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Medical technology consultation: GID-MT553 Synergo for non-muscle-invasive bladder cancer

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **EAC Addendum** – an addendum to the independent report produced by the external assessment centre
3. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
4. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
5. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
6. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
7. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
8. **Patient Questionnaires** – patient commentary gathered by the NICE team on the technology.
9. **Patient Organisation submission** – a submission on the technology provided by a patient organisation.

10. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
11. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

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Medical technologies guidance
MT553 Synergo for non-muscle-invasive bladder cancer
External Assessment Centre report

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Number of attached appendices: 8

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Glossary

Term	Definition
Ablative dose	Higher dose of chemotherapy, used for patients with carcinoma in-situ.
Adjuvant dose	Standard dose of chemotherapy, used for patients with papillary tumours only.
Bacillus Calmette-Guérin (BCG)	Immunotherapy treatment for high-risk non-muscle invasive bladder cancer.
BCG-Failure	Overarching term for people in whom BCG treatment did not work. Encompasses people who are intolerant, refractory, resistant or who relapsed.
BCG-Intolerant	People with disease recurrence after incomplete BCG treatment due to toxicity or serious adverse events.
BCG-Refractory	Failure to achieve disease free state within a defined period of time due to persistent or rapidly recurring disease - usually 6 months after initial BCG treatment. People with stage or grade progression at 3 months despite BCG therapy.
BCG-Relapsing	People with recurrence after achieving disease-free state within a defined period of time – usually 6 months.
BCG-Resistant	People with recurrence or persistence of a lesser stage or grade after initial BCG that is resolved with further BCG.
Cystectomy Free Survival (CFS)	Period of time patients survive from treatment to having a radical cystectomy.
Carcinoma in-situ (CIS)	Early, high grade cancer cells present only in the inner lining of the bladder.
Electromotive Drug Administration (EMDA)	Treatment approach in which an electrical field is created across the bladder wall which helps to improve the absorption of chemotherapy.
Hyperthermic intravesical chemotherapy	Treatment approach during which heat is used to improve tissue penetration of the drug. This is achieved either through heating of the chemotherapy drug or via heating of the bladder wall while the drug remains tepid (See Radiofrequency induced chemohyperthermia).
Intravesical Chemotherapy	Chemotherapy is administered directly to the bladder via a urinary catheter.
Induction	Initial treatment cycle with the aim of destroying all tumour cells and achieving remission state.
Maintenance	Further regular treatment to help ensure cancer does not recur. This phase can last up to 2 years.
Muscle invasive bladder cancer (MIBC)	Transitional/urothelial cell bladder cancer that have grown into the muscle layer.
Mytomycin C	Chemotherapy drug for the treatment of non-muscle invasive bladder cancer. Also used for other cancer types.
Non-muscle invasive bladder cancer (NMIBC)	Early or superficial cancer confined to the lining of the bladder

Radiofrequency-induced chemohyperthermia (RF-CHT)	A type of chemotherapy treatment approach which involves heating the bladder wall to 42-44°C through controlled delivery of radiofrequency (non-ionising microwave radiation) using the Synergo device.
Risk group	Risk group refers to the risk of cancer spreading or recurring after treatment. There are 3 risk groups; low, intermediate and high.
Radiofrequency-Induced Thermo-Chemotherapeutic Effect (RITE)	See Radiofrequency-induced chemohyperthermia (RF-CHT).
Transitional cell carcinoma (TCC)	Cancer arising from the transitional cell lining of the bladder. Can also be referred to as urothelial cell carcinoma.
Transurethral resection of the bladder tumour (TURBT)	Removal of bladder tumour through the urethra. Usually the first treatment for early bladder cancer.
Urothelial cell carcinoma (UCC)	Cancer arising from the transitional cell lining of the bladder. Can also be referred to as transitional cell carcinoma.

Abbreviations

Term	Definition
BCG	Bacillus Calmette-Guérin
CFS	Cystectomy Free Survival
CI	Confidence interval
CIS	Carcinoma *in-situ*
CR	Complete Response
DFS	Disease Free Survival
DHSC	Department of Health and Social Care
EAC	External Assessment Centre
EMDA	Electromotive Drug Administration
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MIBC	Muscle invasive bladder cancer
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
MMC	Mitomycin C
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
NMIBC	Non-Muscle Invasive Bladder Cancer
OS	Overall Survival
PFS	Progression Free Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
RF-CHT	Radiofrequency-induced chemohyperthermia
RFS	Recurrence Free Survival
RITE	Radiofrequency-Induced Thermo-Chemotherapeutic Effect
SD	Standard deviation
TCC	Transitional cell carcinoma
TURBT	Transurethral Resection of Bladder Tumour
UCC	Urothelial cell carcinoma
VAS	Visual analogue scale
Vs.	Versus

Executive summary

Synergo is a minimally invasive technology, device assisted approach for the treatment of non-muscle invasive bladder cancer (NMIBC) which uses radiofrequency-induced thermo-chemotherapeutic effect (RITE) to deliver chemotherapy.

There is currently no recognised clinical pathway for device assisted chemotherapy, including Synergo, in the UK. However clinical expert input suggests that Synergo is an alternative to BCG and radical cystectomy for people with high risk NMIBC or people with intermediate risk NMIBC who are being managed on the high-risk pathway. It may be offered as first or second line treatment, and opinions vary as to where it is most appropriate.

The primary evidence comprises three randomised trials comparing Synergo to either standard intravesical chemotherapy or to BCG immunotherapy. A number of non-randomised studies of Synergo were also available. The evidence for Synergo is variable in terms of how the device is being used (place in the clinical pathway); regimens used (adjuvant or ablative); populations included (intermediate or high risk); comparators (MMC, BCG or EMDA) and outcome reporting. As a result, the clinical effectiveness of Synergo is not certain and may be dependent on a number of factors including stage/grade of tumour, presence/absence of CIS, previous treatments and reasons for using Synergo and MMC dose used. Broadly however, RITE using the Synergo device appears safe with most side effects limited to during treatment and resolving afterwards.

Economic modelling is limited by the availability of evidence to meet the most relevant pathways for NHS use. Synergo compared with MMC alone, for a patient group that are unable to use BCG, is found to be cost saving however, this does not reflect a common treatment choice. Modelling based on a small subgroup analysis comparing Synergo with BCG for 2nd line treatment found Synergo to be cost incurring. It may be cost-effective, however uncertainties around QALY values mean this cannot be properly assessed.

Synergo is likely to be a beneficial addition to the current treatment options for NMIBC, giving patients more options to avoid radical cystectomy for longer however

consideration should be given to the most appropriate place for Synergo to ensure most clinical and cost benefit.

1 Decision problem

The company has not proposed any change to the decision problem however they have stated that no robust evidence is available comparing Synergo with other device assisted hyperthermic chemotherapy options. The company included limited evidence comparing Synergo with electromotive drug administration. The EAC agrees with this and has made no changes to the decision problem (Table 1).

The EAC notes for clarity that the appropriate comparator for Synergo will depend on a number of factors including risk status, previous treatments a patient has received and suitability of specific treatments for patients. This is discussed in more detail in section 3.

Table 1: Summary of Decision Problem

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	People with intermediate or high-risk non-muscle-invasive bladder cancer (as determined by NICE guideline NG2)	None	The EAC notes that, according to NICE Guidelines, treatment options differ according to whether they have intermediate or high-risk NMIBC.
Intervention	Radiofrequency-induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 System	None	For clarity the EAC notes that the most commonly used chemotherapy agent is Mitomycin C (MMC) however epirubicin has also been used where there are MMC shortages or where patients are intolerant of MMC.
Comparator(s)	Intermediate and high-risk • Other device-assisted chemotherapy options (hyperthermic or electromotive drug administration) Intermediate-risk • Passive intravesical chemotherapy High-risk • Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy • Cystectomy	None	For clarity the EAC notes that the comparator for Synergo will depend on factors including risk status, previous treatments and patient suitability for specific treatments. The company submission state that no robust evidence is available for Synergo vs.. other device assisted hyperthermic chemotherapy options. Very limited evidence exists comparing Synergo with EMDA approach. The EAC notes that a lack of evidence does not mean that other device assisted options are not appropriate comparators.
Outcomes	• Recurrence rates and time to recurrence • Disease progression and changes to treatments	None	

	indicative of advanced disease • Rates of cystectomy • Complete response rate in papillary non-muscle-invasive bladder cancer • Complete response rate for carcinoma in-situ • Disease specific and overall survival • Health related quality of life • Treatment tolerability • Length of hospital stay • Treatment delivery rates in inpatient or outpatient settings • Rates of failed treatment delivery due to device related issues • Adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which can include scenarios in which different numbers and combinations of devices are needed when relevant.	None	
Subgroups	• People in whom previous intravesical therapy has failed • People with papillary tumours only • People with carcinoma in-situ, with or without papillary tumour (ablative therapy) • Subgroups based on risk group (intermediate or high), stage and grade of cancer • Intravesical agent used		

2 Overview of the technology

The Synergo system is a minimally invasive technology for the treatment of non-muscle invasive bladder cancer (NMIBC). The system comprises

- Radiofrequency Hyperthermia Device
- Transurethral Radiofrequency Ablation Applicator and Tubing Line Disposable Set
- Synergo System Software

The transurethral radiofrequency ablation applicator and tubing line disposable set has two versions. Version one (LI932B) is currently in use while the second (LI932B-S) will start distribution in 2022. The difference between the two versions is that the catheter tip is softer in the newer version. An additional Closed Drainage Set is available as an optional accessory. An updated version of the Synergo software (A_133) will be installed in the UK once Covid-19 restrictions are lifted, however the company state that the updated software will have only minor changes and none of the changes affect the device functionality (Table 2). Discussion with the company also indicated that the hardware will likely be updated in 2021, Covid permitting.

Table 2: Synergo Versions

Component	Version	Year
Required		
Radiofrequency Hyperthermia Device	SB-TS 101	2014
Transurethral Radiofrequency Ablation Applicator and Tubing Line Disposable Set	LI932B LI932B-S	2002 2020
Synergo System Software	A_132	2019
Optional		
Closed Drainage Set	CDS932B	2013

Synergo is a class IIb medical device manufactured by Medical Enterprises Group in the Netherlands. The CE mark covers the Synergo radiofrequency device for delivery of chemotherapy under hyperthermia and the catheter tubing lining set. The closed drainage set is an accessory to the radiofrequency device and is a Class IIa medical device. Documentation relating to the CE mark, declaration of conformity and instructions for use for Synergo have been provided to Cedar and checked. The CE mark covers Synergo and is valid until 22/05/2024. The company has also submitted details to the MHRA to obtain UK conformity assessment (UKCA) which will be a requirement from 2023.

The indicated use is for treatment of NMIBC. Synergo is a minimally invasive device which uses radiofrequency-induced thermo-chemotherapeutic effect (RITE) to improve how chemotherapy is given to treat non-muscle-invasive bladder cancer. It delivers controlled radiofrequency (non-ionising microwave radiation) which heats the superficial layers of the bladder wall while simultaneously flushing the bladder with a chemotherapy drug (thermo-chemotherapy). To prevent over-heating, the drug solution is continuously pumped out of the bladder, cooled and recirculated.

Synergo represents an additional treatment option for people with intermediate-risk or high-risk NMIBC whose disease has recurred following intravesical BCG therapy, patients who are refractory to BCG, patients who are resistant to BCG or patients who cannot tolerate BCG. Synergo can also be used in response to patient preference or when supply of the drug is limited or delayed.

The company claim there are a number of benefits to the patient including reduced rates of tumour recurrence, reduced disease progression, and reduced need for cystectomy in some people which results in reduced morbidity and mortality associated with cystectomy. Use of Synergo does not require a general anaesthetic, however the company state that treatment is usually conducted using local anaesthetic lubricating gel. In addition, the company claim several benefits to the healthcare system including reduced number of cystectomies potentially leading to fewer post-surgery

complications, reduced hospital stay, treatment moved from an inpatient to an outpatient setting and reallocation of hospital resources.

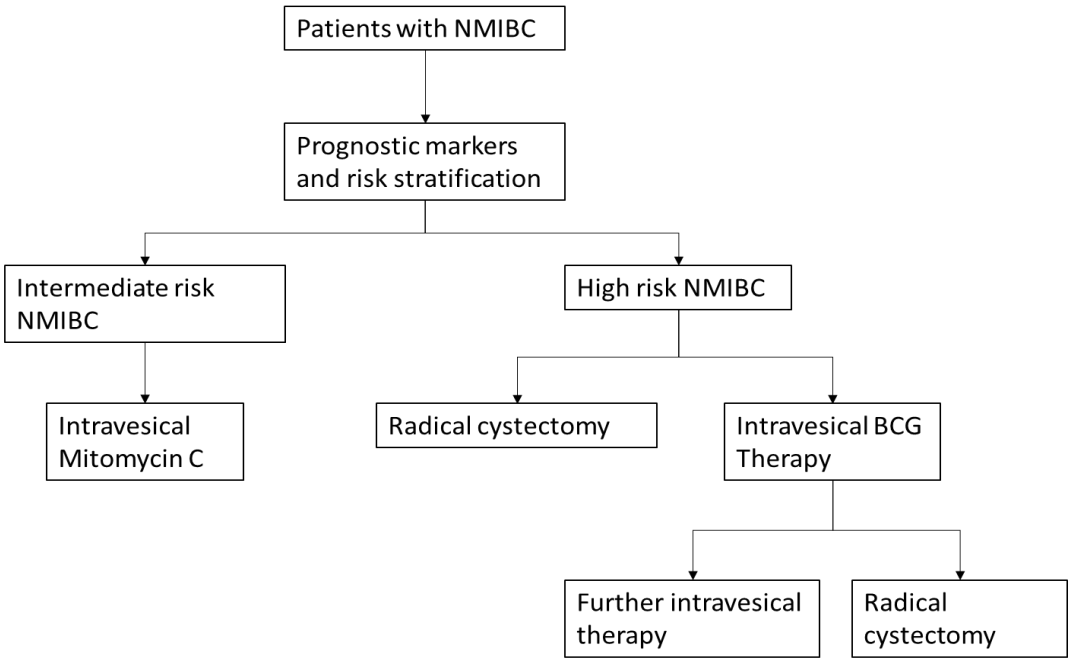
3 Clinical context

People with suspected bladder cancer are usually offered a transurethral resection of bladder tumour (TURBT) which involves complete removal of all visible papillary tumours where feasible and obtaining a sample for biopsy. The outcome of TURBT is used to stratify cancers according to risk (high, intermediate or low risk) depending on size and number of tumours, histological stage and grade of cancer.

The company defined care pathway for people with NMIBC is based on NICE Guideline 2 for diagnosis and management of bladder cancer and outlined in Figure 1.

It is not clear from the company submission what is the proposed place in the pathway for Synergo. The company appear to propose that Synergo is an alternative to passive intravesical mitomycin C for people with intermediate risk NMIBC and as an additional treatment option for people with high risk NMIBC as an alternative to further intravesical therapy.

Figure 1: Company representation of the current treatment pathway for intermediate and high risk NMIBC



The EAC has revised the clinical pathway based on the recommendations in the NICE guideline for bladder cancer (NG2) and discussions with clinical experts (See EAC correspondence log for details). Discussion with clinical and patient experts highlighted some key differences between the company proposed pathway and what happens in clinical practice. In particular, clinical experts noted that people with intermediate risk NMBIC who do not respond to MMC will have their treatment managed as if they had high-risk NMIBC and will be treated with intravesical BCG unless histology suggests progression to high risk disease when radical cystectomy will be offered.

The EAC notes that the current clinical pathway does not include device assisted chemotherapy as a treatment option for NMIBC but considers that the most likely place in the current clinical pathway for RITE delivered using Synergo is primarily as a second line treatment option for

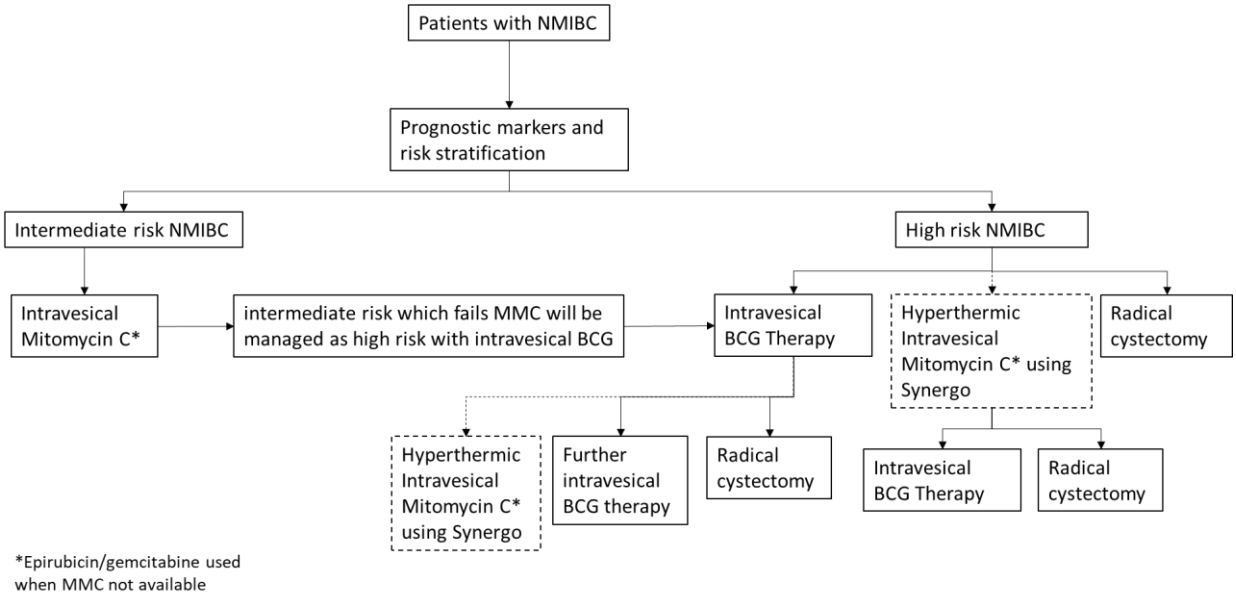
- people with high-risk NMIBC that do not respond to BCG immunotherapy or with recurrence following treatment with BCG

- alternative to radical cystectomy for people with high-risk NMIBC in whom BCG immunotherapy is contraindicated or is not tolerated

It is possible that for people with high-risk NMIBC, RITE using Synergo might be a suitable first line treatment option (as an alternative to BCG or radical cystectomy) though the clinical experts consider 2nd line to be the most likely.

