Benefit at 12 months	n/a	HR = 0.63 (0.49 to 0.82)	0.001	Random effects inverse variance pooling applied to study-level estimates of HR. Absolute difference estimated at 12 months using method of Tierney et al
		WLC	996					
Recurrence	[11,12]	NBI	379	Change in recurrence-free survival: +37.0% (--7.7%% to +416.6%) Benefit at 12 months	n/a	HR = 0.74 (0.42 to 0.1.32)	0.308	Random effects inverse variance pooling applied to study-level estimates of HR. Absolute difference estimated at 12 months using method of Tierney et al
		WLC	366					
Progression	[2,3,10,19]	HAL	484	Change in progression-free survival: +5.1% (+0.3% to 8.8%) Benefit at 60 months	n/a	HR = 0.69 (0.48-0.98)	0.02	Random effects inverse variance pooling applied to study-level estimates of HR. Absolute difference estimated at 12 months using method of Tierney et al
		WLC	477					
HRQoL	[6]	HAL	209	Change in reported HRQoL at	0.854	RR:0.652 (0.24 – 1.60)	0.33	

		WLC	217	12 months-0.006 (-0.067-0.056),				
AEs (safety)	[10, 12]	NBI	481	Difference in intraoperative bleeding: +0.4% Difference in bladder perforation: +0.8%	0.348			Log-rank test and shown as Kaplan-Meier curves
		WLC	484					
AEs (safety)	[6, 35,36]	HAL	209			RR 0.62;95%CI (0.24-1.60),	0.33	Log rank
		WLC	217					

11.5 List of existing health economic analyses

Table 35: List of existing health economic analyses.

Ref.	Peer-reviewed	Year	Country of origin	Analysis type (e.g. CEA, CUA)	Patient population (age, gender, etc.)	Comparator	Time horizon	ΔC	ΔE*	ICER*	Used as inspiration for structure of analysis
[96]	Yes	2023	USA	Cost analysis	NMIBC – Retrospective claims database analysis	BLC vs WLC	5 years	-$1,172 per patient on BLC	-	-	No
[97]	Yes	2013	Canada	Cost-utility analysis	NMIBC – data sourced from published RCTs	BLC vs WLC	4.5 years	-$4,660 per patient on BLC	+0.5 utility index per patient on BLC	BLC Dominant	No

[6]	Yes	2022	UK	Cost-utility analysis	NMIBC – data sourced from single RCT	BLC vs WLC		+£876 per patient on BLC	-0.007 QALYs per patient on BLC	WLC dominant	No
[98]	Yes	2023	Canada	Cost analysis	NMIBC – data sourced from meta-analysis of published RCTs	BLC vs WLC	5 years	+$1,236 - $1,372 per patient on BLC	-	-	No
[99]	Yes	2023	Japan	Cost analysis	NMIBC – data sourced from retrospective review of records	BLC vs WLC	3 years	+¥484 per patient per year on BLC	-	-	No
[79]	Yes	2015	France	Cost-utility analysis	NMIBC – data sourced from published RCTs	BLC vs WLC	Lifetime	-EUR 670 per patient on BLC	+0.075 QALY per patient on BLC	BLC dominant	No
[100]	Yes	2021	Germany	Cost analysis	NMIBC – Retrospective claims database analysis	BLC vs WLC	3 years	+EUR 889 per patient on BLC	-	-	No

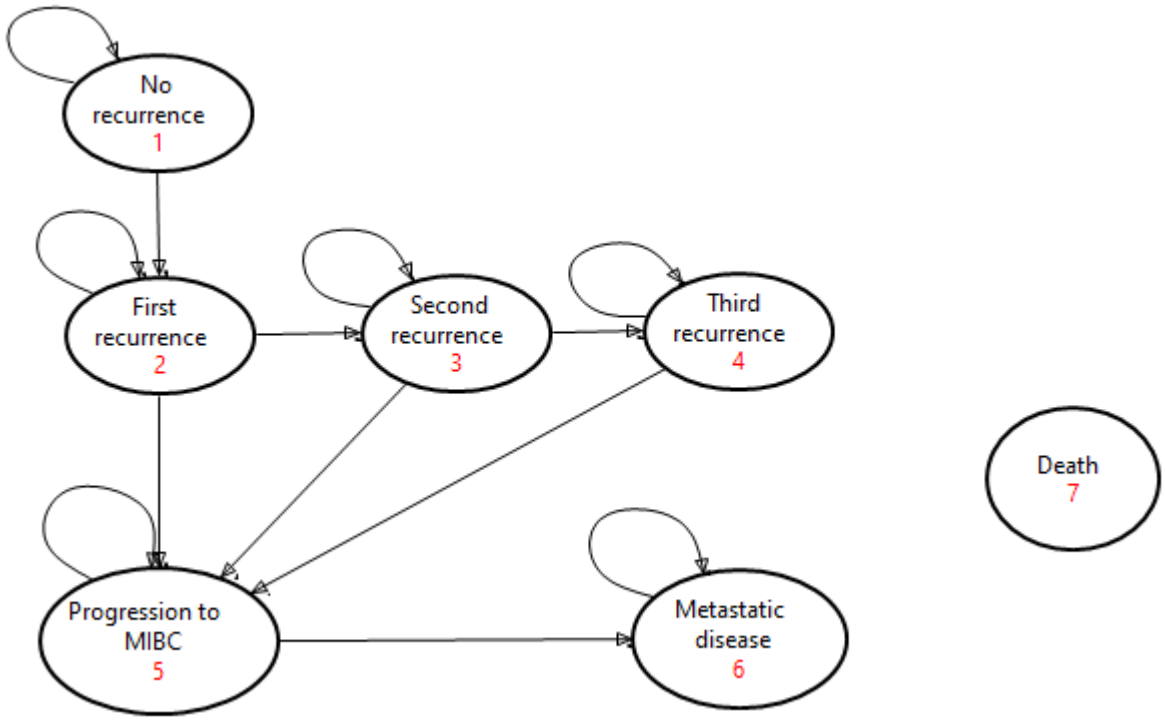
11.6 Description of the model design

References refer to economic section references.

Model structure

The model as finally implemented is a conventional semi-Markov cohort design, based on 6 active health states:

Figure 7: State transition model for final model



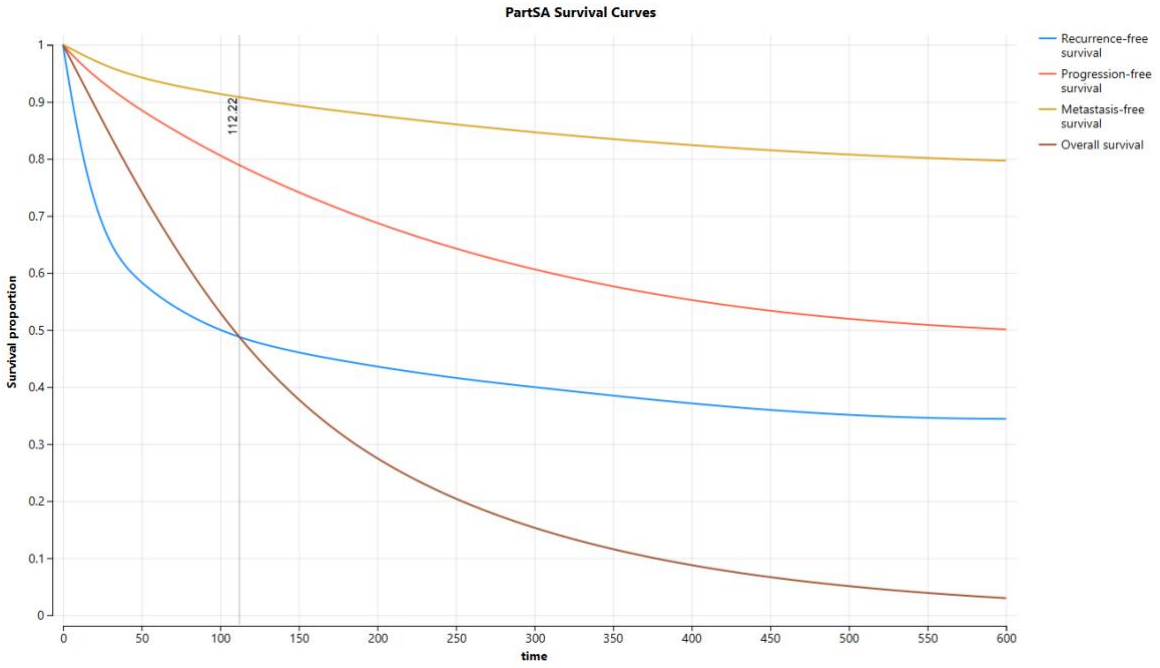
In the conceptualisation stage, consideration was given to using a partitioned survival analysis, in common with many contemporary oncological cost-utility models. This approach inherently captures the time to event nature of clinical outcomes in cancer studies, rather than having to use a more inelegant semi-Markov approach. There were, however, several issues that made the partitioned survival approach non-viable.

Firstly, the available trial data for HAL-guided TUR-BT and NBI-guided TUR-BT are restricted to time to first recurrence. Although subsequent recurrences are implicitly acknowledged, there are no published data that allow us to implement these events as distinct survival curves within the model. This is a major limitation, given that the resource use associated with the Danish bladder cancer treatment guidelines is intimately connected to the time since the most recent occurrence occurred.

Secondly, there is a significant crossover problem once overall survival is integrated into a potential partitioned survival model. As the curves below show, all cause mortality rapidly overtakes all cancer-specific outcomes. As Figure 8 overleaf shows, death from any cause is a more common outcome from the outset than either disease progression or metastases, and by 10 years follow-up it exceeds the risk of recurrence. Although there are techniques that allow modest degrees of mortality crossover to be

mitigated, the problem in this situation was too severe to allow any remedial steps to be taken. The use of a semi-Markov model was therefore the only option open to us.

Figure 8 – approximate state-specific survival curves used at model conceptualisation stage



Logic structure

The evidence base for NBI-guided TUR-BT is extremely limited, with no published RCTs following up patients for more than 12 months. Although longer follow-up (up to 55 months) is available for one RCT in HAL-guided TUR-BT [19], there remains insufficient data to allow a meaningful long term projection of outcomes for both treatments to be evaluated. The strategy adopted, therefore, was to take 10-15 year clinical outcomes data for WLC-guided TUR-BT [102-104] and use these to create a state transition backbone for the model, referencing the six primary health states. Given that RCTs exist that compare both HAL-guided TUR-BT and WLC-TUR-BT from the perspective of time to first recurrence, we were able to extract data from these studies and carry out two parallel meta-analyses that provided estimates of the hazard ratios for each treatment option. These HRs could then be applied to the core WLC-TUR-BT recurrence curves, in order to model the impact of each on the baseline transition from recurrence-free to the point of first recurrence. For the base case, the other three survival curves were used in the unmodified state, using the assumption that progression, metastasis and death would be uninfluenced by the technology used for the initial TUR-BT.

The steps taken to implement this approach are detailed in Annex 11.7.

One may question whether a hazard ratio derived from – in the case of NBI-GUIDED TUR-BT– as little as 12 months follow-up can legitimately be applied to a 10 year time to event curve. This is a reasonable question but it is worth considering:

- Unlike a risk ratio or odds ratio, the hazard ratios constitute an estimate of the instantaneous risk of an event of the entire duration of a study. As such, they can legitimately be applied to any time point.
- The majority of recurrence events occur early in the post-treatment follow-up period, as evidenced by the blue curve in figure 8. This effect is reflected in the treatment guidelines where, for most patients, surveillance follow-up is recommended to cease after 5 years without a first recurrence. Any concern regarding projecting a hazard ratio forward by 10 or 20 years is therefore mitigated by the fact that the point hazard by this point will be negligible, with any impact being further reduced by the effect of discounting.
- The duration of follow-up for HAL-guided TUR-BT is substantially longer than that for NBI-guided TUR-BT– the derived HR will consequently be more representative of real-world practice and should capture any waning of benefit in the medium to long term. For this reason, the approach that we have adopted is conservative from the perspective of the research question, in the projected results for NBI-guided TUR-BT are likely to be more optimistic than those for HAL-guided TUR-BT.

Use of trackers

Although no economic model can (or should) be a perfect representation of all aspects of disease management, in the case of this assessment we were keen to capture the key components of the management guidelines issued by the Danish Multidisciplinary Cancer Group. The follow-up recommendations, which have resource implications, are predicated on a sliding scale of reducing surveillance. However, where a patient experiences a recurrence, they are required to revert to the previous level of follow-up.

Within a semi-Markov structure, the magnitude of cost and effectiveness rewards are normally driven by the number of cycles that the patient has passed through. In order to allow patients to revert back to earlier stages of follow-up, it is necessary to capture the point at which a recurrence occurred and for time elapsed since this event to drive subsequent rewards. This is achieved by using trackers within the model. One consequence of using trackers, however, is that a simple EV (expected value) approach can no longer be used to calculate aggregated costs and QALYs, as these depend on whether and when a specified event has taken place, which will not be consistent for the entire cohort.

Instead, we have to use microsimulation to drive the model analysis, analogous to the approach used for a discrete event model. Unlike the discrete event simulation, however, the only factor that varies in the simulation is the path through the model. No attempt is made to vary the patients' baseline characteristics as a driver of outcome, so the result remains a cohort-level calculation. In our case we used 10,000 simulated paths through the model to derive estimates of incremental cost and effectiveness.

11.7 Transformation of data

There are two major transformation processes used in this model. The first relates to the use of meta-analysis to generate estimates of hazard ratio for the two technologies of interest, while the second describes the use of hazard functions to incorporate survival data in the model.

1a. Meta-analysis for time to disease recurrence

The systematic literature review identified 16 publications that included a quantitative meta-analysis of potential relevance to the DTC specification [15-18, 20-31]. In order to contribute useful estimates of effectiveness for the model, the following basic criteria would need to be met:

- Systematic literature review carried out in the last 5 years
- Results presented for time to recurrence (Hazard ratio)
- Comparison of HAL-guided TUR-BT or NBI-guided TUR-BT vs WLC-guided TUR-BT
- Included studies were appropriately pooled

Of the sixteen identified analyses, seven [20-26] were carried out using a literature review that was more than 5 years old (range 2012-2016).

Of the nine remaining analyses, four provided an assessment of time to recurrence [28,17,29,31]

Of these four analyses, two compared HAL-guided TUR-BT with WLC-TUR-BT [17,31], one compared NBI-guided TUR-BT with WLC-TUR-BT [29], and one carried out both comparisons [28].