The EAC proposed clinical pathway with the addition of Synergo is outlined in Figure 2.

Figure 2: EAC proposed treatment pathway with Synergo



The EAC notes that Synergo is primarily used with mitomycin C (MMC) however the instructions for use state that the choice of chemotherapeutic agent is the responsibility of the prescribing physician and further, that clinical experts have reported using epirubicin with the Synergo device due to shortages of MMC. Clinical evidence reviewed by the EAC also suggests that epirubicin is used where MMC cannot be used such as due to allergy or intolerance.

The EAC has identified the following guidelines and guidance as relevant to the decision problem.

- NICE Guideline [NG2]: Bladder Cancer: Diagnosis and Management

- Interventional Procedures Guidance [IPG628]: Intravesical microwave hyperthermia and chemotherapy for non-muscle invasive bladder cancer

- Interventional Procedures Guidance [IPG638]: Electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer

- Cancer Service Guidance [CSG2]: Improving Outcomes in Urological Cancers

- European Association of Urology (EAU) Guidelines: Non-muscle-invasive Bladder Cancer

Special considerations, including issues related to equality

Bladder cancer is more common in men than in women, and most cases happen in people aged 60 and over. Women diagnosed with bladder cancer are more likely to present at an advanced stage and have worse prognosis and outcomes than men. Bladder cancer is more common in white people than in black or Asian people. Age, sex and race are protected characteristics under the Equality Act. People with cancer are considered to have a disability under the Equality Act.

The EAC noted that adverse events and treatment side effects may differ for male and female patients. Expert input suggested that male patients have a risk of urethral injury due to difficulties inserting the rigid catheter. For female patients, there is a risk of from residual chemotherapy leaking and potentially causing injury to the genital area when the catheter is removed.

The EAC has not identified any additional equalities concerns.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The company's search strategy was comprehensive using a combination of free text terms and, where appropriate, indexed terms. The search was conducted across 3 databases, identifying in total after deduplication, 110 references. It is likely that the company have identified all relevant literature,

however in order to be completely confident of this, the EAC conducted their own systematic search. Details of the company and EAC searches are provided in appendix A. The EAC literature searches identified 458 references, these were screened by title and abstract in accordance with the scope by one researcher. 103 were selected for further screening and full texts were retrieved and reviewed by one researcher, queries were checked by another researcher. All studies included by the company were also checked for eligibility against the scope before final selection for inclusion was concluded. PRISMA flowcharts outlining the number of studies excluded at each stage for both the company and EAC are in Appendix A.

The inclusion and exclusion criteria applied by the company are summarised in table 3. The EAC consider the inclusion and exclusion criteria to be appropriate.

Table 3: Company inclusion and exclusion criteria

Inclusion criteria	
Population	People with intermediate or high-risk NMIC who are • BCG unresponsive/resistant • Indicated for BCG after failing previous instillations other than BCG but who cannot tolerate it, do not wish to be treated with it, are contraindicated or cannot be treated due to supply shortage.
Comparator	None defined
Interventions	Radiofrequency induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 system
Outcomes	• recurrence rates • time to recurrence • disease progression • changes to treatment indicative of advanced disease • rates of cystectomy • complete response rate for carcinoma in situ • disease specific and overall survival • health related quality of life, treatment tolerability • length of hospital stay • treatment delivery rates in outpatient or inpatient settings • device related adverse events
Study design	Original clinical research Prospective or retrospective studies with one or more arms that report outcome data by target population
Other	English language studies only
Exclusion criteria	
Population	None reported
Interventions	None reported
Outcomes	None reported
Study design	Insufficient detail of methods and results to enable data extraction such as dosage of drug or number of treatments administered not reported
Other	None reported

4.2 *Included and excluded studies*

The company submission included 24 studies from 31 publications, including 16 studies reported in 20 publications (3 of which were abstracts not full publications) to inform the evidence and 5 systematic reviews which were not used to inform the evidence as the company chose to use the primary studies

instead. The company submission included an additional 6 abstracts (covering 3 studies) as relevant to the decision problem.

The EAC largely agreed with the inclusions in the company submission with some small differences, including a total of 19 studies (from 20 full publications). The EAC also identified a number of systematic reviews of device assisted chemotherapy, one of which (Colombo 2016) specifically reviewed device assisted chemotherapy delivered using Synergo. The EAC considered that as the systematic reviews included a broad range of studies, some of which did not include the Synergo device as well as because the reviews relating to Synergo reported narrative results, the primary studies should be appraised instead.

The EAC identified abstracts relating to 14 studies reported in a total of 19 abstracts. One additional, unpublished data abstract from a thesis was provided by the company and included for information only (Hiebeler 2020) – this is a small section of a German language thesis which has been translated and therefore accuracy of content cannot be verified by the EAC. Where an abstract reported on a study that had an available full publication, the abstract was excluded by the EAC. The EAC note that the company submission did not include data extraction or critical appraisal of 4 studies (Colombo 1995, Colombo 1996, Sooriakumaran 2016, Volpe 2012), however they were included as a source of evidence to support claimed benefits of Synergo.

The EAC has excluded two studies that were included in the company submission (Colombo 1995 and Colombo 1996) as the study dates overlap and it was unclear whether there was patient overlap. The EAC considers that the series of papers relating to the randomised trial including a pilot safety and tolerability study (Colombo 2001), short term trial results (Colombo 2003) and long-term trial results (Colombo 2011) to be of more benefit to decision making primarily as these are comparative studies. The EAC does not consider that exclusion of these two early studies will have an impact on the evidence base as both studies would be considered to be of low quality due to the retrospective study design as well as uncertainty over the possibility of

overlap in the patient populations. A comparison of the individual studies included by the Company and the EAC is included in table 4.

Table 4: Company and EAC study selection comparison

Study	Included in Company Submission	Included in EAC Assessment Report	EAC Comment
Arends 2016	✓	✓	Randomised trial. An additional abstract was included by the company as a prior publication but has been excluded by the EAC in favour of the full publication.
Arends 2014	✓	✓	Non-randomised study with no apparent overlap with Arends 2016.
Bahouth 2016	✓	X	Systematic review referenced but not discussed in company submission.
Brummelhuis 2021	✓	✓	No change
Colombo 1995	✓	X	No data extraction in the company submission. Reference to this paper is as supporting evidence for claimed benefits and was not included in the clinical evidence section or as part of the PRISMA flow diagram. Study dates: 1988-1992 The EAC has excluded this publication as it is unclear whether there is overlap between this and Colombo 1996 and considers the series of studies relating to the clinical trial to be more informative.
Colombo 1996	✓	X	No data extraction in the company submission. Reference to this paper is as supporting evidence for claimed benefits and was not included in the clinical evidence section or as part of the PRISMA flow diagram. Study dates: 1989-1993 The EAC has excluded this publication as it is unclear whether there is overlap between this and Colombo 1995 and considers the series of studies relating to the clinical trial to be more informative.
Colombo 2001	✓	✓	Safety and feasibility study Included in company reference list and in supporting evidence in the claimed benefit table but no data extraction
Colombo 2003	✓	✓	Randomised Trial – Short term results
Colombo 2011	✓	✓	Randomised Trial – Long term results
Colombo 2016	✓	X	Systematic review referenced and included in PRISMA but not discussed in company submission. EAC has mentioned this study for reference in section 7 but not data extraction/critical appraisal has been done as primary studies are included.
Erturhan 2015	✓	✓	No change

Gofrit 2004	✓	✓	No change
Kiss 2015	✓	✓	No change
Lammers 2011	✓	X	Systematic review referenced and included in PRISMA but not discussed in company submission.
Maffezzini 2014	✓	✓	No change
Moskovitz 2005	✓	✓	No change
Moskovitz 2012	✓	✓	No change
Nativ 2009	✓	✓	No change
Sooriakumaran 2016	✓	✓	No data extraction in the company submission. Reference to this paper is as supporting evidence for claimed benefits and was not included in the clinical evidence section or as part of the PRISMA flow diagram. EAC has included the study in data extraction and evidence summary
Soria 2015	✓	X	Systematic review referenced and included in PRISMA but not discussed in company submission.
Sri 2020	X	✓	Additional study identified by EAC. Retrospective comparison of cystectomy following Synergo compared with either primary cystectomy or cystectomy following BCG failure
Tan 2019	✓	✓	Randomised trial. An additional 2 abstracts were included by the company as a prior publication but have been excluded by the EAC in favour of the full publication.
van der Heijden 2004	✓	✓	No change
van valenberg 2016	✓	X	Systematic review referenced and included in PRISMA but not discussed in company submission.
van valenberg 2018	✓	✓	No change
Volpe 2012	✓	✓	No data extraction in the company submission. Reference to this paper is as supporting evidence for claimed benefits and was not included in the clinical evidence section or as part of the PRISMA flow diagram. EAC has included the study in data extraction and evidence summary
Witjes 2009	✓	✓	No change
Witjes 2019	✓	X	Letter to editor, no data.

The EAC noted that there were some key themes emerging from the evidence base including

- comparative studies are limited and the comparators are variable (standard MMC, BCG, EMDA or no comparator). It is unclear whether Synergo should be offered only to people who are refractory to BCG (2nd line) or who are intolerant to BCG (any line) or whether Synergo is an alternative to standard MMC. It should be noted that in some

studies, patients are treated with epirubicin if they are allergic/intolerant to MMC.

- risk classification for included patients varied (intermediate risk, high risk or both and how risk was assessed). Clinical experts indicated that if using the EAU risk classification system, patients classified as intermediate risk might be classified high risk in the UK (see correspondence log for details). This is unlikely to change the approach to device assisted chemotherapy but may impact what patients would be eligible as currently device assisted chemotherapy is not commonly used for intermediate risk patients in the UK.

- treatment regimens depended on whether patients were treated prophylactically (adjuvant regimen) or therapeutically (ablative regimen) and studies included a mix of adjuvant and ablative regimens. It is unclear whether comparisons between adjuvant and ablative regimens are applicable to UK practice as clinical experts suggest that people with CIS would be treated with an ablative dose.

- the evidence base includes subgroup analysis reporting comparisons such as previous treatments vs. no previous treatments; patients intolerant to BCG vs. non-responders to BCG; responses in people with or without CIS.

The EAC suggests that these themes may have an impact on the generalisability of the evidence and that the degree to which any of the evidence can be considered applicable and informative to the UK setting specifically will depend on the clinical pathway for device assisted chemotherapy. As there is currently no defined place in the clinical pathway for device assisted chemotherapy, the EAC considers that the evidence presented in this report may contribute to identifying the most appropriate place in the pathway for device assisted chemotherapy.

A high-level summary of the included studies (full publications) is presented in Table 5 and Table 6. It should be noted that the traffic light system used in table 5 and table 6 relates only to whether the study can be considered

applicable to the decision problem as outlined in the scope and, while briefly highlighting some of the potential limitations and areas for concern, is not a quality appraisal. Critical appraisal of all included studies is reported in section 5 and appendix C.

Table 5: Comparative Studies

Study	Participants, Intervention(s) and Comparator(s)	Outcomes	EAC comments
Arends 2016 ***Design***: RCT ***Location***: 11 centres from 6 countries (Israel (3), Italy (3), the Netherlands (1), Austria (1), France (2), Belgium (1)) ***Setting***: Outpatients ***Follow-up*** At least 24 months after randomisation	***Participants***: 190 patients with intermediate and high-risk NMIBC according to 2001 European Association of Urology risk category definitions *Applicability*  ***Intervention***: Intravesical Chemohyperthermia with MMC using Synergo system (n=92) *Adjuvant regimen* comprising 2x20mg MMC in 50ml distilled water, local hyperthermia 42±2C for 6 weekly sessions (induction) followed by 5 maintenance sessions at 6-week intervals in year 1 ***Comparator***: BCG Immunotherapy (n=98) *Regimen* BCG as a 1-year schedule, 6 weekly induction sessions and 3 weekly maintenance sessions at months 3, 6 and 12. BCG was retained in the bladder for 120 mins *Applicability* 	***Primary*** Recurrence free survival (RFS) in the intention to treat and per protocol analyses ***Secondary*** • Proportion of complete response (CR) in CIS patients (defined as negative biopsy and/or cytology at 3 months) • Disease progression to higher than stage T1 and/or metastatic disease • Safety *Applicability* 	• Study is underpowered due to early closure (slow recruitment) • Study population, comparator and outcomes are all applicable to decision problem although this study does not include UK patients. • Some consideration to whether patients classified as intermediate risk would be managed as high risk in the UK. *Overall Applicability* 

Colombo 2001 ***Design:*** Pilot feasibility study (prospective, non-randomised, comparative) ***Location:*** Italy ***Setting:*** Outpatients ***Follow-up*** Not reported	***Participants***: 80 patients with superficial transitional bladder cancer (Ta-T1, G1-G2, recurrent, single small [<2cm] bladder tumours previously untreated by MMC) • Hyperthermic regimen: 40mg in 50ml distilled water at 42.5C, 4 weekly sessions (n=29) • EMDA regimen: 40mg MMC in 150ml distilled water and 20mA of electric intensity (n=15) • Standard MMC: 40mg in 50ml saline, 4 weekly sessions (n=36) *Applicability*  ***Intervention:*** Device assisted MMC (hyperthermic or electromotive) *Hyperthermic Regimen* Synergo system with 40mg MMC in 50ml distilled water, local hyperthermia at a mean temp. of 42.5C for 4 weekly sessions, mean session duration was 60mins *Electromotive (EMDA) regimen* Intravesical MMC solution according to EMDA procedure with 40mg MMC in 150ml of distilled water and 20mA of electric intensity for 4 weekly sessions, 20min duration ***Comparator:*** Standard intravesical MMC *Regimen:* 40mg in 50ml saline for 4 weekly sessions *Applicability* 	Feasibility and tolerability of the different treatment approaches *Applicability* 	• Unclear whether the study included high risk NMIBC or just intermediate risk • Safety and tolerability only, therefore results likely to have limited applicability • Not a UK based study and unclear how applicable the comparison between hyperthermic MMC and standard intravesical MMC is to the UK setting *Overall Applicability* 

Study	Participants, Intervention(s) and Comparator(s)	Outcomes	EAC comments
Colombo 2003 Colombo 2011 ***Design:*** RCT ***Location:*** Italy, Israel ***Setting:*** Outpatients ***Follow-up*** 2 years (Colombo 2003) 10 years (Colombo 2011)	***Participants:*** 83 patients with primary/recurrent stage Ta and T1, grade G1 to G3 TCC of the bladder, treated by TURB. *Applicability*  ***Intervention:*** RITE Chemotherapy (n=42) *Adjuvant Regimen:* Synergo system with 2x20mg MMC in 50ml distilled water, local hyperthermia at a mean temp. of 42C±2C ***Comparator:*** Standard intravesical MMC (n=41) *Regimen* 40mg MMC in 50ml distilled water Patients in both groups received 8 weekly, 60 min treatment sessions, followed by 4-monthly sessions. *Applicability* 	Short-term (Colombo 2003) • Response to treatment • Side effects and clinical complications Long-term (Colombo 2011) • Disease free survival • Progression and radical cystectomy • Bladder preservation rate • Death *Applicability* 	• Not a UK based study and unclear how applicable the comparison between hyperthermic MMC and standard intravesical MMC is to the UK setting • Adjuvant regimen of hyperthermic MMC is used (Prophylactic) which is applicable to UK setting. *Applicability* 

Study	Participants, Intervention(s) and Comparator(s)	Outcomes	EAC comments
Tan 2019 ***Design:*** RCT ***Location:*** UK ***Setting:*** Outpatients ***Follow-up*** 24 months	***Participants:*** 104 patients with recurrence of intermediate or high risk NMIBC according to European Association of Urology Guidelines following induction or maintenance BCG randomised to RITE (n=48) or control (n=56) *Applicability*  ***Intervention:*** radiofrequency-induced thermo-chemotherapy effect (RITE) *Adjuvant Regimen:* • Synergo system with 2x20mg MMC in 50ml sterile water, local hyperthermia at 42±2C for 6 weekly induction instillations • Dose reduction was not permitted • Maintenance treatment was one instillation every 6 weeks for 1st year and one every 8 weeks for 2nd year for patients who were disease free 3 months after treatment commencement ***Comparator:*** BCG Immunotherapy ***or*** institutional standard of care defined at randomisation *BCG Regimen:* 6 weekly instillations of BCG (50ml saline) followed by maintenance therapy of 3 consecutive weekly instillations at 3, 6, 12, 18 and 24 months *Applicability* 	Primary Outcomes • Disease free survival time • 3-month complete response for patients with biopsy proven carcinoma in-situ (CIS) at randomisation Secondary Outcomes • Progression free survival (PFS) time • Overall survival (OS) time • Disease-specific survival time • Recurrence free survival (RFS) time in non-CIS patients • Health related quality of life • Safety and tolerability *Applicability* 	• UK based study comparing hyperthermic MMC with BCG immunotherapy which is likely to be applicable to the UK setting based on discussions with clinical experts • Comparator also included 'institutional standard of care' as an option, patients received either BCG (n=33), MMC alone (n=10) or MMC with EMDA (n=13) • No subgroup analyses are included for the different treatment types *Overall Applicability* 