Assessment of the appropriateness of the studies pooled in these four analyses is shown in Table 36 below:

Table 36: Assessment of appropriateness of pooling in eligible meta-analyses (recurrence-free survival)

Reference	Comparison	Studies pooled	Inappropriate inclusions	Studies not included	Result HR (95%CI)
Li 2021 [28]	BLC vs WLC[1]	[1-2,4,7,9-10, 19,118]	[1,118] – *note 1*	[3,6]	0.69 (0.58-0.82)
	NBI vs WLC[2]	[11-14, 73-74, 81]	[73-74, 81] - *note 2*	-	0.73 (0.60-0.69)
Maisch 2021 [17]	BLC vs WLC[3]	[2-4,7,9-10, 19,76-77]	[76,77] – *note 3*	[6]	0.60 (0.45-0.78)
Lai 2022 [29]	NBI vs WLC[4]	[11-14, 73,75]	[13-14, 73,75] – *note 4*	-	0.63 (0.45-0.89)
Zhao 2023 [31]	BLC vs WLC[5]	[1-2,4,7,9,19,72]	[1,72] – *note 5*	[3,6,10]	0.79 (0.67-0.92)

Notes

1.Li et al's comparison for HAL-guided TUR-BT vs WLC-TUR-BT inappropriately included one study [1] that was an interim report of more complete results that were published subsequently [2], and a second study that investigated surveillance cystoscopy rather than TUR-BT [118]. They omitted one potentially relevant study [3] and undertook the analysis prior to the publication for another relevant study [6].

2. The comparison for NBI-guided TUR-BT vs WLC-TUR-BT in Li et al. inappropriately included three studies [73-75]. One was a randomised comparison of NBI-guided bipolar plasma vaporization vs WLC-TUR-BT [73] and therefore did not address the research question. The second was a comparison of NBI-guided flexible cystoscopy vs WLC-guided flexible cystoscopy for second look following TUR-BT, and was therefore out of scope [74]. The third study was a comparison of NBI-guided flexible cystoscopy vs WLC-guided flexible cystoscopy in a surveillance role, and was therefore also out of scope [81].

3. Maisch et al's inclusion of two studies with short term (3 month) recurrence outcomes [76,77] is probably appropriate, given that hazard ratio is not specific to a given duration of follow-up. However, the omission of these studies by the other authors cannot be considered a negative. The analysis was undertaken prior to the publication of another relevant study [6] and consequently the results did not include these data. Dahm et a [78] recalculated the meta-analysis including the relevant study [6]. The pooled effect size changed only to a small degree (HR 0.68; 95% CI, 0.56 to 0.82) including all studies using BLC with either 5-ALA or HAL .

4. Lai et al nominally identified six studies to include in their meta-analysis of NBI-guided TUR-BT vs WLC-TUR-BT. Of these, however:

- *One was a comparison of NBI-guided bipolar plasma vaporization vs WLC-TUR-BT [73] and was thus out of scope.*
- *One was a comparison of NBI-guided holmium laser resection vs WLC-TUR-BT [75] and was thus out of scope.*
- *One randomised 198 patients but only presented recurrence data on 74 of them [13]. The robustness of the results is therefore subject to significant uncertainty.*
- *One was only ever published as an abstract [14] and thus never underwent full peer review and cannot be assessed for quality.*
- *Concerns regarding the execution and interpretation of the results has been expressed in a letter to the editor by Roupret et al. [79].*

5. Zhao et al, like Li et al, inappropriately included one study [1] that was an interim report of more complete results that were published subsequently [2], and a second study that investigated surveillance cystoscopy rather than TUR-BT [72]. They omitted two potentially relevant studies [3,20] and undertook the analysis prior to the publication for another relevant study [6].

Conclusions

Of the 16 published meta-analyses only one yielded robust results for HAL-guided TUR-BT vs WLC-TUR-BT [17], and even this analysis lacked data from a large randomised trial that was published subsequently [6]. However, the author of the meta-analysis recalculated the analysis including this recent randomised trial demonstrating only a minor change in the effect size referring to BLC studies using either 5-ALA or HAL [78]. For the NBI-guided TUR-BT vs WLC-guided TUR-BT comparison, none of the published meta-analyses yielded usable results. We consequently decided the following:

- To repeat the analysis carried out by Maisch et al including data from the missing study
- To carry out a new meta-analysis for NBI-guided TUR-BT, using the same analytical method as used by both Maisch et al [17] and Lai et al [29]. Three scenarios to be examined:
    - Include only Naito et al and Naselli et al [11,12] in the analysis.
    - Allow Kim et al [13] to be included.
    - Allow Kim et al [13] and Lee et al [14] to be included.

In order to be consistent with the original Cochrane methodology, inverse variance frequentist pooling of study-level hazard ratios was undertaken. Both fixed and random effects models were considered – in the context of significant heterogeneity, the random effects model results were used as primary output. All meta-analyses were carried out using MedCalc v22.021 (MedCalc Software Ltd, Ostend, Belgium).

Results of re-analysis – HAL-guided TUR-BT vs WLC-TUR-BT

Table 37: Results of re-analysis – HAL-guided TUR-BT vs WLC-TUR-BT

Meta-analysis: generic inverse variance method

Variable for studies	Author
Variable for estimate:	logHR
Variable for Standard Error:	SE

Study	Estimate (Log)	Standard Error	Estimate	95% CI	z	P	Weight (%)	
							Fixed	Random
Dragoescu 2017	-0.569	0.256	0.566	0.343 to 0.935			4.98	9.83
Geavlete 2010	-1.022	0.125	0.360	0.282 to 0.460			20.88	13.66
Geavlete 2012	-0.386	0.297	0.680	0.380 to 1.217			3.71	8.72
Gkritsios 2014	-0.199	1.053	0.820	0.104 to 6.454			0.29	1.43
Heer 2023	-0.0619	0.158	0.940	0.690 to 1.281			13.12	12.74
Hermann 2011	-0.545	0.176	0.580	0.411 to 0.819			10.51	12.19
Karaolides 2012	-0.844	0.246	0.430	0.266 to 0.696			5.40	10.12
Neuzillet 2014	-0.151	0.145	0.860	0.647 to 1.144			15.43	13.09
O'Brien 2013	-0.357	0.541	0.700	0.242 to 2.023			1.11	4.31
Stenzl 2010	-0.236	0.115	0.790	0.630 to 0.990			24.57	13.91
Total (fixed effects)	-0.453	0.0571	0.636	0.569 to 0.711	-7.920	<0.001	100.00	100.00
Total (random effects)	-0.460	0.132	0.632	0.487 to 0.819	-3.474	0.001	100.00	100.00

Test for heterogeneity

Q	37.8299
DF	9
Significance level	P < 0.0001
I^2 (inconsistency)	76.21%
95% CI for I^2	55.99 to 87.14

Results of re-analysis – NBI-guided TUR-BT vs WLC-TUR-BT

Table 38: Results of re-analysis – NBI-guided TUR-BT vs WLC-TUR-BT (Naito et al [11] and Naselli et al [12]) only

Meta-analysis: generic inverse variance method

Variable for studies	Author
Variable for estimate:	logHR
Variable for Standard Error:	SE

Study	Estimate (Log)	Standard Error	Estimate	95% CI	z	P	Weight (%)	
							Fixed	Random
Naselli 2012	-0.635	0.251	0.530	0.324 to 0.866			23.58	43.86
Naito 2016	-0.0400	0.139	0.961	0.731 to 1.262			76.42	56.14
Total (fixed effects)	-0.180	0.122	0.835	0.658 to 1.060	-1.481	0.139	100.00	100.00
Total (random effects)	-0.301	0.295	0.740	0.415 to 1.320	-1.019	0.308	100.00	100.00

Test for heterogeneity

Q	4.3041
DF	1
Significance level	P = 0.0380
I^2 (inconsistency)	76.77%
95% CI for I^2	0.00 to 94.71

Table 39: Results of re-analysis – NBI-guided TUR-BT vs WLC-TUR-BT (Naito et al [11], Naselli et al [12], Kim et al [13])

Meta-analysis: generic inverse variance method

Variable for studies	Author
Variable for estimate:	logHR
Variable for Standard Error:	SE

Study	Estimate (Log)	Standard Error	Estimate	95% CI	z	P	Weight (%)	
							Fixed	Random
Naselli 2012	-0.635	0.251	0.530	0.324 to 0.866			22.06	34.03
Kim 2018	-0.124	0.464	0.883	0.356 to 2.194			6.44	16.07
Naito	-0.0400	0.139	0.961	0.731 to 1.262			71.50	49.90
Total (fixed effects)	-0.177	0.118	0.838	0.665 to 1.056	-1.500	0.134	100.00	100.00
Total (random effects)	-0.256	0.216	0.774	0.507 to 1.181	-1.187	0.235	100.00	100.00

Test for heterogeneity

Q	4.3179
DF	2
Significance level	P = 0.1154
I^2 (inconsistency)	53.68%
95% CI for I^2	0.00 to 86.73

Table 40: Results of re-analysis – NBI-guided TUR-BT vs WLC-TUR-BT (Naito et al [11], Naselli et al [12], Kim et al [13], Lee et al [14])

Meta-analysis: generic inverse variance method

Variable for studies	Author
Variable for estimate:	logHR
Variable for Standard Error:	SE

Study	Estimate (Log)	Standard Error	Estimate	95% CI	z	P	Weight (%)	
							Fixed	Random
Naselli 2012	-0.635	0.251	0.530	0.324 to 0.866			20.29	28.44
Kim 2018	-0.124	0.464	0.883	0.356 to 2.194			5.92	15.81
Naito 2016	-0.0400	0.139	0.961	0.731 to 1.262			65.75	36.81
Lee 2014	-0.994	0.398	0.370	0.170 to 0.808			8.04	18.94
Total (fixed effects)	-0.242	0.113	0.785	0.629 to 0.979	-2.147	0.032	100.00	100.00
Total (random effects)	-0.403	0.233	0.668	0.423 to 1.055	-1.730	0.084	100.00	100.00

Test for heterogeneity

Q	8.1932
DF	3
Significance level	P = 0.0422
I^2 (inconsistency)	63.38%
95% CI for I^2	0.00 to 87.65

Given that there is substantial heterogeneity in these datasets, the appropriate pooling approach to use is the random effects model. The summary of results, which were used in the model, are summarised in Table 41 below.

Table 41: Summary of results of the revised meta-analyses for recurrence-free survival (random effects)

Comparison	Studies pooled	Result HR (95%CI)	P-value
HAL-guided TUR-BT vs WLC-TUR-BT	[2-4,6,7,9,10,19,76,77]	0.632 (0.487-0.819)	0.001
NBI-guided TUR-BT vs WLC-TUR-BT	[11,12]	0.740 (0.415-1.320)	0.308
	[11-13]	0.774 (0.507-1.181)	0.235
	[11-14]	0.668 (0.423-1.055)	0.084

1b. Meta-analysis for time to disease progression

For the exploratory analysis of time to disease progression, application of the same inclusion criteria as for the recurrence outcome yielded a single credible result for HAL-guided TUR-BT vs WLC-guided TUR-BT [17]. Although Li et al [28] also report results for progression-free survival, these are based on a single study for HAL-guided TUR-BT and a single inappropriately included study that examined NBI-guided flexible surveillance cystoscopy (see Table 42).

Table 42: Assessment of appropriateness of pooling in eligible meta-analyses (progression-free survival)

Reference	Comparison	Studies pooled			Inappropriate inclusions	Studies not included	Result HR (95%CI)
Li 2021 [28]	HAL vs WLC	[19]	-	[2,3,10]	0.64 (0.41-1.00)		
	NBI vs WLC	[81]	[81]	-	0.47 (0.22-1.03)		
Maisch 2021 [17]	HAL* vs WLC	[2,3,10,19]			0.69 (0.48-0.98)		

*HAL only data

Given the shortcomings of the Li meta-analysis [28] for this outcome, for the purposes of the scenario analysis exploring the possible impact of an independent effect of HAL-guided TUR-BT on time to progression, the result from Maisch et al [17] was used.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.8 Data extrapolation