Study	Participants, Intervention(s) and Comparator(s)	Outcomes	EAC comments
Sri 2020 ***Design:*** Retrospective comparative case review ***Location:*** UK ***Setting:*** Not reported ***Follow-up*** 24 months (median)	***Participants:*** 138 patients (36 treated with intervention, 102 not treated) who underwent radical cystectomy for high risk NMIBC as primary treatment or following treatment failure *Applicability* 🟡 ***Intervention:*** Radiofrequency-induced chemohyperthermia • Synergo system used (40mg MMC at 42C±2C • CIS patients received an 8 week induction cycle and no CIS patients received a 6 week induction cycle. • New referrals received a re-do TUR, urine cytology and upper tract imaging prior to induction. • Failure at induction would lead to a recommendation for radical cystectomy • All patients received maintenance instillation every 6 weeks for the first year followed by every 8 weeks for the second year ***Comparator:*** No Radiofrequency-induced chemohyperthermia (primary cystectomy or BCG) *Applicability* 🟢	• Intra-operative difficulty • Operative time • Intraoperative blood loss • Length of stay • 90-day readmission *Applicability* 🟢	• Results may have limited relevance as patients in this cohort had a radical cystectomy as primary treatment or following treatment failure • The question of whether treatment with radiofrequency-induced chemohyperthermia has an impact on outcomes for patients who go on to radical cystectomy may have more relevance to the wider clinical pathway than for Synergo specifically ***Overall Applicability*** 🟡
Applicable 🟢 Somewhat Applicable 🟡 Not Applicable 🔴			

Table 6: Non-Comparative Studies

Study	Participants and Intervention(s)	Outcomes	EAC comments
Arends 2014 ***Design:*** Retrospective review of medical records ***Location:*** The Netherlands ***Setting:*** Not reported ***Follow-up*** 75.6 months (median)	***Participants:*** 160 patients with NMIBC who are refractory to regular intravesical treatment *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • 6-8 weekly sessions followed by maintenance sessions at 6 weekly intervals during year 1 *Adjuvant:* • 20mg/50ml MMC or 25mg/50ml Epirubicin if allergic to MMC *Ablative* • 40mg/50ml MMC or 50mg/50ml Epirubicin if allergic to MMC • 2 30-minute cycles with bladder wall hyperthermia to a mean 42C±2C *Applicability* ●	Recurrence free survival *Applicability* ●	• Retrospective, non-comparative study will have limited value in informing relative effectiveness of treatments • Adjuvant (prophylactic) and ablative (therapeutic) regimens are included but outcomes are not reported separately • Patients refractory to regular intravesical treatment and most patients (80.6%) had previously been treated with BCG, this is therefore applicable to the decision problem. ***Overall Applicability*** ●
Brummelhuis 2021 ***Design:*** Retrospective review of medical records ***Location:*** The Netherlands ***Setting:*** Not reported	***Participants:*** 274 patients (299 in safety analysis) with histologically proven NMIBC *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • Adjuvant and Ablative regimens used. • Six-weekly induction followed by maintenance regimen of 1 instillation every 6 weeks for year	Outcomes differed for different patient groups *CIS patients* • Complete Response • Durable response *Papillary patients* • Recurrence free survival *All patients* • Overall survival	• Retrospective, non-comparative study will have limited value in informing relative effectiveness of treatments • Some patients were treated with epirubicin which may be reflective of UK practice when there are shortages of MMC or where patients are intolerant of MMC • Study compares the outcomes of an ablative regimen with an adjuvant regimen these

Study	Participants and Intervention(s)	Outcomes	EAC comments
Follow-up 24 months	1. One instillation every 8 weeks for year 2 and every 12 weeks thereafter. • Treatment sessions comprised 2 30 min cycles with intravesical MMC (20mg adjuvant or 40mg ablative) or epirubicin (30mg adjuvant or 50mg ablative) at 40.5-44C *Applicability* ●	• Relative survival • Cancer specific survival *Applicability* ●	regimens would be used for different patients in the UK. ***Overall Applicability*** ●
Erturhan 2015 ***Design:*** Prospective study. Initially planned to be a randomised study with BCG. However, the BCG arm of the study was cancelled due to global BCG supply problem ***Location:*** Turkey ***Setting:*** Not Reported ***Follow-up:*** 16.4 months (median)	***Participants:*** 26 patients with high risk NMIBC *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo Single dose of intravesical mitomycin C (40mg) at 42-44C immediately after TURBT using the Synergo system SB-TS 101. Follow-up treatment consisted of once a week during the first 6 weeks and one a month for six months *Applicability* ●	• Rate of recurrence • Recurrence free survival • Progression • Adverse events *Applicability* ●	• Non-comparative study will have limited value in informing relative effectiveness of treatments • Possible limited applicability of the regimen used in this study ***Overall Applicability*** ●
Gofrit 2004 ***Design:*** Retrospective cohort study	***Participants:*** 52 patients with high grade superficial bladder cancer *Applicability* ● ***Intervention***: Radiofrequency-induced chemohyperthermia using Synergo at 42±2C for 40mins	Outcomes differed for different regimens Prophylactic group: • Tumour recurrence • Tumour progression • Need for cystectomy	• Non-comparative study will have limited value in informing relative effectiveness of different treatments Study reports results by regimen (adjuvant or ablative). ***Overall Applicability*** ●

Study	Participants and Intervention(s)	Outcomes	EAC comments
Location: Italy, Israel, Germany and The Netherlands ***Setting***: Not reported ***Follow-up*** 15.2 months (median)	• *Adjuvant (prophylactic) regimen* – 2x20g MMC after complete transurethral resection of all tumours • *Ablative (therapeutic) regimen* – 2x40mg MMC when visible tumour is seen on video-cystoscopy or bladder biopsies were positive for carcinoma in situ (CIS) • Epirubicin was given to 4 patients who were allergic to MMC (3 from ablative group) • Treatment regimen included eight weekly sessions, followed by four monthly sessions *Applicability* ●	Ablative group: • Complete ablation of tumour *Applicability* ●	
Kiss 2015 ***Design:*** Prospective, non-comparative cohort study ***Location:*** Switzerland ***Setting:*** Urology Department ***Follow-up*** 50 months (median)	***Participants:*** 21 patients with histologically confirmed recurrent NMIBC who were not fit for or had refused radical cystectomy. *Applicability* ● ***Intervention***: Radiofrequency-induced chemohyperthermia using Synergo • Ablative regimen: 12 weekly sessions of 2x40mg MMC in 50ml sterile water at 42±2C • Cystoscopy after 6 sessions to evaluate treatment response. • Adjuvant Regimen: 2x20mg MMC in 50ml sterile water at 42±2C weekly for 6 weeks. *Applicability* ●	Recurrence defined as • No recurrence – negative bladder wash cytology and negative cystoscopy at follow-up visits • Recurrence – biopsy-confirmed visible tumour or positive random biopsies • Adverse events *Applicability* ●	• Non-comparative study will have limited value in informing relative effectiveness of different treatments • Adjuvant and ablative regimens are used and results are not reported separately ***Overall Applicability*** ●

Study	Participants and Intervention(s)	Outcomes	EAC comments
Maffezzini 2014 ***Design:*** Cohort Study ***Location:*** Italy ***Settings:*** Outpatients ***Follow-up*** 38 months (median)	***Participants:*** 42 consecutive patients with high risk NMIBC *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • 40mg MMC in 50ml distilled water, bladder wall temp of 42.5±1.5C • 50mg Epirubicin used for patients with persistent intolerance to MMC • 4 weekly sessions, followed by 6 sessions delivered every 2 weeks and then 4 monthly sessions for a total of 14 sessions over 8 months *Applicability* ●	• Disease free interval • Treatment toxicity *Applicability* ●	• Non-comparative study (not clear if prospective or retrospective) will have limited value in informing relative effectiveness of different treatments • Only high-risk patients are included so potentially limited generalisability to intermediate risk patients • EAU risk classification system used ***Overall Applicability*** ●
Moskovitz 2005 ***Design:*** Retrospective cohort study ***Location:*** Israel ***Setting:*** Not reported ***Follow-up*** Prophylactic group – up to mean 431 days Ablative group – mean 169.4 days	***Participants:*** 32 patients with multiple or recurrent Ta or T1 transitional cell carcinoma of the bladder *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • Adjuvant (Prophylactic) regimen – 40g MMC after complete transurethral resection of all tumours • Ablative (therapeutic) group – 80mg MMC in patients in those with viable tumours *Applicability* ●	Outcomes differed for different treatment regimens Prophylactic group: • Tumour recurrence by biopsy Ablative group • Complete ablation of the tumour proven by multiple random biopsies or mapping TUR-T and urine cytology *Applicability* ●	• Non-comparative study will have limited value in informing relative effectiveness of different treatments • Study reports results by regimen (adjuvant or ablative) however the use of the ablative regimen may have limited applicability to the UK setting ***Overall Applicability*** ●

Study	Participants and Intervention(s)	Outcomes	EAC comments
Moskovitz 2012 ***Design:*** Retrospective Review of patient records ***Location:*** Israel ***Setting*** Outpatients ***Follow-up*** 5 years	***Participants*** 92 patients with intermediate of high risk NMIBC *Applicability* 🟢 ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • Adjuvant (Prophylactic) regimen – 40g MMC after complete transurethral resection of all tumours • Ablative (therapeutic) group – 80mg MMC in patients in those with viable tumours *Applicability* 🟢	Outcomes differed for different treatment regimens Adjuvant protocol • Tumour Recurrence • Bladder Preservation Rate Neo-adjuvant protocol • Response • Bladder preservation rate Treatment complication and adverse events *Applicability* 🟢	• Non-comparative study will have limited value in informing relative effectiveness of different treatments • Unclear if there is any population overlap with Moskovitz 2005 • Study reports results by regimen (adjuvant or ablative) however the use of the ablative regimen may have limited applicability to the UK setting ***Overall Applicability*** 🟢
Nativ 2009 ***Design:*** Retrospective Data Review ***Location:*** Israel, Italy, Netherlands ***Setting:*** Outpatients ***Follow-up*** 16 months (median)	***Participants*** 111 patients with biopsy proven urothelial cell carcinoma of the bladder recurring after previous BCG therapy Presence of CIS was an exclusion criterion *Applicability* 🟡 ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo. Used prophylactically • Weekly for 6 weeks (temp 41-44°C) with 2x20mg MMC in 50ml sterile water. • 6 maintenance sessions at 4-6 weeks intervals *Applicability* 🟢	• Disease Free Survival • Recurrence Free Survival *Applicability* 🟢	• Non-comparative study will have limited value in informing relative effectiveness of different treatments • Some subgroup analysis between different BCG treatment groups (BCG refractory, resistant, relapse, intolerant) • Patients with CIS were excluded ***Overall Applicability*** 🟡

Study	Participants and Intervention(s)	Outcomes	EAC comments
Sooriakumaran 2016 ***Design:*** Longitudinal cohort study (retrospective) ***Location:*** UK ***Setting:*** Outpatients ***Follow-up*** 27 months (median) for TTP 31 months (median) for OS 29 months (median) for CSS	***Participants:*** 97 patients with high risk NMIBC (EAU Guideline) *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • Weekly 1-hour treatments for 6-8 weeks (temp 41-44°C) with 40mg MMC in 50ml sterile water. • Patients with initial CR/PR had 2-year maintenance regimen (20mg in 50ml every 6 weeks for year one and every 8 weeks for year 2) *Applicability* ●	• Time to progression survival (TTP) • Overall survival (OS) • Cancer specific survival (CSS) • Adverse events *Applicability* ●	• UK based study • Only included high-risk patients so limited generalisability to intermediate risk patients ***Overall Applicability*** ●
Van der Heijden 2004 ***Design:*** Retrospective, non-comparative study ***Location:*** Netherlands, Israel, Germany, Italy ***Setting:*** Outpatients ***Follow-up*** 24 months	***Participants:*** 90 patients with histologically confirmed Ta or T1 multiple or recurrent superficial transitional cell carcinoma of the bladder *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • 2x20mg MMC in 50ml distilled water at 41C to 44C for 6-8 weekly 60-minute sessions followed by 4-6 monthly sessions *Applicability* ●	• Pathology proven tumour recurrence • Side Effects *Applicability* ●	• Non-comparative study will have limited value in informing relative effectiveness of different treatments ***Overall Applicability*** ●

Study	Participants and Intervention(s)	Outcomes	EAC comments
Van Valenberg 2018 ***Design:*** Retrospective study ***Location:*** Multicentre, specific locations not reported ***Setting:*** Multicentre, no other details ***Follow-up*** 35.8 months (mean)	***Participants:*** 150 patients with histologically proven CIS with or without co-existing papillary Ta/T1 NMIBC tumours who had been treated with RF-CHT using mitomycin-C. *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • 2x 40mg/50ml, 40.5-44C for 4 to 8 weeks followed by maintenance instillations (1 instillation every 4-8 weeks). • Schedules varied slightly at each centre. *Applicability* ●	**Primary Outcomes** Complete Response (CR) after 6 months **Secondary Outcome** • 2-year recurrence rate • Recurrence free survival (RFS) after CR • Progression Rate • Overall survival (OS) • Cystectomy-free survival (CFS) • Treatment tolerability *Applicability* ●	• Subgroup analysis of patient outcomes by previous treatments received • Ablative (therapeutic dose) used so may have limited applicability to UK setting ***Overall Applicability*** ●
Volpe 2012 ***Design:*** Non-comparative cohort study ***Location:*** Italy ***Setting:*** Outpatients ***Follow-up*** Unclear, planned for 2 years at least	***Participants:*** 30 patients with NMIBC unresponsive to chemotherapy/immunotherapy, suitable for radical cystectomy *Applicability* ● ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • Prophylactic Regimen: 40mg MMC in 50ml distilled water (20+20) • Ablative regimen: 80mg MMC in 50ml distilled water (40+40) continuously pumped out of the • Bladder wall temperature of 42±2°C • Treatment duration 40mins effective heating *Applicability* ●	• Disease free survival Recurrence • Response Rates • Side Effects *Applicability* ●	• Non-comparative study will have limited value in informing relative effectiveness of different treatments • Limited to high risk patients who have not responded to previous treatment – may reflect the likely place in the UK clinical pathway as an option before radical cystectomy but will have limited generalisability to intermediate risk population ***Overall Applicability*** ●

Study	Participants and Intervention(s)	Outcomes	EAC comments
Witjes 2009 ***Design:*** Non-comparative retrospective case series ***Location:*** Israel, Italy, Germany, Switzerland, Austria and the Netherlands ***Setting:*** Outpatients ***Follow-up*** 24 months	***Participants:*** 51 patients with CIS of the bladder (defined as non-papillary high-grade non-invasive urothelial cell carcinoma (UCC) *Applicability*  ***Intervention:*** Radiofrequency-induced chemohyperthermia using Synergo • Weekly treatments for 6 weeks comprising 20mg MMC in 50ml sterile water replaced by a fresh identical solution after 30 mins for a total 40mg MMC in 1 hour • Higher doses for patients with concomitant papillary tumours or wide areas of CIS (40mg twice, 80mg in 1 hours; weekly for 8 weeks) • All patients received 6 maintenance instillations (one every 6 weeks) *Applicability* 	• Eradication of CIS • Tumour recurrence • Adverse Events *Applicability* 	• Non-comparative study will have limited value in informing relative effectiveness of different treatments • Patient group is applicable but limited to CIS so generalisability to wider NMIBC patients may be limited. ***Overall Applicability*** 
Applicable  Somewhat Applicable  Not Applicable 			

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

A total of 5 comparative studies (6 publications) are included in the evidence review.

One RCT (Arends 2016) compared MMC via Synergo with intravesical BCG in intermediate and high risk NMIBC patients. A second RCT (Tan 2019) compared MMC via Synergo with intravesical BCG as second line therapy in people with intermediate or high risk NMIBC who had a recurrence following induction or maintenance BCG treatment.

A third RCT reported short-term results (Colombo 2003) and long-term results (Colombo 2011) comparing MMC via Synergo with standard intravesical MMC in people with primary or recurrent intermediate and high risk NMIBC. An additional non-randomised comparative safety and tolerability study of MMC via Synergo compared with standard MMC (Colombo 2001) was included.

One retrospective comparative study (Sri 2020) may have limited applicability as it compares outcomes in people who went on to radical cystectomy after treatment with MMC via Synergo with people who had radical cystectomy either as a primary treatment or who had initially failed BCG immunotherapy.

An additional 14 non-comparative studies of which only 2 were prospective studies (Erturhan 2015 and Kiss 2015) reporting on the use of MMC via Synergo. Although these studies did not include comparisons with other treatments, most included some subgroup analyses such as comparing adjuvant (Prophylactic) and ablative (therapeutic) regimens or comparing outcomes in previously treated people including comparisons between non-responders and people intolerant to treatment or comparing with treatment naïve people.

The EAC consider all 19 studies are applicable to the decision problem while recognizing that there are some limitations which potentially impact the generalisability of the evidence base. In addition, the randomised trials have

some specific limitations which should be considered in the context of UK practice.

Overarching limitations across the evidence base as a whole include factors such as

- Limited comparative evidence comparing Synergo with key comparator treatments such as MMC or BCG.
- Extremely limited evidence relating to alternative chemotherapies for use in Synergo (e.g. epirubicin).
- Extremely limited evidence comparing Synergo with radical cystectomy
- Studies comparing with MMC may have limited applicability to the UK clinical setting as they were not UK based studies and the trials were underpowered due to early termination.
- Studies comparing with MMC may have limited applicability to the UK clinical pathway as standard MMC is currently used to treat people with intermediate risk NMIBC and device assisted chemotherapy is not currently used in this setting.
- There are a number of non-comparative studies, however this limits the extent to which the efficacy of Synergo compared to other treatment options can be assessed with any certainty.
- Inconsistent inclusion of intermediate and high-risk patients with studies including one, other or both risk groups.
- Inconsistent inclusion of people with carcinoma *in-situ* with some studies specifically excluding people with CIS.
- Variable use of adjuvant and ablative regimens.
- Previous treatments are reported however limited numbers and details mean it is difficult to ascertain the extent to which previous treatments

influence the decision to use device assisted chemotherapy and the impact this has on outcomes.

The EAC note that some studies include subgroup reporting including:

- Subgroup results for people treated with MMC and Epirubicin (Arends 2014, Brummelhuis 2021)
- Subgroup results for people with concomitant CIS, patients with papillary disease only (Arends 2014, Brummelhuis 2021, Tan 2019, van Valenberg 2018, Witjes 2009)
- Subgroup results by BCG treatments (Brummelhuis 2021, Nativ 2009, van Valenberg 2018)
- Subgroup results for people with intermediate versus high risk NMIBC (Nativ 2009)
- Subgroup analysis for ablative dose versus adjuvant dose (Brummelhuis 2021, Gofrit 2004, Moskovitz 2005, Moskovitz 2012, Volpe 2012)

The EAC suggest that these analyses can provide useful information relating to the efficacy of MMC via Synergo in people who have had previous treatments for NMIBC, however caution that the evidence quality for any of the subgroup comparisons is very low.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

The EAC critically assessed the quality of the randomised trials using the Cochrane risk of bias tool (Sterne 2019). Overall risk-of-bias judgement graded as: 'low' risk of bias if low risk of bias for all domains; 'some concerns' if some concerns in at least one domain but not to be at high risk of bias for any domain; 'high' risk of bias if high risk of bias in at least one domain or 'some concerns' for multiple domains in a way that substantially lowers confidence in the result.

EAC assessment indicated that one trial (Arends 2016) had a low risk of bias while two trials (Colombo 2003, Tan 2019) had some concerns overall but no specific concerns of high risk of bias (Table 7).

The EAC note that all 3 randomised trials were stopped early for different reasons. One trial (Tan 2019) closed early due to a higher than expected CIS recurrence rate in the Synergo group. One trial (Colombo 2003, Colombo 2011) was stopped early due to significantly better efficacy of Synergo and one trial (Arends 2016) stopped early due to slow recruitment.

Critical appraisal of non-randomised studies indicated that all studies were low to medium quality. This is due to a number of factors including retrospective analyses, small patient numbers, lack of comparators, limited outcomes reported, unclear reporting of risk classifications and in some cases, uncertainty around whether there is patient overlap between studies (Table 8).

Full details of critical appraisals are reported in Appendix C

Table 7: Quality assessment of included RCTs (n=3) assessed using the Cochrane risk of bias tool for randomised trials (Sterne 2019)

Risk of Bias Domain	Arends (2016)	Colombo (2003/2011)	Tan (2019)
Bias arising from the randomization process	low	low	low
Bias due to deviations from intended interventions	low	some concerns	some concerns
Bias due to missing outcome data	low	low	low
Bias in measurement of the outcome	low	low	low
Bias in selection of the reported result	low	some concerns	low
Overall risk of bias	**Low**	**Some concerns**	**Some concerns**

Table 8: Summary of quality assessment of included non-randomised studies assessed using JBI checklist for case series studies (JBI).

Study	Study Design	Intervention	EAC Comments	Conclusion
Arends 2014	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well reported however non-comparative and retrospective	**Medium Quality**
Brummelhuis 2021	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well conducted and reported however non-comparative and retrospective	**Medium Quality**
Colombo 2001	Pilot Feasibility Study (Comparative)	RITE MMC using Synergo	Pilot feasibility reporting safety and tolerability outcomes	**Low Quality**
Erturhan 2015	Prospective Case Series (non-comparative)	RITE MMC using Synergo	Some concerns around the inclusion/exclusion of patients. Narrative results only	**Low Quality**
Gofrit 2004	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Some concerns around the inclusion/exclusion of patients. Some concerns around the statistical analysis	**Low Quality**
Kiss 2015	Prospective Case Series (non-comparative)	RITE MMC using Synergo	Some concerns around the inclusion/exclusion of patients.	**Low Quality**
Maffezzini 2014	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well reported however non-comparative and retrospective	**Medium Quality**
Moskovitz 2005	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well reported however non-comparative and retrospective	**Medium Quality**
Moskovitz 2012	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well reported however non-comparative and retrospective	**Medium Quality**
Nativ 2009	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well reported however non-comparative and retrospective	**Medium Quality**
Sooirakumaran 2016	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well reported however non-comparative and retrospective	**Medium Quality**
Sri 2020	Retrospective Comparative study	RITE MMC using Synergo	Comparative study but retrospective. Some concerns around the inclusion/exclusion of patients.	**Medium Quality**
Van der Heijden 2004	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well reported however non-comparative and retrospective	**Medium Quality**

Study	Study Design	Intervention	EAC Comments	Conclusion
Van Valenberg 2018	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Well reported however non-comparative and retrospective	**Medium Quality**
Volpe 2012	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Some concerns around the inclusion/exclusion of patients.	**Low Quality**
Witjes 2009	Retrospective Case Series (non-comparative)	RITE MMC using Synergo	Some concerns around the inclusion/exclusion of patients. Narrative analysis with p-values reported.	**Low Quality**

5.3 *Results from the evidence base*

Comparative Studies

Results from 5 comparative studies are summarised in Table 9.

Synergo versus standard intravesical MMC

In one randomised trial, treatment with Synergo or standard intravesical MMC was given with adjuvant intent following compete transurethral resection to patients with intermediate or high risk NMIBC (Colombo 2003 & 2011).

Short term results from one trial (Colombo 2003) report significantly lower recurrence rates in patients treated with Synergo compared with standard MMC (17.1% (6/35) versus 57.5% (23/40) (p=0.0002)) with no significant impact of prognostic factors such as previous tumour size, previous multifocal tumours or previous grade/stage of disease. The trial results indicated that the total number of treatment sessions had a significant effect with lower recurrence rates in patients who received full treatment compared with patients receiving less than complete treatment (p<0.0001). Long-term results reported that disease free survival was significantly better with Synergo (p<0.004) and no significant difference in overall survival (p=0.558) between the groups (Colombo 2011). In the long-term results, previous history of multiple tumour sites (<5 or ≥5) had no effect on results for Synergo treated patients (p=0.77) but had a significant impact on results for MMC treated patients (p=0.001) with all patients with a history of ≥5 tumour sites experiencing tumour recurrence within the first 24 months of their treatment.

Bladder preservation rate for the cohort was 86.1% with Synergo compared with 78.9% with MMC.

Synergo versus BCG immunotherapy

Treatment with Synergo or BCG immunotherapy was given with adjuvant intent to patients with intermediate or high risk NMIBC in two randomised trials (Arends 2016, Tan 2019). In one study (Arends 2016) patients were presumed to have had a transurethral resection of the bladder tumour (TURBT) while in one (Tan 2019) compete transurethral resection of papillary lesions was required for inclusion in the trial.

Recurrence Free Survival

24-month recurrence free survival (intent to treat) was 78.1% (95% CI 65.2%-86.7%) in Synergo group compared with 64.8% (95% CI, 52.2%-74.9%) in the BCG group (p=0.08) (Arends 2016)

Disease Free Survival

24-month disease free survival was 35% in the Synergo group compared with 41% in the BCG group, HR=1.33, 95% CI 0.84-2.10, p=0.23, adjusted p=0.49 (Tan 2019). When looking at patients with baseline CIS however, 24-month disease free survival was 25% (Synergo) vs. 50% (BCG) (HR=2.06, 95% CI 1.17-3.62, p=0.01). For patients without baseline CIS 24-month disease free survival was 53% (Synergo) vs. 24% (BCG) (HR=0.50, 95% CI, 0.22-1.17, p=0.11).

Complete Response Rate

At 3 months, the complete response rate in patients with CIS did not differ significantly between the groups: 88.9% with Synergo compared with 85.7% with BCG (Arends 2016).

Post cystectomy outcomes for Synergo versus primary cystectomy or BCG failure

One additional non-randomised, retrospective comparative study (Sri 2020) reported on outcomes for patients who underwent radical cystectomy either as a primary treatment or following treatment failure with BCG compared with BCG followed by Synergo. The aim of the study was to examine whether

treatment with Synergo impacted operative outcomes for radical cystectomy but reported that pre-operative Synergo was not correlated with 90-day readmission to hospital following surgery for radical cystectomy (p=0.606). Results of the study additionally indicated no statistical difference between time to recurrence in the two cohorts (p=0.513), no difference between the groups for all-cause mortality (p=0.069) and no difference in cancer specific mortality (p=0.129).

Table 9: Results from Comparative Studies

Study	Recurrence	Disease Progression	Survival	Complete Response (CR)	Organ Preservation
Arends 2016 *Synergo (CHT) versus BCG*	*Reported as recurrence free survival (RFS)* *Intention to Treat Population (papillary NMIBC patients with at least one treatment given)* **24 months RFS:** • Synergo: 78.1% (95% CI 65.2%-86.7%) • BCG: 64.8% (95% CI, 52.2%-74.9%) p=0.08	No patient experienced progression to muscle invasive disease in the Synergo group compared with 1 patient in the BCG group.	Not Reported	*CIS patients* 3-month CR Synergo: 89% BCG: 85.7% p=1.00	Not Reported
Colombo 2003 Colombo 2011 *Synergo versus standard intravesical MMC*	*Reported as recurrence* Short term results (2003) • Synergo: 17.1% (6/35) • MMC: 57.5% (23/40) p=0.0002 Long-term results (2011) *Per Protocol* • Synergo: 14/35 (40%) • MMC: 32/40 (80%) P<0.001	Short-term results (2003) • 1 patient in the MMC group had recurrence at 3-month follow-up, developed metastasis and died. Long-term results (2011) Tumour progression requiring radical cystectomy (RC) at time of recurrence • Synergo: 2 patients	*Disease Free Survival* • DFS was significantly better with Synergo (p<0.001) *Overall Survival* • No significant difference in overall survival between the groups (p=0.558)	Not Reported	• Synergo: 86.1% • MMC: 78.9%

Study	Recurrence	Disease Progression	Survival	Complete Response (CR)	Organ Preservation
		• MMC: 3 patients • 4 additional patients had RC for recurrent high-risk NMIBC			
Tan 2019 *Synergo versus institutional standard of care (BCG)*	Reported as recurrence free survival rate in the per protocol population only Synergo: 23% BCG: 40% p=0.98	Reported as progression free survival rate in the per protocol population only Synergo: 83% BCG: 87% P=0.16	*24-month Disease Free Survival (patients without DFS events)* Synergo: 35% BCG: 41% HR=1.33 (95% CI 0.84-2.10), p=0.23, adjusted p=0.49 *24-month Disease Free Survival (with baseline CIS)* Synergo: 25% BCG: 50% • HR=2.06, 95% CI 1.17-3.62, p=0.01 *24-month Disease Free Survival (without baseline CIS)* Synergo: 53% BCG: 24% • HR=0.50, 95% CI, 0.22-1.17, p=0.11	3-month complete response Synergo: 30% BCG: 47%, OR=0.43, (95% CI 0.18-1.28, p=0.15)	Not reported
Colombo 2001 Synergo vs. MMC and EMDA	Not Reported	Not Reported	Not Reported	MMC: 27.7% Synergo: 66% EMDA: 40%	Not Reported
Sri 2020	• 20 patients (19.6%) developed locoregional recurrence or	Not Reported	• No significant difference between groups for all-cause	Not Reported	• Not applicable as all patients have

Study	Recurrence	Disease Progression	Survival	Complete Response (CR)	Organ Preservation
Synergo compared with radical cystectomy	metastatic disease in the no Synergo group • Mean time to recurrence was 24.6 months • 6 patients (16.7%) developed recurrence in the Synergo group • Mean time to recurrence was 37 months		mortality (p=0.069) or cancer specific mortality (p=0.129)		received radical cystectomy • Synergo was not correlated with 90-day hospital readmission

Non-Comparative Studies

A number of non-comparative studies were identified with key results discussed briefly (detailed results are summarised in Table 10).

All studies reported outcomes relevant to the decision problem however outcome reporting was variable and inconsistent across all studies.

- Recurrence was reported as an outcome in 13 studies reported variably as a recurrence free survival, probability of recurrence or number of patients with a recurrence during follow-up. Recurrence rates varied depending on whether an ablative or adjuvant regimen was used, whether patients had received previous BCG treatments and whether patients had concomitant CIS.

- Treatment response (reported as complete response) was reported as an outcome in 9 studies – all patients were treated with an ablative regimen.

- Disease progression was reported as an outcome in 10 studies.

- Survival outcomes were reported in 6 studies and included overall survival, disease free survival, progression free survival and cancer-specific survival.

- Bladder preservation rates were reported in 5 studies and further treatments such as radical cystectomy were reported in 9 studies.

All Patients

Recurrence

Three studies (Maffezzini 2014, Witjes 2009, Volpe 2012) reported that 30.9%, 49% and 56.7% of all patients responding to treatment respectively recorded a recurrence. This compared with one study (van Valenberg) in which recurrence rate in all patients with a complete response to treatment was 18.8%.

Recurrence free survival for all patients in three studies was 60% at 1 year and 47% at 2 years (Arends 2014), 88.4% (Erturhan 2015) and 71% (Gofrit

2004). A second study (Brummelhuis 2021) reported recurrence free survival in all patients with papillary tumours of 77.9% at 1 year, 57.5% at 2 years and 37.2% at 5 years. Recurrence-free probability, reported in one study (Nativ 2009) was 85% at 1 year and 56% at 2 years for all patients. In one study (Sooriakumaran 2016), 35/97 patients experienced disease progression.

Treatment Response

Treatment response was reported primarily for patients treated with ablative regimens. Initial complete response rate at 6 weeks was 77.5% in the ablative group (Arends 2014).

Complete response was 75% (Gofrit 2004), 80% (Moskovitz 2005), 79% (Moskovitz 2012) and 42.85% (Volpe 2012) all ablative regimens.

At 6 months, complete response rates were 66.2% with ablative regimen (van Valenberg 2018) and 72.2% with adjuvant regimen (Sooriakumaran 2016) for all patients, 56% for patients with CIS and 52.4% for patients with residual papillary tumours (both adjuvant and ablative regimens used) (Brummelhuis 2021).

No significant differences in complete response rates were reported when comparing patients with CIS and no CIS (Arends 2014) or with and without concomitant papillary tumours (Witjes 2009).

Disease Progression

In one study (Arends 2014) 4.3% of patients progressed to muscle invasive disease and in one study (Moskovitz 2012) 4.7% of patients experienced disease progression (adjuvant regimen only). In one study (Brummelhuis) the rate of progression to muscle invasive disease was 8.5%, while in two studies (van Valenberg 2018, Volpe 2012) disease progression rates were 13.3%, and 17.64% respectively.

Three studies (Erturhan 2015, Moskovitz 2005, van der Heijden 2004) reported no disease progression.

Survival

Overall Survival in one study (Brummelhuis 2021) was 72.3% at 5 years and 51% at 10 years while in one study (van Valenberg 2018) overall survival at final follow-up was 78%.

Disease free survival in one study (Volpe 2012) was 77% at 12 months and 55% at 24 months.

Bladder Preservation Rate

Bladder preservation rate for all patients was reported in three studies (Brummelhuis 2021, Sooriakumaran 2016, van Valenberg 2018) and were 70.8%, 81.4%, and 78.5% respectively.

Radical Cystectomy

One study (Sooriakumaran 2016) reported that 51.4% of patients (18/35) who experienced disease progression had a radical cystectomy (18.6% (18/97) of whole cohort). One study (Brummelhuis 2021) reported that 29.2% of patients received a radical cystectomy with or without neoadjuvant chemotherapy. One study (Kiss 2015) reported that 29% and one study (Maffezzini 2014) reported that 16.6% of patients went on to radical cystectomy.

One study (Witjes 2009) reported that 5 patients had a radical cystectomy (because of recurrent tumour) and one study (Erturhan 2015) reported no radical cystectomies.

Adjuvant versus Ablative Regimens

Five studies (Brummelhuis 2021, Gofrit 2004, Moskovitz 2005, Moskovitz 2012, Volpe 2012) reported results separately for adjuvant and ablative regimens.

Recurrence

From 2 studies (Gofrit 2004, Brummelhuis 2021) recurrence free rates were higher in patients undergoing ablative regimens compared with adjuvant regimens. Recurrence free survival in one study (Gofrit 2004) was 80.9% for responders with the ablative regimen and 62.5% with the adjuvant regimen. Recurrence free survival for the second study was 86.9% at 1 year, 71.9% at 2 years and 47.6% at 5 years for the ablative group and 74.0% at 1 year 54.2% at 2 years and 33.9% at 5 years for the adjuvant group (Brummelhuis 2021).