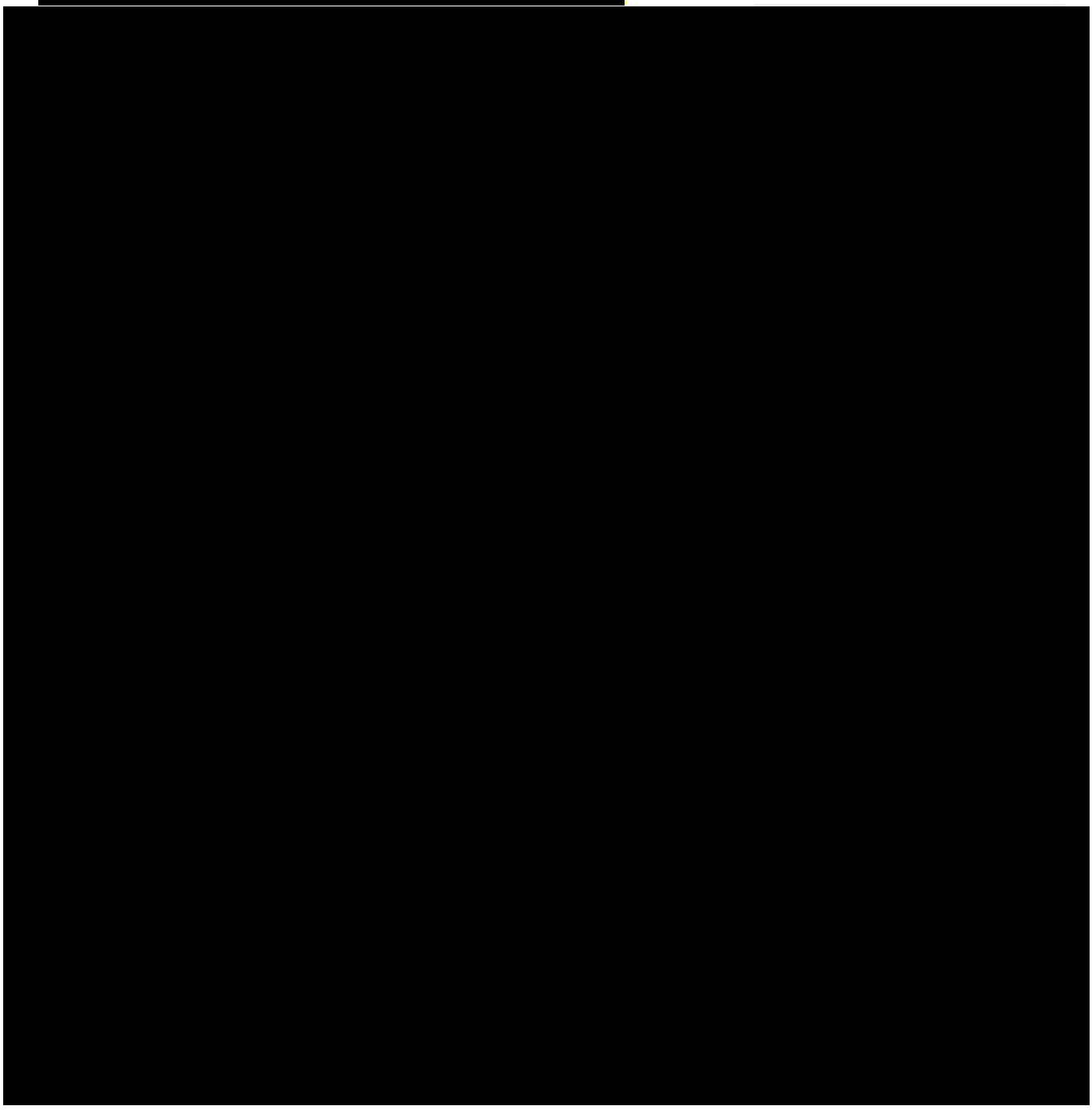
11.8.1 Hazard table approach

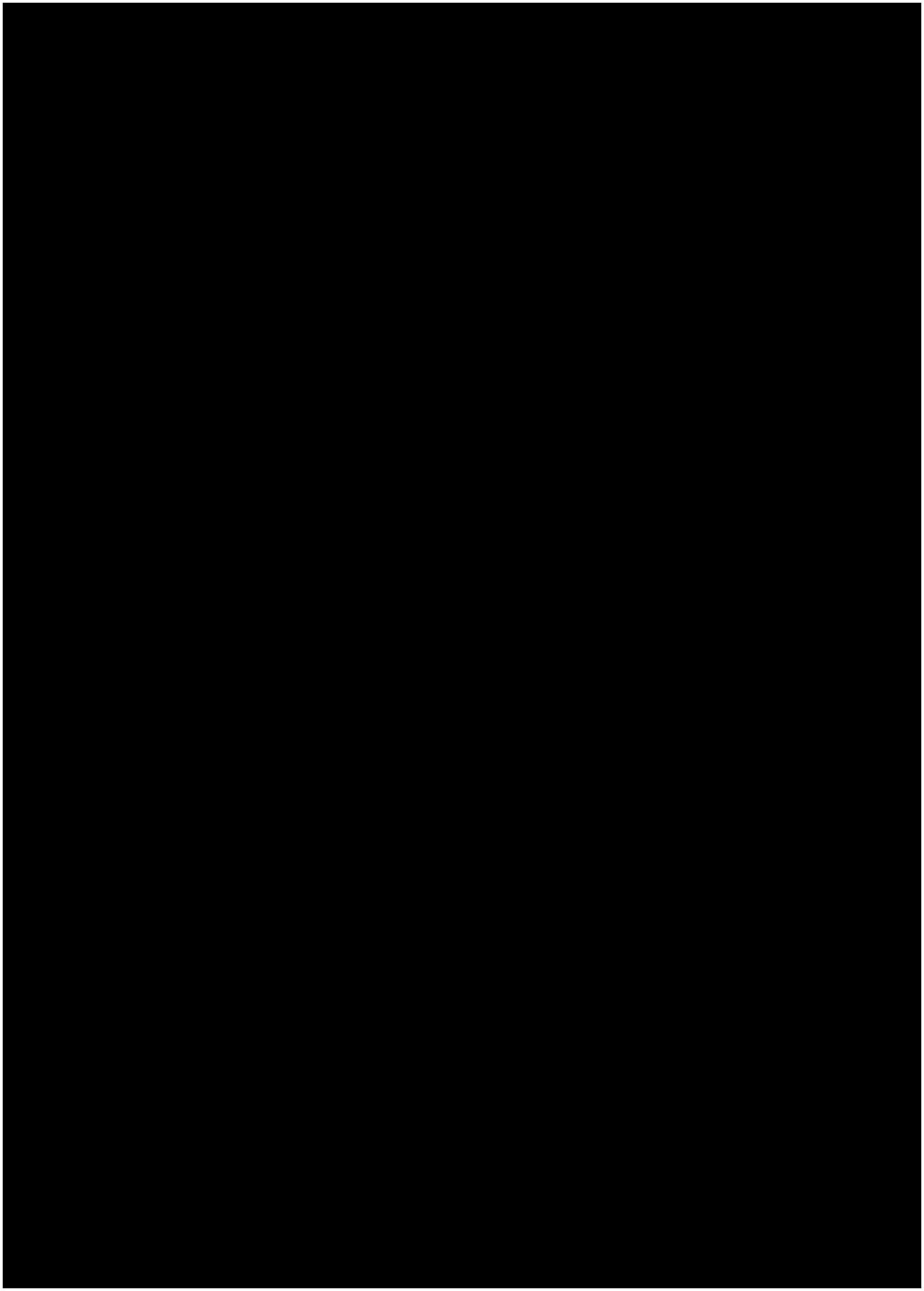
The hazard table approach described in the previous section is equally applicable to the process of extrapolation. Traditionally, estimates for long term survival probability are carried out either using standard parametric survival functions (eg Gompertz, Weibull, lognormal etc) or more sophisticated spline or parametric mixture models, that allow for greater variation in the hazard function, as it is not reasonable to expect this to remain constant of the extended period required for a lifetime horizon.

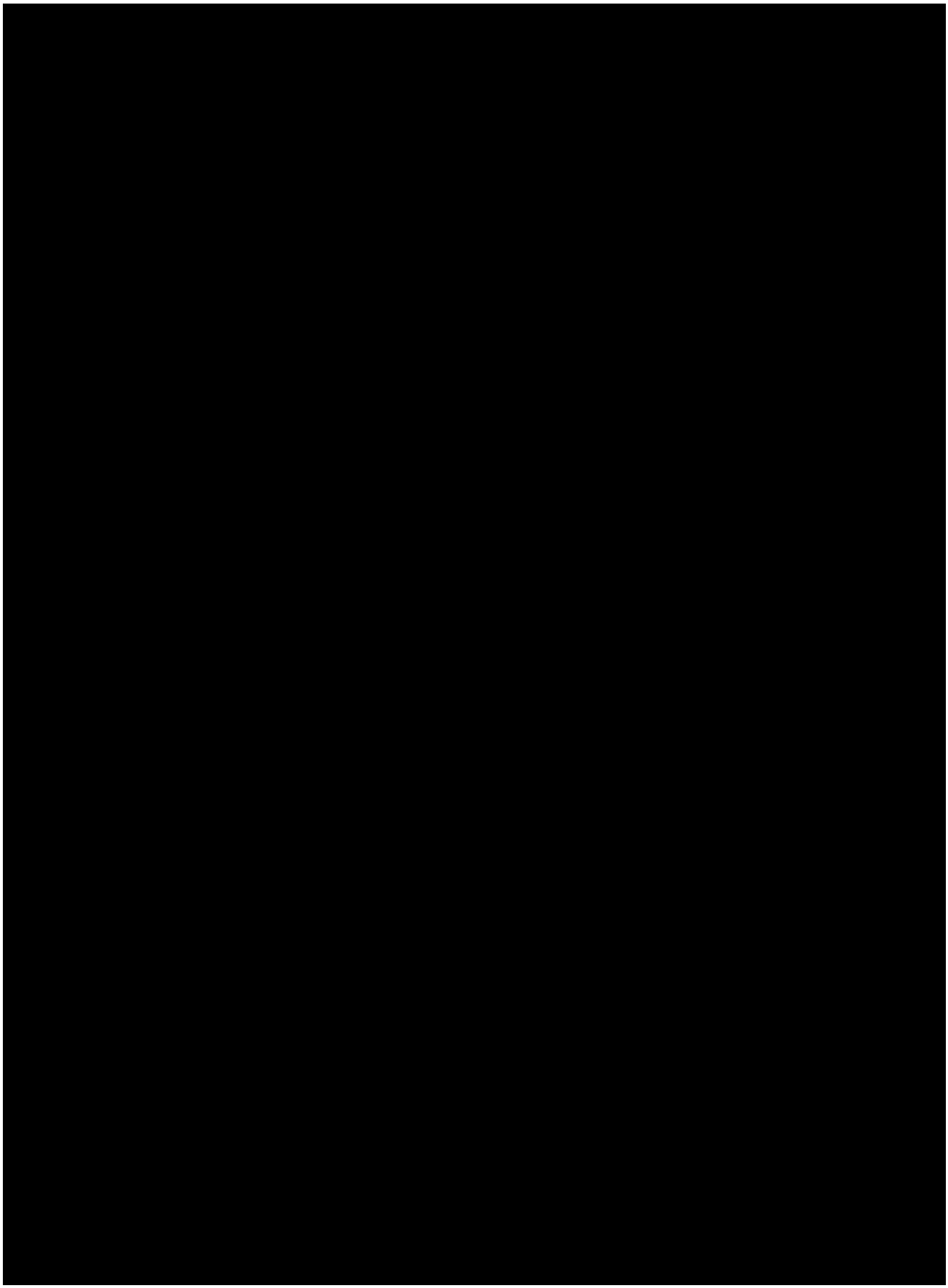
Whichever method is adopted, the simulated curve is required to match the parent data-derived Kaplan-Meier curve, while simultaneously providing a clinically plausible roll-out that matches the expected long term outcomes. Ultimately, although indicators of fit can help guide the process, the choice of the appropriate parametric function for extrapolation is an informed opinion of the individual modeller.