In three studies (Moskovitz 2005, Moskovitz 2012, Volpe 2012) 91% of patients, 72% and 43.75% of patients respectively in the adjuvant regimen

were recurrence free. Recurrence rates for the ablative regimens were not reported.

Treatment Response
In one study (Brummelhuis 2021), ablative doses were associated with non-statistically significant higher 6-month CR rate (Adjusted OR 0.49, p=0.08).

Survival
Disease free survival was 87% at 1 year and 58% at 2 years in the adjuvant group compared with 85% at 1 year and 48% at 2 years (Volpe 2012).

Median disease free survival in the adjuvant group was 6.9 years in one study but not reported for the ablative group (Moskovitz 2012).

Bladder Preservation Rate
In one study (Gofrit 2004) bladder preservation rates were 95.8% in the adjuvant group and 78.6% in the ablative group. In a second study (Moskovitz 2012) bladder preservation rates were 95.3% in the adjuvant group and 91.7% in the ablative group.

Radical Cystectomy
From one study (Gofrit 2004), there was 1 radical cystectomy and 8 transurethral resections in the adjuvant group compared with 4 radical cystectomies and 3 transurethral resections in the ablative group.

Previous BCG Treatments
Six studies (Brummelhuis 2021, Nativ 2009, Sooriakumaran 2016, van der Heijden 2004, van Valenberg 2018, Witjes 2009) reported outcomes separated by whether patients had previous BCG treatment or not and by reason for stopping BCG.

Recurrence
Recurrence free survival in BCG refractory patients was 79.2% at 1 year, 65.5% at 2 years and 38.7% at 5 years for patients with concomitant CIS and 72.5% at 1 year 54% at 2 years and 31.7% at 5 years for patients with papillary disease (Brummelhuis 2021). One study (Nativ 2009) reported a 56% recurrence rate at 2 years for BCG refractory patients and one study

(van der Heijden 2004) reported a risk of recurrence in patients with previous BCG treatment of 23.1% (SE 7.7%) at 1 year and 41.2% (SE 9.9%) after 2 years.

Treatment Response

One study (van Valenberg 2018) reported that 46% of patients who were classed as BCG non-responders had a complete response following treatment with Synergo compared with a 71.7% complete response rate for all of BCG treated patients ($p<0.0001$). One study (Witjes 2009) reported no difference in response between BCG responders/non-responders ($p=0.63$).

Survival

One study (Brummelhuis 2021) reported overall survival rates of 70.5% at 5 year and 43.9% at 10 years in BCG refractory patients while one study (van Valenberg 2018) reported overall survival at final follow-up of 76% for BCG non-responders. One study (Sooriakumaran 2016) reported that out of 7 bladder cancer deaths, 6 (85.7%) were in men who had previously had BCG, and 1/7 (14.3%) was BCG-naïve.

Bladder Preservation Rate

Bladder preservation rate, reported in one study (van Valenberg 2018) was 71.4% in BCG non-responders compared with 84.1% in other BCG treated patients ($p=0.006$).

Intermediate Risk compared with High Risk NMIBC

Two studies (Nativ 2009, van der Heijden 2004) reported limited results separated by whether patients had high or intermediate risk NMIBC. The probability of recurrence in one study (Nativ 2009) was 18% in intermediate risk patients versus 49% in high risk patients ($p=0.006$). In one study (van der Heijden 2004) patients with intermediate risk TCC had a significantly longer time to recurrence and a lower risk of recurrence compared with patients with high risk TCC (92% disease free and 64% disease free ($p=0.03$) at 24 months respectively).

MMC versus Epirubicin

Two studies (Arends 2014, Brummelhuis 2021) reported limited results by whether patients were treated using MMC or epirubicin. This is likely due to the fact that although a number of studies allowed epirubicin as an alternative, its use was limited to patients who were intolerant or allergic to MMC therefore the number of patients treated with epirubicin are small. Results from Arends (2014) reported no significant difference in recurrence free survival between epirubicin and MMC (p=0.303). Multivariate analysis results from Brummelhuis 2021 indicated no significant difference in recurrence free survival and durable response for MMC vs. Epirubicin (adjusted HR: 1.23 (0.71-2.14, p=0.46).

Table 10: Summary of results from non-comparative studies

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments

Arends 2014
 	
Intravesical MMC or Epirubicin (12.5%) with Synergo in patients refractory to regular intravesical therapy
 	
80.6% of patients had previous BCG
	Recurrence Free Survival
	• All patients: RFS was 60% at 1 year and 47% at 2 years
	• Recurrence frequency before CHT was independently associated with decreased RFS (HR 2.4, 1.30-44.43, p=0.005)
	
	Epirubicin vs. MMC
	• 1-year RFS for epirubicin was 64% vs. 59% for MMC
	• 2-year RFS for epirubicin was 55% vs. 46% for MMC
	• Not significant: p=0.303
		• Initial CR rate 6 weeks after induction therapy was 77.5% (n=41) in the ablative group
		• No significant difference in CR rate comparing
		  • CIS/no CIS
		  • pTa/pT1 or low/high grade
			• 7 patients (4.3%) progressed to muscle invasive disease	*Not Reported*	*Not Reported*	*Not Reported*

Brummelhuis 2021 *Intravesical MMC or Epirubicin with Synergo* *Previous Treatments* • *85.4% BCG* • *50.4% MMC*	*Durable response rate* *Patients with concomitant CIS* • 79.7% at 1 year • 66.5% at 2 years • 40.3% at 5 years *BCG refractory patients* • 79.2% at 1 year	• 6-month complete response rate was 56% (CIS) and 52.4% (residual papillary tumour)	• 22 patients (8.5%) of all patients progressed to MIBC • 11 patients (4.3%) had distant metastases	*Overall Survival* • 72.3% at 5 years • 51% at 10 years. *BCG refractory subgroup* • 70.5% at 5 years • 43.9% at 10 years *Relative survival (RS)*	• Bladder preservation rate was 70.8%	• 29.2% received radical cystectomy with/without neoadjuvant chemotherapy

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments
• *RF-CHT 4.4%* *Reason for discontinuing BCG* • *65% BCG refractory disease* • *7.7% BCG intolerance* • *27.3% reason not reported*	• 65.5% at 2 years • 38.7% at 5 years *Recurrence free survival* *Patients with papillary disease* • 77.9% at 1 year • 57.5% at 2 years • 37.2% at 5 years *BCG refractory patients* • 72.5% at 1 year • 54% at 2 years • 31.7% at 5 years *MMC versus Epirubicin* Multivariate analysis reports no significant difference in recurrence free survival and durable response for MMC vs. Epirubicin (adjusted HR: 1.23 (0.71-2.14, p=0.46).			• 80.6% at 5 years • 65.1% at 10 years. *BCG refractory subgroup* • 78.6% at 5 years • 57.5% at 10 years		• Other treatments included systemic chemotherapy, chemoradiation with/without TURB, other intravesical chemotherapy
Erturhan 2015 *Intravesical MMC with Synergo*	• 3 patients (11.5%) recurrent urothelial carcinoma • Recurrence free survival was 88.4%	• *Not Reported*	• No disease progression reported	*Not Reported*	*Not Reported*	• No radical cystectomy required
Gofrit 2004 *Intravesical MMC or epirubicn (n=4) with Synergo*	*Recurrence free survival* • All patients: 71% • Adjuvant group: 62.5% • Ablative group: 80.9%	*Ablative Group* • 75% complete response 25% non-responders	Disease Progression • All patients: no cases progressed to stage T2 • Adjuvant group: 6 patients developed	*Not reported*	*Adjuvant group* • 95.8% (n=23) bladder preservation	*Adjuvant group:* • 1 radical cystectomy

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments
			stage pTa and 3 developed stage pT1 recurrence • Ablative group: 4 patients developed recurrence		*Ablative group* • 78.6% bladder preservation	• 8 transurethral resections *Ablative group* • 4 radical cystectomies • 3 transurethral resections
Kiss 2015 *Intravesical MMC with Synergo* *Previous treatments not reported*	• 6/21 patients showed no signs of tumour recurrence • Post-interventional recurrence rates were lowest in patients with an initial pTaG1 tumour stage and highest in pT1 initial tumour stage.	*Not Reported*	*Not Reported*	• 33% (7/21) patients died (2/7 of metastatic disease and 5/7 of other non-cancer related causes)	*Not Reported*	• 29% (6/21) patients underwent cystectomy for multifocal recurrence or progression to muscle invasive disease.
Maffezzini 2014 *Intravesical MMC or Epirubicin (n=10) with Synergo* *Previous treatments not reported*	• 57.1% of patients showed no evidence of disease and 30.9% had disease recurrence • Patient EORTC scores (HR 41.1, p=0.01), multifocality (HR 17.7, p=0.02)	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	• 16.6% (7) of patients went on to recurrent radical cystectomy

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments
	and tumour stage (HR 8.5, p=0.02) were associated with higher risk of recurrence					
Moskovitz 2005 *Intravesical MMC with Synergo* *Previous treatments not reported*	*Adjuvant Group* • 91% (n=20) were recurrence free • 2 patients (9%) had recurrence	*Ablative Group* • 80% (n=8) patients achieved complete response • 20% (n=2) had a partial response	• No disease progression reported in patients with recurrence	*Not Reported*	*Not Reported*	*Not Reported*
Moskovitz 2012 *Intravesical MMC with Synergo* *Previous treatments not reported*	*Adjuvant Group* • 28% (n=18) had tumour recurrence • Median time to recurrence was 13 months • Estimated 2-year recurrence rate was 32.8%	*Ablative Group* • Complete response observed in 79% of patients(n=19) • Durable response observed in 67% of patients (n=16)	*Adjuvant Group:* • Disease progression rate was 4.7% (n=3)	*Adjuvant Group:* • Median disease-free survival was 6.9 years	*Adjuvant Group* • Bladder preservation rate was 95.3% *Ablative Group* • Bladder preservation rate was 91.7%	*Not Reported*
Nativ 2009 *Intravesical MMC with Synergo* *Previously treated with BCG* • *BCG refractory*	*Recurrence Free Probability* All patients • 85% at 1-year • 56% at 2 years • No significant difference in recurrence rates	*Not Reported*	3% experienced recurrent muscle invasive disease	*Not Reported*	*Not Reported*	All patients • 1 radical cystectomy • 2 not eligible/refused

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments
• *BCG resistant* • *BCG relapse* • *BCG intolerant*	between BCG treatment groups (p=0.38) BCG Refractory • 56% recurrence rate at 2-years compared to 44% in other groups (p=0.06) Patients with fewer than 10 treatments compared with patients completing maintenance • 2-year recurrence 61% vs.. 39% (<10 treatments), p=0.01 History of highly recurrent tumours (n=67) • 16.6% versus 11.9% in other patients at 1 year • 50.2% versus 27.6% at 2 years compared with (p=0.09) Intermediate risk patients versus high risk patients • 18% at 2 years compared to 49% (high risk) p=0.006					

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments
	• No significant impact of disease stage, histological grade, sex, or prior MMC					
Sooriakumaran 2016 *Intravesical MMC with Synergo*	*Not Reported*	• 72.2% (n=70) reported compete response	• 61.9% (n=60) of patients did not progress	• 2 deaths attributable to bladder cancer (without progression) • 17.5% (17/97) of patients died over the study period (7/17 of bladder cancer) • Mortality was lower in the CR group compared with no CR (survival: 88.6% versus 66.7%)	81.4%	• 51.4% (n=18) patients who experienced progression underwent radical cystectomy. • 8.6% (n=3) were treated with other treatments including BCG, chemoradiation and diverticulectomy.
Van der Heijden 2004 *Intravesical MMC with Synergo* *Some patients previously treated with BCG*	• 14 patients had tumour recurrence Risk of recurrence • 14.3% (SE 4.5%) at 1 year • 24.6% (SE 5.9%) after 2 years • Significantly longer time to recurrence and a lower risk of recurrence for	*Not Reported*	• No progression in disease/stage observed during follow-up	*Not Reported*	*Not Reported*	*Not Reported*

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments
	patients with intermediate risk TCC compared with high risk TCC (92% DFS versus 64% DFS respectively, p=0.03). Risk of recurrence in patients with previous BCG treatment • 23.1% (SE 7.7%) at 1 year • 41.2% (SE 9.9%) after 2 years					
Van Valenberg 2018 *Intravesical MMC with Synergo* *Some patients previously treated with BCG*	• In all patients with a CR, subsequent recurrence rate was 18.8% and RFS was 74.5%. • No significant difference between any treatment groups for RFS or recurrence rate	Complete Response after 6 months • All patients: 66.2% • BCG non-responders: 46% • Other BCG treated patients – 71.7% • Treatment Naïve: 83% • Significant difference in response rates when compared BCG non-responders with other BCG treated patients (p<0.0001) and treatment naïve CIS patients (p<0.0001)	• Progression to MIBC (with/without lymph node or distant metastasis) was observed in 13.3% of patients. • 16% of progressions were in BCG non-responders, 13% in other BCG treated and 10.6% in treatment naïve CIS patients (p=0.74).	• OS was 78% at final follow-up • Mean survival time was 89.5 months (95% CI 74.7-104.8) • For BCG non-responders, OS was 76% and mean survival time was 79.7 months (95% CI 65.2-94.3)	Bladder preservation rate • All patients: 78.5% • BCG non-responders: 71.4% • Other BCG treated patients: 84.1% • Treatment naïve CIS patients: 86.7% • Significant difference in bladder	Mean cystectomy free time • All patients: 99.9 months (95% CI86.7-113.1). • BCG non-responders: 45.2 months (95% CI 35.7-54.7)

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments
					preservation rates when comparing BCG non-responders with both other BCG treated and treatment naïve CIS patients (p=0.006).	
Volpe 2012 *Intravesical MMC with Synergo for patients unresponsive to chemotherapy or immunotherapy*	*Recurrence* All patients • 56.7% (n=17) had a recurrence • Mean time to recurrence was 10.7 months Prophylactic • 46.25% (n=9) had a recurrence • Mean time to recurrence was 8 months Ablative • 47.15% (n=8) had were considered non-responders for persistence of disease	• 42.85% (6/14) patients in the ablative group had a compete response	• 17.64% (n=3) of non-responders had progression to MIBC	*Disease Free Survival* All patients • 77% at 12 months • 55% at 24 months Treated only with BCG • 100% at 12 months • 77% at 24 months Treated with multiple agents • 64% at 12 months • 46% at 24 months Prophylactic • 87% at 12 months • 58% at 24 months Ablative • 85% at 12 months • 48% at 24 months	*Not Reported*	*Not Reported*

	Recurrence	Treatment Response	Disease Progression	Survival	Bladder Preservation	Further treatments
	• Mean time to recurrence was 12.5 months					
Witjes 2009 *Intravesical MMC with Synergo for patients with CIS, failing BCG*	• 49% (n=22) of responders had a recurrence at a mean follow up time of 27 months	• 92% (n=45) had no CIS at 3 months • 2 patients had no CIS with persistent papillary tumour • No difference in response between patients with/without concomitant papillary tumours (p=0.94) • No difference in response between BCG responders/non-responders (p=0.63)	*Not Reported*	*Not Reported*	*Not Reported*	• 5 patients had a cystectomy due to recurrent tumour • 1 patient had a cystectomy due to contracted bladder

Abstracts

Due to the volume of evidence available and some uncertainties around potential overlap of study data, the EAC has not included data from abstracts in the main report however a summary of each abstract is included in Appendix B for information.

6 Adverse events

The company submission included a search of the MHRA and FDA (Maude) databases and no adverse events were identified. The EAC searched the MHRA's field safety notices and medical device alerts and the FDA (Maude) database and no adverse events were identified.

Outcomes related to safety, tolerability and adverse events of RITE chemotherapy were reported in 18 studies and overall they were reported to be mild to moderate, transient with few patients stopping treatment due to side effects.

The most common adverse events during treatment included pain and spasms while after treatment the most common adverse events were dysuria, nocturia and urinary frequency. A summary of the most common adverse events and serious adverse events is presented in Table 11. This summary reports only adverse events for radiofrequency induced chemohyperthermia.

Table 11: Summary of most commonly reported adverse events reports with radiofrequency induced chemohyperthermia.

Study	Adverse events during treatment	Adverse Events after treatment	Severe Adverse Events/Patients stopping treatment due to adverse events
Arends 2016	• Bladder Spasms (14.4%) • Bladder pain (14.1%)	• Dysuria (11.7%) • Nocturia (10.3%) • Urinary frequency (9.9%)	• 5/92 probably related serious adverse events (contracted bladder, urethral bleeding and fever)
Arends 2014	• Bladder spasms (23.3%) • Bladder pain (16.8%)	• Dysuria (22.6%) • Frequency/urgency (27.3%)	• 10/160 patients stopped treatment due to adverse events
Brummelhuis 2021	• Bladder spasms (62.2%)	• Dysuria (53.1%) • Hematuria (29.9%)	• 30/299 patients experienced a severe

	• Bladder pain (27.8%)		(CTCAE grade 3) adverse event • 34/299 patients discontinued treatment due to side effects
Colombo 2001	None reported	None reported	• No treatment sessions suspended
Colombo 2003/Colombo 2011	• Bladder pain (n=17, 3 severe)	• Dysuria (n=10, 1 severe) • Posterior wall thermal reaction (n=10, 4 severe)	• No patient stopped treatment
Erturhan 2015	• Pain (38.4%)	• Dysuria (42.3%)	• No patient stopped treatment
Gofrit 2004	None reported	• Posterior wall thermal reaction (65.2% in prophylactic group, 62% in ablative group) • Dysuria (60.1% in prophylactic group, 55% in ablative group)	• Treatment was stopped in 2/52 patients after 4 or 5 sessions due to palmar rash.
Kiss 2015	• Bladder spasms (n=5, 2 severe) • Pain (n=8, 3 severe) • Urothelial perforation (n=1)	None reported	• Planned therapy was abandoned in 8/21 (38%) due to serious adverse events
Maffezzini 2014	None reported	None reported	• Bladder spasms were associated with reduction in bladder capacity and caused treatment interruption in 5/42 patients
Moskovitz 2005	• Pain (n=31 (7.8%) of total treatments).	• Posterior wall thermal reaction (prophylactic group; 7 (21.2%), ablative group; 2(14.3%).	• None reported
Moskovitz 2012	• Bladder pain (29.3%) • Bladder spasms (21.7%)	• Stenosis in 5.5% (5/92) • Urethral stricture in 3.3%	• 4.4% (4/92) patients withdrew before treatment completion
Nativ 2009	• Bladder Pain • Bladder Spasms	• Haematuria, • Dysuria • Transient incontinence	• 6/111 (5.4%) patients withdrew due to adverse events (2 MMC allergy, 1 each pain, haematuria, difficult catheter insertion and incontinence.
Sooriakumaran 2016	None reported	• haematuria (24.7%) • UTI (14.4%)	• 7.2% (7/97) patients were hospitalised due to haematuria, urinary sepsis and transient non-specific abdominal pain.
Tan 2019	• Bladder pain (46%)	• Dysuria (54%) • Increased frequency (54%)	• 5/48 patients stopped treatment due to adverse events

		• Increased urgency (42%) • Haematuria (48%)	
Van der Heijden 2004	None reported	None reported	• One case of severe, prolonged asymptomatic posterior wall thermal reaction with a lesion >2cm which took 3 months to heal.
Van Valenberg 2018	• pain or spasms during instillation (7.8%),	• allergy (8.2%) and frequency or urge between instillations (7.5%).	• 13.4% of patients receiving any amount of RF-CHT instillations had to stop induction and 17.8% had to stop maintenance due to adverse events.
Volpe 2012	• Bladder Spasm (prophylactic 27.3%; ablative 32.1%) • Pain (prophylactic 30.3%, ablative 31%)	• Posterior wall thermal reaction (prophylactic 58%, ablative 72%) • Dysuria (prophylactic 21.2%, ablative 24.4%)	• None reported
Witjes 2009	• Pain (12.7% per session) • Bladder spasms (13.1% per session)	• Dysuria (6.2% per session) • Haematuria (3% per session)	• 1/49 patient stopped treatment due to haematuria, 1 treatment session was delayed for 1 week and 1 session was shortened.

7 Evidence synthesis and meta-analysis

The company submission did not include a meta-analysis of the clinical data due to heterogeneity between the primary studies. The EAC agrees with this decision and has not conducted any meta-analysis.

The EAC note that one systematic review (Colombo 2016) of MMC via Synergo reported primarily narrative results for the same reason.

Although not included as part of the review, the EAC note that the conclusions of all the systematic reviews indicate that device assisted chemotherapy is promising for intermediate and high-risk bladder cancer (Colombo 2016, Lammers 2011, Liu 2020, Longo 2020) however all reviews acknowledge there is a lack of comparative evidence and that there is significant heterogeneity between the individual studies available.

8 Interpretation of the clinical evidence

The EAC consider that the available evidence for Synergo is variable in terms of how the device is being used (place in the clinical pathway), regimens used (adjuvant or ablative), populations included (intermediate or high risk), comparators (MMC, BCG or EMDA) and outcome reporting – all of which impacts the quality and certainty of the evidence. Radiofrequency induced chemohyperthermia using the Synergo device appears safe with most side effects limited to during treatment and resolving afterwards. The clinical effectiveness of radiofrequency induced chemohyperthermia using Synergo is less certain however and may be dependent on a number of factors including stage/grade of tumour, presence/absence of CIS, previous treatments and reasons for using Synergo and MMC dose used.

The EAC recognises that there is currently no established place in the clinical pathway for device assisted chemotherapy in the NHS and therefore the applicability and generalisability of the available evidence is somewhat limited as a result. Identification of key studies and outcomes to inform the use of Synergo is dependent on the identification of a clear place in the NHS for device assisted chemotherapy for NMIBC.

The EAC note that, based on discussion with clinical experts, two randomised trials (Arends 2016, Tan 2019) comparing BCG with MMC via Synergo most accurately reflect the likely place in the NHS for Synergo based on current practice.

This is because

- Clinical expert input indicates that standard intravesical MMC is used to treat intermediate risk NMIBC and that device assisted chemotherapy is not used for the treatment of intermediate risk NMIBC unless people have not responded to standard intravesical MMC and are having their treatment managed as if it were high-risk. One expert said this was because it was not likely to be needed first line and one expert noted that it is not practical in terms of time, staff and resources.

- For people with intermediate risk NMIBC who are having their disease managed as high-risk NMIBC the current treatment is BCG immunotherapy or radical cystectomy. Clinical expert input suggests that Synergo is most likely to be used as an additional treatment option to avoid radical cystectomy. It would be used either as a 2nd line treatment option for high risk patients who are refractory to BCG immunotherapy or as an alternative to BCG immunotherapy where BCG is not tolerated, contraindicated or unavailable. It is unclear whether in these circumstances, standard intravesical MMC would ever be used as a treatment option to avoid radical cystectomy

One of these randomised trials (Tan 2019) is a UK based trial and therefore the EAC consider it to be directly applicable to the NHS setting. This trial reported no significant difference in disease free survival between treatment groups for the population as whole. In patients with baseline CIS, disease free survival was significantly longer with BCG compared with Synergo (p=0.01) however the EAC note that this result cannot be considered with any certainty due to the fact that patients were treated with only an adjuvant dose of Synergo. In addition, not all patients in the comparator arm were treated with BCG which further limits the certainty and strength of the results from this trial. Overall the EAC note the following specific issues with this trial which will limit the quality and certainty of the results including:

- The comparator was BCG *or* Institutional standard of care. A number of patients in the comparator arm received MMC or MMC-EMDA and not BCG.

- The dose used in the study was the adjuvant dose of MMC (6 instillations of 2x20mg MMC) which meant that a number of patients with CIS were undertreated as they should have the ablative dose (6 instillations of 2x40mg).

- The trial closed early due to a higher than expected CIS recurrence in the Synergo arm.

- Treatment arms were unbalanced with a higher number of people with concurrent papillary and CIS tumours in the Synergo arm – possibly as a result of the trial closing early as randomisation processes state that randomisation was stratified by a number of factors including presence/absence of CIS.

- The trial recruited a heterogenous group of BCG refectory, resistance, and intolerance. These groups are not included in patient demographic results, although the numbers receiving less or more than 6 instillations are reported.

Arends (2016) was not set in the UK, but compared Synergo to BCG as a 1st line treatment. This reflects the NHS pathway however

- people with intermediate risk NMIBC would not be offered BCG as a 1st line treatment in the UK.

- 22% of people had CIS tumours but received adjuvant Synergo regimen

The third randomised trial (Colombo 2003, Colombo 2011) showed a significantly longer disease-free survival in the Synergo arm compared with the standard MMC arm. The EAC considered this trial to less accurately reflect the use of Synergo within the NHS as this compared Synergo with standard intravesical MMC which the clinical experts indicated would not be a standard treatment choice particularly for people with high-risk NMIBC. In addition, the trial included only one patient with CIS. This means that the adjuvant regimen was appropriate for all but 1 patient, but limits the generalisability of the results to patients without CIS.

All studies, comparative and non-comparative, include people with both intermediate and high-risk NMIBC and currently, in the UK, device assisted chemotherapy is used to treat only high-risk NMIBC, therefore the extent to which results can be generalized to any specific risk group is uncertain. One study (Nativ 2009) reported a significantly higher risk of recurrence in people with high risk NMIBC compared with intermediate risk NMIBC however as this

is a non-comparative study, this result is probably to be expected and what cannot be determined from the available evidence is whether the risk of recurrence in people with high risk NMIBC is lower with Synergo compared with other treatment options.

Comparisons between ablative and adjuvant regimens as reported in four non-comparative studies (Gofrit 2004, Moskovitz 2005, Moskovitz 2012, Volpe 2012) are of limited value as it is now seems to be established that the ablative regimen should be used to treat people with CIS. The question therefore is whether the ablative regimen using Synergo is more effective than other treatment options in people with CIS and this cannot be answered from the currently available evidence.

Comparisons between different BCG treatments previously received prior to treatment with Synergo (as reported in Brummelhuis 2021, Nativ 2009, van der Heijden 2004, van Valenberg 2018, Witjes 2009) may be of some use as they may provide information on whether some people should be considered for radical cystectomy rather than further treatment with Synergo if they have already failed with BCG as the possibility of successful treatment with Synergo may be affected by the reason for BCG failure.

Comparison between the use of MMC and alternative chemotherapy drugs such as Epirubicin with Synergo may be of interest. Reported only in two studies (Arends 2014, Brummelhuis 2021), no significant difference in recurrence free survival between epirubicin and MMC was observed however only patients who were allergic or intolerant to MMC were treated using Epirubicin therefore the comparison is unbalanced, underpowered and cannot be viewed with any certainty.

Overall, the generalisability and certainty of results across the whole body of clinical evidence is primarily impacted by the fact that there currently no recognised clinical pathway for device assisted chemotherapy and by extension, Synergo, in the UK. Without an agreed pathway, the generalisability of clinical trials comparing Synergo with standard intravesical MMC is uncertain because while device assisted chemotherapy is being used

in the UK there appears to have been no assessment of the evidence for the approach or where it might best fit into the clinical pathway.

8.1 *Integration into the NHS*

There is currently no recognised pathway for device assisted chemotherapy for bladder cancer in the NHS, therefore if Synergo was to be recommended for use, this would represent a change to the clinical pathway as outlined in current NICE guidance (NG2), In addition, an interventional procedure guidance (IPG628) recommends that intravesical microwave hyperthermia and chemotherapy should only be used with special arrangements due to well-recognised adverse events, although from the evidence reviewed these adverse events appear to be transient and manageable. It is clear, from clinical expert input that device assisted chemotherapy is being used to treat high-risk NMIBC in the UK therefore is likely already integrated into NHS practice. Clinical expert input also indicated a high degree of variation in availability and access for patients which would need to be addressed to ensure equality of access for all people with NMIBC as required.

The current evidence base supports the occurrence of adverse events however in most cases these were reported to be transient (during treatment) and of mild to moderate severity with few patients stopping treatment as a result (see section 6). Discussion with clinical experts indicate that although devices assisted chemotherapy is used in the NHS and the Synergo device is already being used in some centres in the UK, access for patients is limited. One patient expert noted that clinical teams did not appear aware of Synergo as a treatment option and expressed concerns some patients may miss out as a result.

Clinical experts noted that there can be issues with patients being referred from other centres to a centre providing Synergo treatment. Some patients may not be suitable for MMC via Synergo and experts suggested that clear processes need to be in place to ensure that full, up to date staging and histology information is available before treatment using Synergo is offered. Clinical experts agreed that they would recommend an up to date cystoscopy and repeat TURBT before Synergo. One expert noted that this is because bladder needs to be cleared of disease and the prostatic urethra needs to be

assessed and free of disease before treatment. All of these factors will have resource implications for the NHS.

Clinical experts expressed an opinion that there is a need for a network approach to delivering treatment using Synergo.

8.2 *Ongoing studies*

The EAC searched ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP) and identified 1 study where Synergo was used or mentioned (Table 12). In total, 11 studies relating to device assisted chemotherapy (but not specifically Synergo) for bladder cancer were considered potentially relevant to the decision problem (Appendix D).

The EAC note that the company did not identify any ongoing studies relevant for inclusion.

Table 12: Potentially relevant ongoing studies

Trial ID	Title	Recruitment Status	Target size	Intervention	Condition	Primary outcome
NCT01955408	Severity of Overactive Bladder Symptoms in Patients After Synergo Treatment (OABSYNERGO)	Completed	35	Synergo	Bladder Cancer	Severity of overactive bladder

The EAC note that although this study is reported as being complete, no results have been posted and the last verified update on the trial registration was October 2017.

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The company conducted a combined search for both clinical and economic evidence, identifying 110 records in total, however no economic evidence was identified. The EAC also conducted a combined search for clinical and economic evidence but did not identify any studies relevant to the economic section.

Published economic evidence review

No relevant evidence

Results from the economic evidence

No relevant evidence

9.2 *Available clinical evidence for de novo cost analysis*

The EAC identified 3 clinical trials (Colombo 2003, 2011; Arends 2016; Tan 2019) which were considered to provide the most appropriate clinical data to populate an economic model. The relevance of these studies to current NHS pathways has been summarised in Section 8, and key features relevant to economic modelling summarised in table 13 (full details are given in the clinical evidence tables).

Each of the three comparative studies have significant drawbacks for populating an economic model. The comparator of MMC alone in Colombo 2011 is not relevant for most patients in the NHS, however both Tan (2019) and Arends (2011) include patients with CIS (68% and 22% respectively) who did not receive an ablative Synergo regimen (which has now been accepted as normal practice). Tan (2019) include a sub-group analysis that allow use of data for patients without CIS, who received an appropriate regimen. No evidence was identified that would allow economic modelling including patients with CIS.

Appendix E attempts to show the approximate positioning of each of the studies in the NHS patient pathway that was agreed by experts.

Table 13: Summary of Key Clinical Trials Relevant to Economic Model

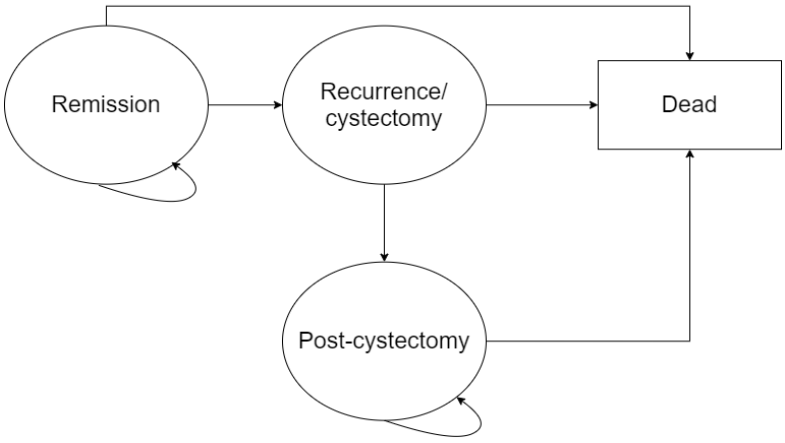
	Columbo (2003/2011)	Arends (2016)	Tan (2019)
Location	Israel, Italy	Israel, Italy, Netherlands, France, Austria, Belgium	UK
Recruitment	1994-1999	2002-2011	2010-2013
Population	Company report intermediate (77%) high risk (23%) but figures not included in publication N=65 (with long term follow-up) Some recurrence (37%)	Intermediate (69%) high risk (31%) reported in publication using 2001 guidelines. 60% high risk in ITT group using 2016 guidelines.(Arends 2017) N=190	**Recurrence following BCG** Intermediate (13%) and high risk (87%) N=104
Intervention	**Synergo with MMC** **2 x 20mg** Induction: 8 x weekly Maintenance: Every 4 months, duration unclear	**Synergo with MMC** **2 x 20mg** Induction: 6 x weekly Maintenance: Yr1: every 6 weeks	**Synergo with MMC** **2 x 20mg** Induction: 6 x weekly Maintenance: Yr1: every 6 weeks Yr2: every 8 weeks
Comparator	**MMC:** 2 x 20mg Induction: 8 x weekly Maintenance: Every 4 months, duration unclear	**BCG:** Induction: 6 x weekly Maintenance: 3 x weekly at 3, 6, 12 months	**BCG or Institutional Standard of Care** **BCG (59%)** Induction: 6 x weekly Maintenance: 3 x weekly at 3,6,12, 18, 24 months **MMC alone (18%)** **EMDA MMC (23%)**
Work up treatment	TURBT Confirmed tumour free Negative cytology and cystoscopy	TURBT Negative cytology and cystoscopy unless CIS	Complete TUR of papillary lesions For pT1 confirm no MIBC
Previous treatments	Failed intravesical treatment (58%)	No MMC <12 months No BCG <48 months Prior bladder instillations (including BCG or MMC) n=43 (23%)	Failed BCG (includes refractory, resistance and intolerance): ≤6 sessions: n= 37 (36%) >6 sessions: n= 67 (64%)
CIS	N=1	N=42 (22%)	N=71 (68%)
Median follow up	91 months for tumour free patients	25.3 months	36 months for patients without recurrence
Comments	Stopped early due to decision at interim analysis that there was enough evidence for superiority of Synergo	Stopped early due to slow recruitment.	Stopped early due to higher than expected CIS recurrence in Synergo arm
Suitability	• Longest follow-up • Synergo regimen appropriate for included patients • Small sub group of patients • Does not reflect NHS pathway • Company report 23% high risk	• Shorter follow-up • Synergo regimen not appropriate for 22% of patients with CIS • Position in NHS pathway is 1st line treatment of high risk NMIBC, or 2nd line of intermediate • 69% are intermediate risk NMIBC	• Shorter follow-up • Synergo regimen not appropriate for 68% of patients • Sub group analysis of non-CIS patients available • Position in NHS pathway is 2nd line treatment of high risk NMIBC • 87% are high risk NMIBC

9.3 *Company de novo cost analysis*

Economic model structure

The company submitted a Markov model with a one-month cycle, a life time horizon and an initial patient age of 64 years. The model is based on an NHS and personal social services perspective with a 3.5% discount rate. Four possible states are modelled: remission, recurrence (which is treated with radical cystectomy in all cases), post-cystectomy and death. The company provided a diagram of the model structure (figure 3), which is the same structure for both the intervention and comparator arms.