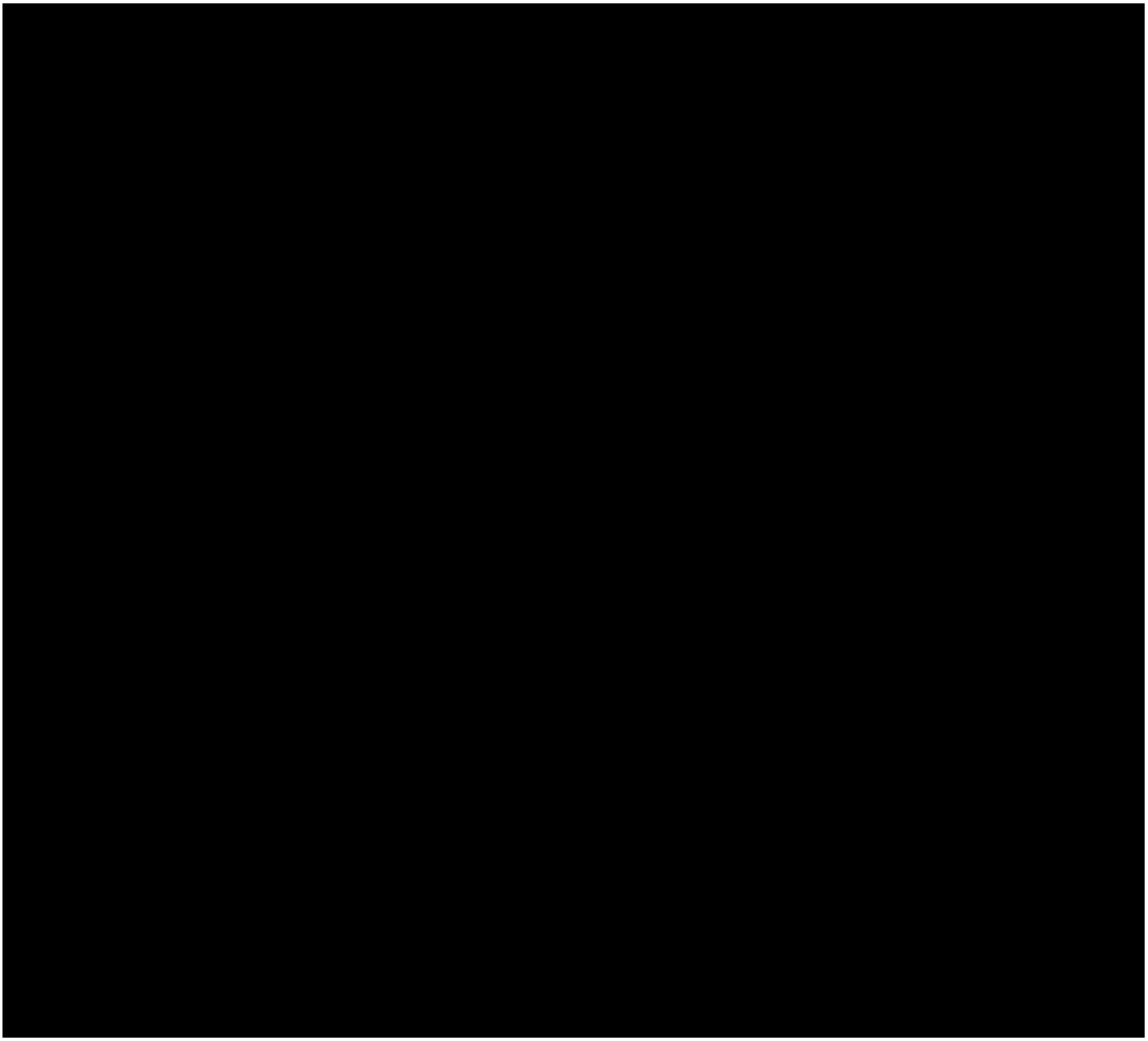
In the case of this model, [redacted]

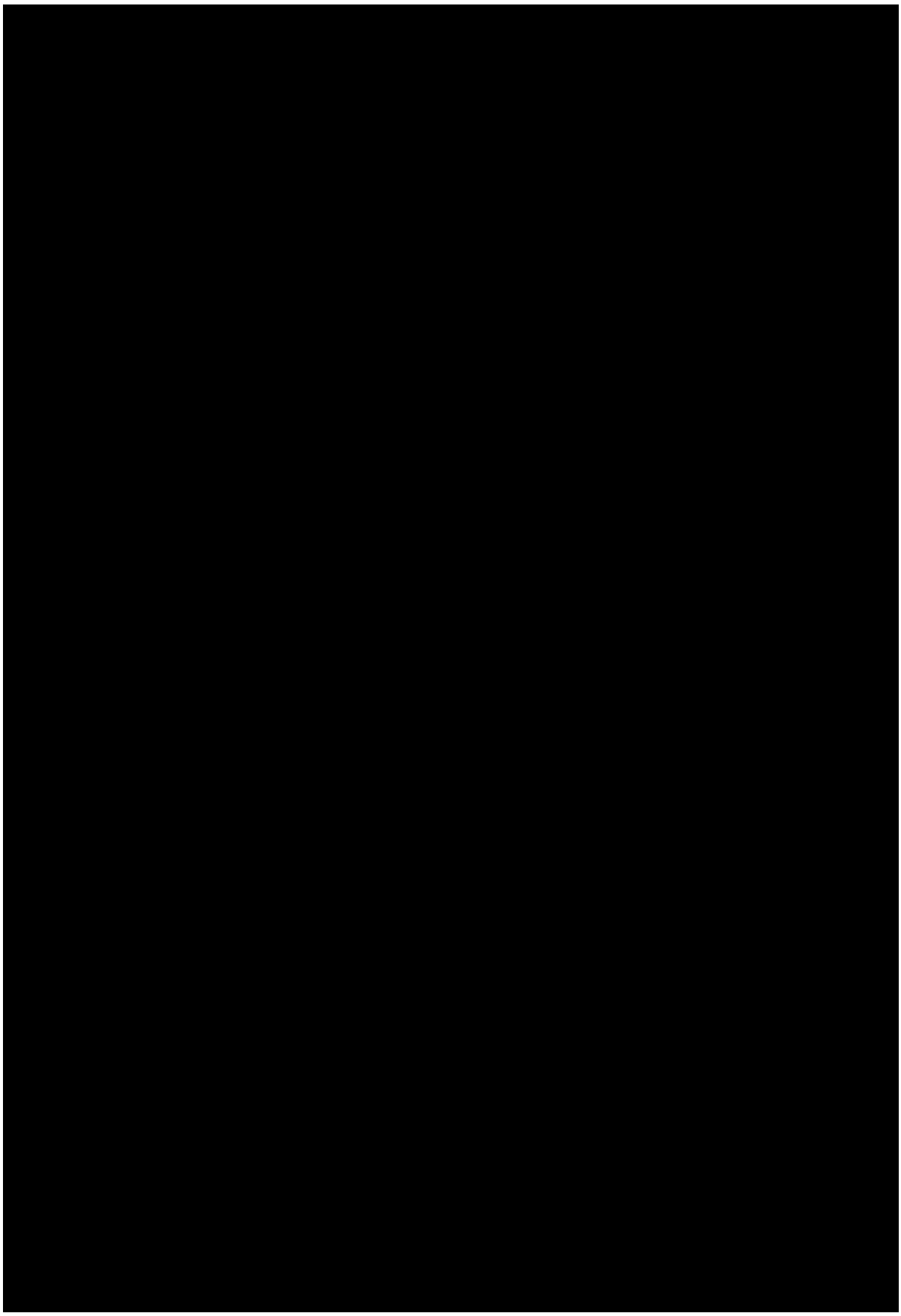
[redacted]