Figure 3: Company Markov Model Structure



The submitted model does not include BCG as a comparator or as part of the pathway, which was identified as the most relevant analysis to reflect current use in the NHS. It instead focuses on a particular subset of patients and circumstances where treatment with BCG is not suitable for that patient or is unavailable. The company submission agrees that this is narrower than the scope, but felt that the comparative evidence between Synergo and BCG was not appropriate for use.

The submitted model compares delivery of MMC using Synergo to the use of MMC alone for patients with intermediate and high risk NMIBC. The model structure is appropriate for the scenario that is being modelled, but does not include many aspects of the scope or normal pathway found in the NHS. The EAC note that there are some particular limitations with the model submitted by the company including:

- Diagrams of the typical pathway in the NHS, as shown in figure 1 and figure 2, demonstrate that both the company and the EAC (following expert advice) consider that MMC alone is normally offered as first line treatment for patients at intermediate risk of NMIBC.

- People at high risk, or people at intermediate risk who require secondary treatment would be offered BCG or radical cystectomy.

- Where Synergo is currently used in the NHS, expert advice was that it is offered as an alternative treatment to radical cystectomy for people who are intolerant to BCG, who are refractory to BCG or who have relapsed following treatment with BCG

- Synergo is not normally offered as a first line treatment to people with intermediate risk NMIBC, however clinical expert advice indicates that it could be used as a first line option for people with high risk NMIBC.

The EAC note that the limitations identified in the submitted model refer to current use within the NHS. The use of Synergo as an alternative to MMC alone is not currently part of the clinical pathway as outlined by the clinical experts however it may be that it should be considered.

Assumptions

The company included a number of assumptions in the submitted model. Table 14 summarises the assumptions included by the company and additional assumptions identified by the EAC.

The EAC have not made any changes to these assumptions during their amendments to the submitted model. Many of the assumptions are a product of the available clinical evidence and the resulting position in the clinical pathway. An additional EAC analysis is presented in section 9.4 using BCG as a comparator.

Table 14: Assumptions in Model

Assumption	Justification	EAC comment
Patients with recurrence move to RC	Consistent with NICE guideline, NICE (2015)	NICE guidance (NG2) states that people with high risk NMIBC should initially be offered BCG or radical cystectomy. "For people in whom induction BCG has failed, the specialist urology multidisciplinary team should assess the suitability of radical cystectomy, or further intravesical therapy if radical cystectomy is unsuitable or declined by the person, or if the bladder cancer that recurs is intermediate- or low-risk."
Age on model entry of 64 years	Mean age of RC is 66.8 years and median, national RC analysis NHS Digital	The EAC accept that there will be a difference between starting age and the need for radical cystectomy and have accepted this assumption. Starting age is included in sensitivity analysis, and has an impact on lifetime costs.
Males are 75% of population	Consistent with national RC analysis, NHS Digital	The EAC agree this is consistent with NHS digital data and has not made any changes.
Additional assumptions identified by the EAC		
BCG is not an available option for the modelled patients	This is stated in the submission, but is an important consideration as the normal treatment for patients with high risk NMIBC would be either BCG or RC (NG2). The choice of clinical evidence means that MMC was used as the comparator.	
MMC would be a suitable treatment for these patients in the NHS pathway	MMC is normally offered as a first line treatment to patients with intermediate risk NMIBC, however NICE guidance (NG2) states that its use may be discussed as an alternative to RC for people in whom induction BCG has failed, for whatever reason.	
RC is an available option to patients in the model	The existing NICE guidance (NG2) would suggest that MMC alone is an option for patients with high risk NMIC only where BCG induction has failed and radical cystectomy is unsuitable or declined by the person, or if the bladder cancer that recurs is intermediate- or low-risk.	
All patients with RC will have a stoma	NICE guidance (NG2) recommends that people who have chosen RC are offered a urinary stoma or continent urinary diversion, unless there are strong contraindications. Expert advice was that the majority of patient would receive a urinary stoma therefore the EAC has accepted this assumption.	
The treatment is adjuvant only	The modelled treatment is adjuvant, and the population for clinical data include only one patient with carcinoma in situ. Therefore, it would not be appropriate to generalise the results of the model to people with CIS as the regimen recommended for is the higher, ablative dose.	
Treatment is only included for year 1 for both arms	The model includes treatment for 12 cycles over year one. The EAC notes that a full treatment plan may include reduced treatment cycles in year 2 and 3, but there is variation in normal practice and the EAC have accepted this assumption.	

Economic model parameters

Clinical parameters and variables

Patient start age: The model starting age was 64 years, and 75% male, based on the population recorded as receiving radical cystectomy on NHS Digital Hospital Episode Statistic, 2018/19 (code M34 or M34.1 to M34.9). The mean age for this procedure was 66.8 years. The EAC have assumed that the difference between 64 years and 67 years is because patients take some

years to reach the need for radical cystectomy. The EAC have not made changes to these variables, and they are included in the sensitivity analysis.

Disease free survival: Columbo (2011) compares the use of Synergo to deliver MMC with the use of standard intravesical MMC in 83 patients with primary or recurrent NMIBC, treated in Italy and Israel. The patients include one patient with carcinoma *in-situ*, and all are treated with an adjuvant regimen of 40mg MMC for 8 weekly sessions, followed by 4 monthly sessions. All treatments were in an outpatient setting.

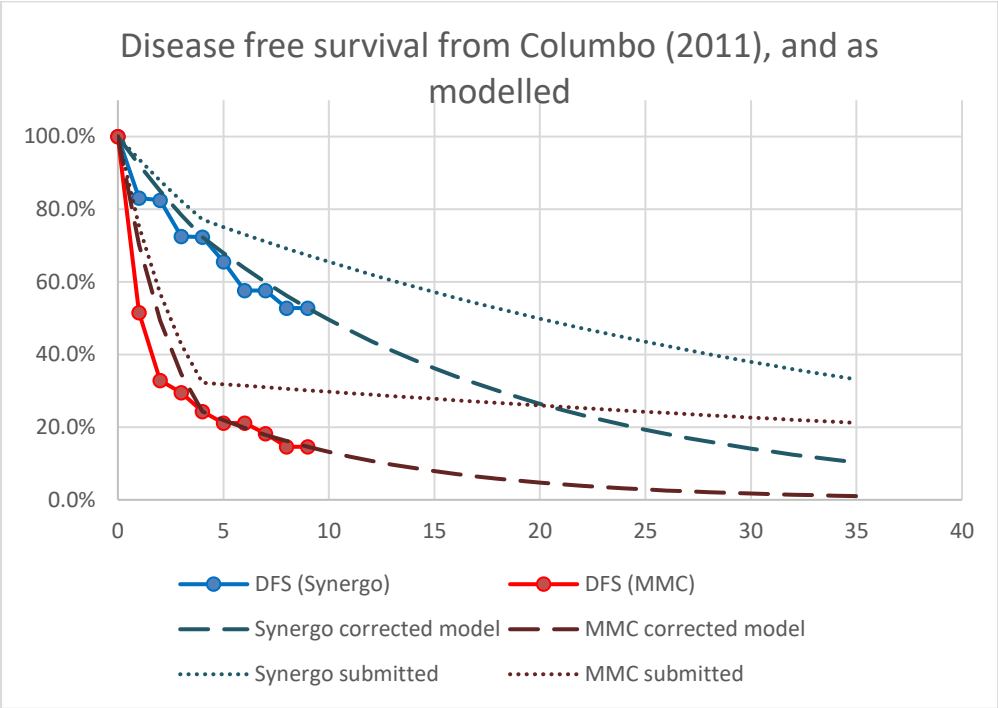
This is the study with the longest follow-up, and where the treatment regimen meets the current recommendation for the patients included in the study (with an adjuvant dose and only 1 patient with CIS). Therefore, the model findings would not be applicable to patients with CIS. The EAC could not determine the percentage of patients that were considered to have high or intermediate risk NMIBC, however the company submission reports them as 77% and 23% respectively.

The submitted model takes the 10-year Kaplan Meier graph and splits it into two fixed transition probabilities:

- 0-4 year results are used for cycles 0-4
- 5-10 year results are used for cycles 5 onwards

The EAC corrected the calculation of both rates (Appendix G). The use of fixed transition probabilities based on data points rather than a survival analysis model may limit how well the modelled disease-free survival fits the observed clinical data. The EAC investigated the fit visually using the graph in figure 4.

Figure 4: Disease Free Survival



The EAC accept that, once the calculation has been corrected, this is a reasonable extrapolation of the clinical data. The disease-free survival is used to calculate the number of recurrences. The actual number in the remission and recurrence states varies from that in figure 4 due to the addition of mortality into the Markov model (see Appendix F).

Treatment after recurrence: All patients who have a recurrence of disease are assumed to receive radical cystectomy and a permanent urinary stoma.

Adverse events: Adverse events specifically associated with Synergo are included in the model, with data taken from Columbo (2011). The included adverse events are urinary tract infection (UTI) and incontinence.

Mortality: Mortality is calculated appropriately using a population wide rate, with the addition of a 30-day mortality for radical cystectomy (applied for one cycle only). Following radical cystectomy, an alternative, higher rate of mortality is used. The source of the 30-day and post cystectomy mortality rate (and also re-intervention) is Afshar 2018. This is a retrospective review of radical cystectomies since the introduction of Improving Outcomes Guidance

for urological cancers (CSG2). It takes data from Hospital Episode Statistics between 2003 and 2013/14, with 15,292 cases.

The EAC accepted the choices of input for mortality and made a correction to the calculation of post-cystectomy mortality to ensure that the value used in the Markov calculations was for mortality rather than survival.

Quality of life: Utility values for patients in remission were taken from Cox (2020) who state that they were derived from the EQ-5D-3Ltool administered as part of the BOXIT trial, reported in Kelly (2019). However the EAC have been able to find no information suggesting that EQ-5D-3L was used as part of the BOXIT trial in either Kelly (2019) or the trial registration site.

State diagrams for the intervention and comparator arm are presented in Appendix F. The clinical parameters and variables in the model are summarised in table 15.

Table 15: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value	Source	EAC Value	EAC comment
Recurrence years 0 - 4				
Annual risk of recurrence – MMC	24.6%	Colombo 2011	29.8%	Derived from the difference in survival between year 4 and 0. EAC changed calculation to take risk over 4 years, not 5, but used same data source.
Annual risk of recurrence – Synergo	6.3%	Colombo 2011	7.8%	
Recurrence years 5-9				
Annual risk of recurrence - MMC	1.4%	Colombo 2011	9.7%	Overall disease-free survival at 10 years is 14.6% (Columbo 2011). Correction to calculate difference in survival between 5 and 10 years as a percentage of those in cohort at 5 years.
Annual risk of recurrence - Synergo	2.7%	Colombo 2011	6.1%	Overall disease-free survival at 10 years is 52.8% (Columbo 2011). Correction as above.
Radical Cystectomy				
Reintervention following radical cystectomy	30%	Afshar 2018	No change	
Patients with stoma after	100%	Assumption	No change	Experts agreed that the majority of patients would receive a urostomy.

radical cystectomy				
Mortality				
Whole population mortality		National life tables UK (ONS, 2017-19)	No change	Variable with age / model cycle
30-day mortality risk with radical cystectomy	2.1%	Afshar (2018)	No change	This is risk applied at the point of cystectomy, for a single cycle only. It includes Improving Outcomes Guidance (IOG) compliant and IOG non-compliant procedures.
Annual mortality risk after radical cystectomy	5.0%	Afshar (2018)	8.8%	This is an annual risk applied instead of the overall survival calculation to those patients in the post-cystectomy state. This figure includes both IOG compliant and non-compliant procedures and is derived from KM survival graph. EAC correction to calculate mortality rather than survival
Health Related Quality of Life				
Utility for patients in remission	0.85	Cox 2020	Not suitable for use	The original trial used EORTC QLQ rather than EQ-5D-3L, and it is unclear if this has been mapped to EQ-5D-3L values. The EAC do not feel these values are suitable for use, but have not identified an alternative.
Utility for patients with recurrence and a radical cystectomy	0.65	Mason 2018		A 0.2 HRQOL decrement for patients following cystectomy. This is an extrapolation based on data in Mason 2018, but cannot be applied if the utility for remission is unsuitable.

Resource identification, measurement and valuation

Throughout the model, costs have been inflated to either 2020/21 or 2021/22, using the rate for 2019/20 that was published in PSSRU (2020). This includes an assumption that the inflation rate for NHS costs will remain unchanged. The EAC have changed costs to be consistently inflated to 2020/21 throughout the model. The impact of these changes on the incremental cost is minimal.

Intravesical MMC costs: These are composed of the cost of the MMC drug and a cost of treatment time. There is some uncertainty about the use of day or outpatient costs, however as these are applied equally across both arms it does not affect the case for cost saving.

BCG costs: The cost of BCG is £71.61 per cycle (BNF 2021). Although BCG is not included in the company submitted model, or the EAC base case for

Synergo vs MMC, it is discussed in later scenarios and included here for ease of comparison of procedure costs (table 16).

Additional Synergo costs: These are composed of the costs associated with the device (annual lease costs, training costs and consumables), adverse events specific to Synergo, and an additional length of time that is taken to deliver Synergo. The EAC adjusted some inflation calculations, but have accepted these costs with the exception of wait time. There is uncertainty around: the additional time that is required for treatment with Synergo; the most appropriate cost source; and if this should include staff time. Three expert advisors agreed that a treatment session for Synergo was 75 – 90 minutes long, and from 10 to 30 minutes for MMC. One expert said that the patient would be at the day unit for about four hours. Three experts felt that a clinical nurse specialist, or other member of staff was with the patient for the duration of the session, one expert estimated staff time for Synergo as 30 minutes and for MMC as 10 minutes. The submitted model used 30 minutes additional time for Synergo. The EAC have used 70 minutes additional time for Synergo.

The submitted model costed additional time at £116 per hour for non-staff time (2019) based on costs on an oncology consultant led outpatient clinic. The EAC considered that staff time should be included, however using the same source of costs (ISD R044, Scottish Cost Book 2019/20) gives a cost of £691 per hour, which seems disproportionately high compared to NHS reference costs of £223 for subsequent chemotherapy outpatient appointments (SB15Z, NHS Reference costs 2018/19). The EAC have chosen to model the cost of a band 7 specialist nurse for an additional 70 minutes, using a cost that includes some facilities and estates cost (£61 per hour, PSSRU 2020). The EAC also carried out additional sensitivity analysis, due to the uncertainty around these inputs.

Summary of procedure specific costs for Synergo, MMC and BCG: All three alternative therapies include a drug cost per cycle, plus costs of the patient visit. These clinic costs, or administration costs, are based on NHS reference costs for a day case visit initially and an outpatient visit on

subsequent cycles. There are additional costs for Synergo for the device, consumables, additional treatment time and potentially for cystoscopy prior to the initial treatment. The Synergo device costs £9,806 and the model assumes that this is split across 30 patients over the lifetime of the device, at a cost of £327 per patient. The Synergo consumables are priced at £7,350 per box of 15 units (excluding VAT).

Table 16: Summary of procedure specific costs for Synergo, MMC and BCG

	Synergo vs MMC		**Synergo vs BCG (no CIS)**	
	Synergo	**MMc**	**Synergo**	**BCG**
Costs for all therapies			No change	
Drug cost	£135	£135		£72
First cycle - clinic cost	£402	£402		£402
Subsequent cycles - clinic cost	£233	£233		£233
Additional Synergo costs*				
Device per patient	£327	£0		£0
consumables per use	£490	£0		£0
additional wait cost	£72	£0		£0
First cycle / procedure cost	**£1,426**	**£537**		**£474**
Per subsequent procedure	**£930**	**£368**		**£305**
Number of procedures modelled	**12**	**12**	**21**	**22**
Total Cost of intervention	**£11,650**	**£4,585**	**£20,016**	**£6,871**
*A later scenario was created that included £261 for cystoscopy prior to the first treatment with Synergo. Inclusion of this brings the total cost of the Synergo to £11,911 for 12 procedures, or £20,277 for 21 procedures				

The number of procedures is taken from the clinical paper for each scenario. For Synergo vs BCG (no CIS) the costs per procedure for Synergo are unchanged, however treatments are extended through to the second year resulting in a higher number of cycles. This higher number of cycles increases the difference in the cost of the intervention between the two arms.

Adverse event costs: This is included in the additional Synergo costs with the assumption that other than UTI and incontinence all other adverse events associated with the initial treatment are similar in both arms. No adverse events are included for cystectomy other than re-intervention. The EAC have not made any changes to these assumptions.

Annual follow up costs: These are based on NICE guidance NG2, summarised in table 17. The submitted model takes the 5-year total visits and calculates an average annual cost for the first 5 years, using 77% intermediate risk and 23% high risk, which is stated as the population described in Columbo 2003. The submitted model uses 13 visits in the first 5 years, which the EAC has amended to 11 visits (see table 17).