11.9 Studies regarding health-related quality of life

Table 43: Summary description of studies regarding health-related quality of life.

Ref.	Patient population	Year of publication	Population size, number	Instrument applied to estimate preferences	Weights applied (value)	Statistical treatment
[113]	General public (TTO study)	2023	202	Disease state vignettes + time trade off analysis	See table 44	Time trade off analysis scaled to EQ-5D utility valuations

Table 44: Utility results from Cooper et al [113]

Utility scores	No high grade recurrence	High grade recurrence	>1 year post cystectomy	MIBC with metastases	First year post cystectomy (men)	First year post cystectomy (women)
Minimum	0.175					
Lower quartile	0.675	0.475	0.425	0.125	-0.042	0.104
Median	0.825	0.625	0.675	0.375	0.375	0.458
Mean	0.781	0.586	0.572	0.283	0.249	0.334
Upper quartile	0.925	0.775	0.825	0.600	0.625	0.708
Maximum	0.975	0.975	0.975	0.975	0.958	0.958

11.10 Annuitization and use of allocation keys

NA

11.11 Budget impact analysis

11.11.1 Treatment pathway

The budget impact analysis follows the treatment pathway as defined in section 7. It assumes that HAL-guided TUR-BT is potentially used for the initial TUR-BT procedure, following a presumptive diagnosis of NMIBC. In line with the DTC specification, HAL-guided TUR-BT will not be routinely used for any subsequent procedures.

11.11.2 Patient population

Estimates of the number of patients using of HAL-guided TUR-BT is predicated on the assumption that only patients undergoing a first TUR-BT procedure will be eligible. For this reason the relevant statistic is the annual incidence of NMIBC.

Data from NORDCAN [114] provide the numbers of cases of bladder and other urinary tract cancers registered in Denmark in 2021, broken down by age group. Of these, approximately 67% will be bladder cancers [115] and 75% of the bladder cancers will be NMIBC at the time of diagnosis [116]. The figures can be used to calculate the age-specific incidence rates of NMIBC, using the population estimates for 2021, provided in the same reference (Table 45).

Table 45: Estimated age-specific incidence of NMIBC (Denmark 2021)

Age group	N (2001)	Rate/100,000	
		All urinary tract cancer	NMIBC
0-9	0	0.0	0.0
10-19	0	0.0	0.0
20-29	12	1.5	0.8
30-39	9	1.3	0.6
40-49	43	5.8	2.9
50-59	217	27.0	13.6
60-69	589	87.9	44.2
70-79	963	166.2	83.5
80+	577	200.6	100.8
TOTAL	**2410**	**41.2**	**20.7**

Based on population projections for Denmark [117], and assuming that the age-specific incidence rate remains constant, we can then estimate the trend in NMIBC incidence over the period 2024-2028 (Table 46).

The data from this table are then used to estimate the total number of new NMIBC patients every year, who would be eligible for HAL-guided TUR-BT (Table 47).

Table 46: Projected population and new cases of NMIBC by age in Denmark from 2024-28

Age group	2024		2025		2026		2027		2028	
	Population	NMIBC	Population	NMIBC	Population	NMIBC	Population	NMIBC	Population	NMIBC
0-9	620,704	-	620,090	-	625,067	-	629,799	-	637,715	-
10-19	670,950	-	657,356	-	650,124	-	644,900	-	639,929	-
20-29	781,705	6	771,952	6	766,487	6	764,261	6	761,401	6
30-39	760,330	5	770,761	5	784,348	5	793,891	5	802,485	5
40-49	716,944	21	698,870	20	686,659	20	681,884	20	680,527	20
50-59	808,364	110	798,907	108	791,303	107	775,073	105	761,761	103
60-69	695,463	307	706,460	312	721,253	319	737,918	326	749,304	331
70-79	584,839	488	580,063	484	575,048	480	569,399	475	565,556	472
80+	319,202	276	336,920	293	357,001	311	378,194	331	396,685	346
TOTAL	**5,958,501**	**1,213**	**5,941,379**	**1,229**	**5,957,290**	**1,249**	**5,975,319**	**1,268**	**5,995,363**	**1,284**

Table 47: Summary of eligible population

Relevant patient population	Year 1	Year 2	Year 3	Year 4	Year 5
All newly diagnosed NMIBC	**1,213**	**1,229**	**1,249**	**1,268**	**1,284**

11.11.3 Resource use

There are two potential resource consequences of adopting HAL-TUR-BT alongside NBI-guided TUR-BT.

The first is the incremental cost per use associated with the technology. Over and above the standard procedure with NBI, the use of BLC requires a pre-operative intravesical infusion of hexaminolevulinate, which is followed by a waiting period of 1 hour to allow the fluorescent molecule to accumulate preferentially in malignant cells in the bladder. There is a dedicated DRG for the HAL-guided TUR-BT procedure (11MP17: DKK 20,385), which is associated with a tariff that is DKK 7,905 higher than the standard WLC/NIB-TUR-BT DRG (11MP24: DKK 12,480). This additional element captures the costs of supplying and administering the hexaminolevulinate, together with the associated staff costs. Similarly, the costs of servicing any associated capital investment or a leasing arrangement are intended to be captured within the DRG.

In all other regards, there would be no difference anticipated in the routine hospital care associated with HAL-guided TUR-BT than with NBI-guided TUR-BT.

The second cost component relates to any requirements to purchase or upgrade the equipment required for carrying out HAL-guided TUR-BT. Although there are exceptions, in general the equipment used to carry out NBI or WLC-guided TUR-BT cannot simply be repurposed for use with HAL. However, the actual investment required will vary substantially depending on the current situation in the hospital. HAL-guided TUR-BT was once the standard technology used in Denmark and it is still the preferred method to use in around 5% of hospitals. For these centres, no new investment would be required. For hospitals that used to use HAL-guided TUR-BT but have currently changed, it is likely that their equipment will need to be upgraded to current standards – potentially needing an investment in the region of DKK 100,000 – 200,000 (assumed). Finally, for those hospitals who do not have any level of equipment that is usable for HAL-guided TUR-BT, a significantly higher investment will be required – perhaps around DKK 500,000 (assumed).

Based on a potential number of patients per year of 1,213-1,284 and approximately 40 public hospitals in Denmark, we would estimate that each hospital would treat around 30 patients per year and would require a typical one-off investment of around DKK 300,000 to upgrade their equipment. Ongoing funding for depreciation against this capital purchase would be incorporated within the DRG differential.

Table 48: Costs of using HAL-guided TUR-BT (typical hospital).

Cost item			Unit cost, DKK	0	1	Ref
Costs not shared (per patient)	HAL-guided TUR-BT	DRG to cover package of care (11MP17)	20,385	0	30	110
Shared cost	Equipment upgrade	Implementation	250,000	0	40	Assumption
	Training, staff	Implementation/follow-up	0	0	40	
	Training, specialists	Implementation/follow-up	0	0	40	
	Support	follow-up	0	0	40	

Table 49: Costs of using NBI-GUIDED TUR-BT (typical hospital).

Cost item			Unit cost, DKK	0	1	Ref
Costs not shared (per patient)	NBI-guided TUR-BT	DRG to cover package of care (24MP17)	12,480	0	30	110
Shared cost	Equipment upgrade	Implementation	0	0	0	Assumption
	Training, staff	Implementation/ follow-up	0	0	0	
	Training, specialists	Implementation/ follow-up	0	0	0	
	Support	follow-up	0	0	40	

11.11.4 Market share

Table 50: Expected break-down of market shares of the intervention and comparator(s) if the Danish Health Technology Council recommends the intervention.

Intervention and comparator(s)	Current year	Year 1	Year 2	Year 3	Year 4	Year 5
Annual patient population	1,200	1,213	1,229	1,249	1,268	1,284
Market share of HAL-guided TUR-BT	5%	10%	15%	20%	25%	30%
Market share of NBI-guided TUR-BT	95%	90%	85%	80%	75%	70%

Table 51: Expected break-down of market shares of the intervention and comparator(s) if the Danish Health Technology Council does not recommend the intervention.

Intervention AND comparator(s)	Current year	Year 1	Year 2	Year 3	Year 4	Year 5
Annual patient population	1,200	1,213	1,229	1,249	1,268	1,284
Market share of intervention	5%	5%	5%	5%	5%	5%
Market share of comparator A	95%	95%	95%	95%	95%	95%

11.11.5 Likely five-year budget impact

Table 52: Expected 5-year budget impact calculation.

Patient population	Current year	Year 1	Year 2	Year 3	Year 4	Year 5
Total patient population of relevance for the intervention	1,200	1,213	1,229	1,249	1,268	1,284
Population expected to use the intervention	60	121	184	250	317	385
Scenario without the intervention						
Disease management	15,450,300	15,617,678	15,823,682	16,081,187	16,325,817	16,531,821
Total costs	15,450,300	15,617,678	15,823,682	16,081,187	16,325,817	16,531,821
Scenario with the intervention						
Disease management	15,450,300	16,097,117	16,795,207	17,562,189	18,330,525	19,069,326
Equipment upgrade*		500,000	500,000	500,000	500,000	500,000
Total costs	**n/a**	16,597,117	17,295,207	18,062,189	18,830,525	19,569,326
Budget impact	**n/a**	**979,439**	**1,471,525**	**1,981,002**	**2,504,708**	**3,037,505**

*assumes that 2 hospitals per year will upgrade their equipment at a mean cost of DKK 250,000 per centre

11.11.6 Benefits and savings

This budget impact analysis considers only the direct hospital costs attributable to the use of HAL-guided TUR-BT. No offset has been applied to take into account the consequential delay in requirement for repeat TUR-BT for recurrent disease, or potentially later-stage treatments. This aspect of the benefit has been fully explored in the cost utility model but, because it is essentially an opportunity cost, rather than a direct reduction in budgetary spend, it was decided to omit it. This means that the estimated cost impact may be considered an upper estimate.

The projected growth in market share is relatively modest, with an expected share of 30% at the end of year 5. One of the consequences of this is that many of the hospitals making a switch will have reached a point when their cystoscopy equipment will need replacing anyway. The additional costs assigned to upgrading their equipment may not, in consequence, be a true incremental exposure – instead they may simply reflect a re-direction of planned funding to equipment that can support HAL-guided TUR0BT

The final issue to consider is that we have assumed that HAL-guided TUR-BT will only be used for the first TUR-BT procedure, in line with the DTC specification. Experience from other countries , however, suggests

that BLC is also likely to be used in selected patients beyond their initial treatment, particularly where there is a particularly high risk of recurrence (eg patients with CIS) or in patients undergoing treatment with BCG. In this circumstance, the projected budget impact may be an underestimate of the potential exposure.

11.12 Estimation of hazard ratios from study summary data

Although studies in NMIBC frequently report time-to-event data, in general they fail to report the hazard ratio (HR). As this metric is central to any meta-analytical approach for comparison of recurrence-free and progression-free survival rates, a wide range of methods have been developed to estimate the HR and its variance. These have been summarised by Tierney et al [80], who aggregated the approaches into a single analytical strategy, which is widely used within Cochrane reviews, including by the team who carried out the meta-analyses of BLC vs WLC (Maisch et al [17]) and NBI vs WLC (Li et al [28]).

Tierney described 10 different approaches, depending on what information is available for the study:

Report presents hazard ratio (HR) and variance (V)
Report presents HR and observed-expected (O-E) from logrank test
Report presents O-E and V
Report presents observed and expected events on research and control
Report presents HR and confidence intervals (Cis)
Report presents HR and total events and randomisation ratio is 1:1
Report presents HR and events in each arm and randomisation ratio is 1:1
Report presents HR, total events and the numbers analysed on each arm and randomisation ratio need not be 1:1
Report presents p-value and total events and randomisation ratio is 1:1
Report presents p-value and events on each arm and randomisation ratio is 1:1
Report presents p-value, total events & numbers analysed on each arm and randomisation ratio need not be 1:1
Data extracted from Kaplan-Meier curves assuming constant censoring

A calculation spreadsheet is available as open-access software, to simplify the process of data entry and processing (http://www.biomedcentral.com/content/supplementary/1745- 6215-8-16-S1.xls)

For any given study, the software is likely to generate several different estimates, based on the data available and the analytical approach used. In this circumstance, the authors wmust make a qualitative decision as to the best estimate. In order to provide consistency between our de novo meta-analysis and the published results in the two Cochrane analyses (Maisch et al and Li et al), we used the same estimates of HR, LogHR, and SE(Log HR) as were published in the Cochrane reviews for 9 of the 10 papers included [2-4,7,9,10,19,76,77]. For the additional study included in the recurrence meta-analysis (Heer et al; [6]), the authors provided sufficient information in the published paper to allow direct input of the required HR and variance metrics.

12 Appendix 1: Network meta-analysis for recurrence data – extract from report

NMA: structure and assumptions

NMA serves to yield quantitative comparisons between treatments where direct evidence linking them may be incomplete, or not yet available. Where there exists evidence of how well two or more treatments may perform individually for example, there may not be evidence demonstrating how these compare against each other. NMA can therefore be an extremely useful tool in clinical medicine for guiding evidence-based decision-making.

Depending on the amount of direct evidence available, an NMA can be a mixed-treatment comparison (MTC), where some direct evidence between treatment arms is available, or an indirect treatment comparison (ITC), where no direct evidence is available.

For an NMA to be a valid analysis, the data it is modelled on must have a common reference treatment. If treatment A and B have been respectively compared to treatment C in multiple pairwise meta-analyses, then an indirect comparison between A and B can be estimated from the difference between the combined effects of A vs C, and B vs C [5]. This can only be true however, if the studies analysing treatments A and B against C are comparable in terms of baseline characteristics and outcomes. The assumption made here is that the more similar the study populations are, the more it can be said that the effect being evaluated (A vs B) is due to a real trend rather than random error arising from baseline heterogeneity.

Because there is no direct evidence linking the efficacy of HEX vs NBI in terms of the clinical outcomes of interest, this study proposes developing an ITC analysis for each outcome with WLC as the common comparator across all studies.