Table 17: Summary of follow up recommended for patients with intermediate and high risk NMIBC

	Intermediate risk	High risk
Year 1	3 and 9 months	Every 3 months (3,9,12)
Year 2	18 months	Every 3 months (3,9,12)
Year 3-4	Annually	Every 6 months (6,12)
Year 5	Annually	Annually
Total visits to year 5	6	11 (13 in submission)
Subsequently	No follow up	Annually

After year 5, the model takes the high-risk annual cost from years 0-5 (£575 after all EAC changes) and applies to the proportion of people (23%) with high-risk NMIBC for the remaining years. The EAC has amended this to be an annual cost of £261 applied to 23% of people, which is the cost of a single annual cystoscopy as per recommendations. Both of these amendments result in a small increase in cost saving.

The EAC have not been able to identify the proportion of people with intermediate and high-risk in the Colombo trial (Colombo 2003, 2011). There is information on patient demographics including tumour grade, stage and multifocality which may support the company submission, however there is no clear risk categorization reported. The EAC have not changed these percentages.

Radical cystectomy costs: In addition to the operative cost which is sourced from NHS reference costs, this includes stoma clinic visits (1 pre-operative

and 4 post-operative in first year), 2 telephone consultations and 2 home visits by a band 6 nurse. For 30% of the patients, the cost of re-intervention is also included. One year's worth of stoma products is also included, and costs discussed below.

Stoma care costs: The submission used an annual cost of £2,008 (inflated to £2,144) for stoma care products. This is quoted in a report by the East of England NHS Collaborative Hub (2019) as a typical cost per patient in the UK. No additional information was given, although costs in the East of England region were given that averaged at £1,925 per patient per year in 2018 (£2,011 in 2020/21). The EAC took product use from Black (2009) as a one-part urostomy bag per day plus one night bag per week. Prices for products were taken from NHS supply chain to give an annual cost of £2,245. As in the submitted model, undergarments were added at £100, and no cost for skin care creams, adhesive or remover were included. All methods discussed resulted in similar costs for stoma products, however this is a key driver for the model and additional sensitivity analysis was also carried out.

In addition to products, annual stoma care costs (after year 1) included 1 stoma clinic and two telephone contacts. This EAC found patient leaflets stating that follow up visits would be every 6 months to 1 year (Guys and St Thomas) and have made no changes to these submitted costs.

Palliative care: The submitted model bases the cost of palliative care on Cox (2020) who give a cost of £12,968 for 2017. There is no additional information on the calculation of this by Cox (2002) other than a reference to Mowatt (2010). These authors calculated £12,825 based on £95 daily x 135 days (SD01A, stated as 'Inpatient specialist palliative care 19 years and over" NHS Ref costs 2005/6). The EAC suspect this is a reporting error and the cost used was Specialist palliative care Outpatients (TSALOP: SD01A). Currently available outpatient palliative care codes from NHS reference costs (2018/19) are

- SPAL: SD04A (£185) Medical specialist palliative
- SPAL: SD05A (£101) Non-medical specialist palliative care

Applied for 135 days these would result in £25,551.45 or £13,949.95 respectively. The EAC has used the lower cost, however this has minimal impact over a lifetime horizon. The cost of palliative care following bladder cancer used in NG2 was £8,502 for 2012-13.

Key cost parameters are summarised in table 18.

Table 18: Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	EAC value	Source
Intravesical MMC (both arms)			
Intravesical MMC per cycle	£135.00	No change	Mitomycin C 40mg powder and solvent for intravesical solution vials (medac UK) NHS Indicative price, BNF 2021
Number of MMC cycles (year 1)	12	No change	Advice from company, based on Columbo (2011)
Total MMC cost (per patient in year 1)	*£1620*	*No change*	*Cost of MMC per cycle x 12, as above*
Treatment Administration Costs (both arms)			
Day case first attendance (1st treatment)	£411	£402	SB14Z, Daycase. £385 NHS Reference costs 2018/19, inflated to 2021. Error in inflation corrected by the EAC
Subsequent attendance (11 MMC treatments)	£238	£233	SB15Z, Outpatients £223, NHS Reference costs 2018/19, inflated to 2021. Error in inflation corrected by the EAC
Total administration cost (per patient)	*£3,029*	*£2,965*	*As above, year 1 only*
Additional Synergo Costs			
Device Costs			
Device cost per site (annual lease)	£9500	No change	Cost from submission. The EAC confirmed with the company that leasing the device is the only option and all maintenance is included in the lease cost.
Nurse band 7 (per hour)	£61.33	No change	Used in the calculation for training costs. Assumption is that 3 band 7 nurses with be required for a total of 5 hours each.
Consultant	£121.63	No change	Used in the calculation for training costs. Assumption is 1 consultant will be required for a total of 5 hours.
Annual training cost per site	*£305.62*	*No change*	*Calculated for 3 band 7 nurses and 1 consultant (as above), 5 hours training, costs spread over 5 years.*
Number of patients per device (annual)	30	No change	This is an assumption which has been accepted by the EAC following expert advice with values in a range from 10 to 38 patients a year.
Total device cost (per patient)	*£326.85*	*No change*	*Cost per patient is based on annual lease cost plus annual training costs divided by the annual number of patients per device.*
Consumables cost per patient			
Consumables per patient in year 1	£5,880	No change	£490 per cycle for 12 cycles, costs from submission.
Additional Administration Costs			
Cost of additional wait time (30 min) per cycle	£61	£71.55	ISD R044:Speciality Group Costs- outpatients 2019/20. EAC used 70 minutes of band 7 nurse time at £61 per hour (PSSRU 2020)

			Applied for 12 cycles (EAC cost of 858.56)
Adverse events specific to Synergo			
UTI (per event)	£42.92	£42.97	21 Amoxicillin tablets (500mg),(3 x daily x 7 days) £1.72 (BNF, 2021) 1 x Cytology test, £7.47 (NHS Reference Costs 2018/19) 1 x GP attendance, £33.73 (PSSRU 2020) All costs inflated to 2021, correction by EAC as needed. Cost is applied to 16% of patients receiving Synergo
Incontinence (per event)	£77.42	No change	28 Duloxetine tablets (2 x daily x 4 weeks) £9.96 (BNF, 2021) 2 x GP attendances, £33.73 each (PSSRU 2020) All costs inflated to 2021 Cost is applied to 2% of patients receiving Synergo
Adverse events per patient per cycle	*£8.42*	*No change*	*Cost of adverse events per patient per cycle*
Total treatment costs (year 1 only)			
Total Intravesical MMC cost per patient	*£4,649*	*£4,585*	*Cost of MMC plus cost of administration for 12 cycles*
Total Hyperthermic MMC (Synergo) cost per patient	*£11,689*	*£11,751*	*Cost of MMC plus cost of administration for 12 cycles plus additional costs specific to Synergo*
Radical Cystectomy (including 1 year follow-up)			
Radical Cystectomy	£12,539	£12,268	Cystectomy with Urinary Diversion and Reconstruction' LB39C-D, elective surgery, NHS reference costs 2018/19 Inflation corrected by the EAC
Pre surgery stoma clinic	£49	£47.69	£46, N24AF Specialist Nursing, Stoma Care Services, Adult, Face to face NHS reference costs, inflated to 2020/21
Home visit	£51	No change	1 hour band 6 nurse time PSSRU 2020, inflated to 2020/21. 2 visits included
Stoma clinic attendance	£49	£47.69	£46, N24AF Specialist Nursing, Stoma Care Services, Adult, Face to face NHS reference costs, inflated to 2020/21. 4 visits included
Telephone contact	£17.90	£17.51	N24AN Specialist Nursing, Stoma Care Services, Adult, Face to face NHS reference costs, inflated to 2020/21. 2 calls included
Re-intervention after initial cystectomy	£2961	£2897	£2,773 Ureteric or Bladder Disorders with intervention (LB19C & D, NHS reference costs 2018/19) inflation corrected by EAC. Re-intervention rate of 30% (Afshar 2018) applied
Stoma products (year 1)	£2,244	£2,345	Stoma products: £2,008 stated as annual UK cost per patient (East of England NHS Collaborative Hub (2019) inflated to 2021 costs. Undergarments: assumption of an additional £100. EAC calculated costs of products from NHS supply chain and included £100 for undergarments.
Total cystectomy cost (per patient in year 1)	*£16,167.41*	*£15,823*	*Including 30% re-intervention, clinic appointments and stoma care.*
Stoma Management (Year >1)	£2329	£2,427	Based on the cost of stoma in year 1 plus attendance at 1 stoma clinic (£49) and 2 telephone contacts (£18*2) per year (after year 1).
Follow-up Costs for recurrence free patients			
Cost per cystoscopy procedure	£267	£261	NHS Reference costs 2018/19 – LB72A (Unit cost of Diagnostic flexible cystoscopy, 19 years and over) inflated to 2021 prices.

Intermediate risk, annual cost per patient of cystoscopy	£320	£313	Annual cost of flexible cystoscopy for 6 follow-up visits over 5-year follow-up period. Applied to 77% of patients
High risk, annual cost per patient of cystoscopy	£694	£575	Annual cost of flexible cystoscopy for 13 follow-up visits over 5-year follow-up period. Applied to 23% of patients EAC amended to 11 follow up visits
Palliative care costs			
Cost of palliative care	£14,167	£14,244	Submitted cost from Cox, taken from Mowatt (2010): £12,825 based on £95 daily x 135 days (SD01A, NHS Ref costs 2005/6) EAC changed to: SPAL: SD05A (£101) Non-medical specialist palliative care NHS reference costs (2018/19), inflated to 2021. Applied for 135 days.

Sensitivity analysis

The company submitted one-way sensitivity analysis using a 20% increase and decrease of variables. These found key drivers of the model to be the cost of Synergo, the risk of recurrence and the cost of stoma management. The EAC repeated this analysis using their amended parameters, and the same variation in variables.

The EAC completed two-way sensitivity analysis for two of the variables with most uncertainty: the cost of additional treatment time and the cost of one year of stoma care. The EAC also considered the cumulative cost saving over time.

9.4 *Additional EAC model: BCG as comparator for 2nd line treatment (Tan, 2019)*

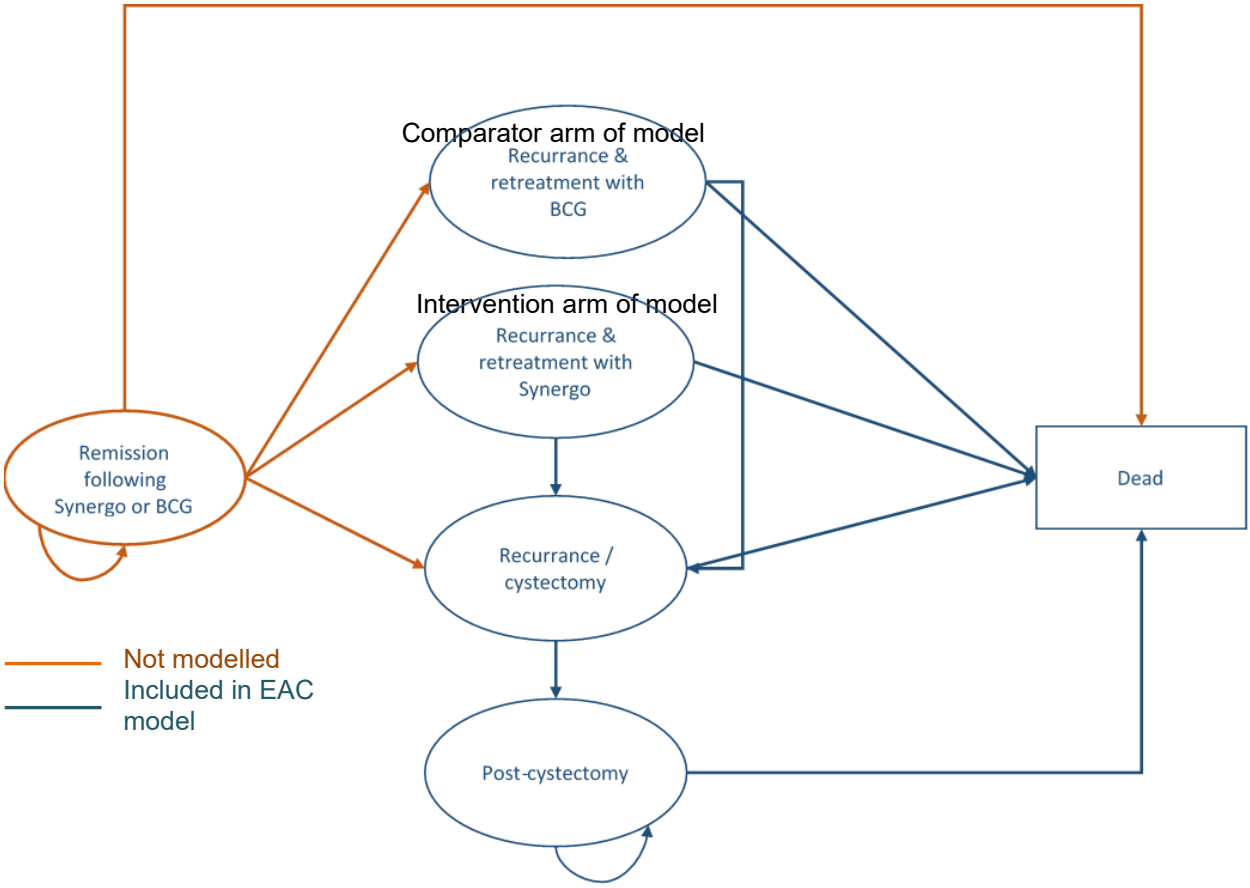
In addition to correcting model errors or adjusting inputs in the existing model, the EAC also considered the available comparative clinical evidence and to create a new model that fitted some aspects of the current NHS use of Synergo. The EAC considered an alternative model structure, and considered that the structure in figure 5 would better reflect current NHS pathways. However, there are strong limitations in the data available to populate such a model, as discussed in sections 8 and 9.2.

The company submission agreed that the population modelled was narrower than the scope, and that they had not modelled BCG as a comparator, nor people who have failed BCG. The company felt that this reflected their positioning for Synergo.

They also stated that Tan (2019) “has such material weaknesses that it could not be used to populate the model”.

Due to limitations of available evidence, the EAC have restricted remodeling to recurrence of NMIBC following treatment with BCG or other standard care in patients with intermediate or high risk NMIBC and no CIS, with the intervention and comparator arm as shown.

Figure 5: EAC Proposed Alternative Markov Model Structure



Clinical inputs

Mortality was unchanged from the submitted model.

Disease free survival: The EAC based the model on clinical inputs from Tan (2019), with the comparator of BCG for 2nd line treatment. The majority of patients treated in Tan (2019) had CIS present, and would, if treated today, receive a higher ablative dose. For these patients the results of Tan (2019)

may not be indicative of expected results in the NHS at this point in time. There is a subgroup analysis of patients without CIS who did receive the recommended Synergo regimen. This subgroup of 33 patients is used for the EAC scenario of Synergo vs. BCG for 2nd line treatment for patients with no CIS.

Data was extracted from the Kaplan Meier graph in Tan (2011) using webplot digitizer.

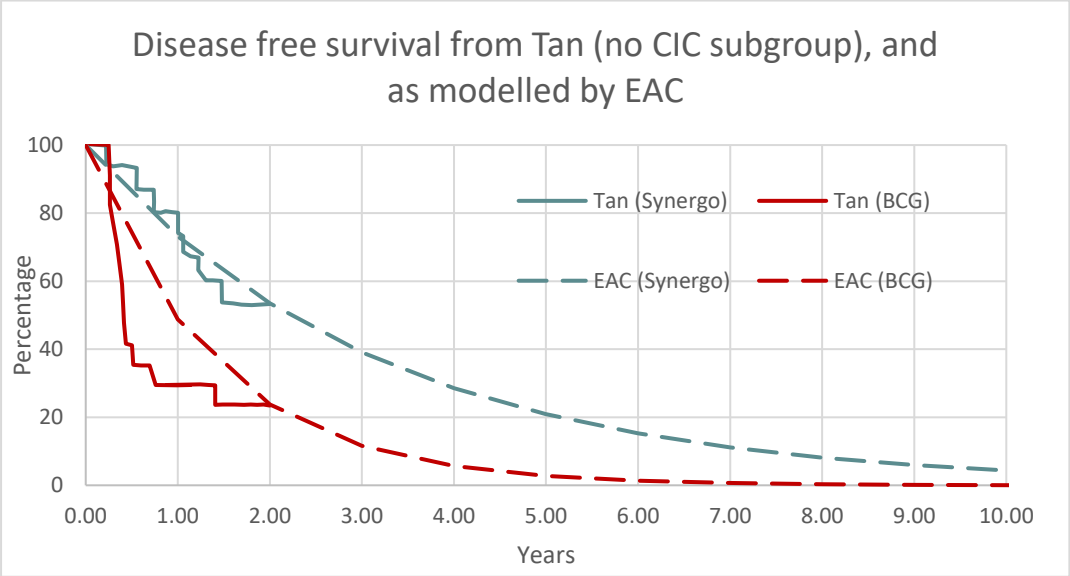
The EAC did not identify any comparative study that would have been able to inform modelling for patients with CIS using any comparator.

The comparator in the trial was standard care, which was BCG for 33 patients (59%), but the remainder received MMC alone (n=10, 18%) or EMDA MMC (n=13, 23%). The paper does not give information on the distribution of standard care within the subgroup without CIS.

The EAC have used the standard care data for the clinical input, but for simplicity have only costed the BCG regimen in the costs.

Tan (2019) report disease free survival at 2 years as 53.5% and 23.8% for Synergo and BCG in the sub group with no CIS. The EAC calculated an annual risk of recurrence (using method described previously) of 26.9% for Synergo +MMC and 51.2% for BCG. The length of follow up is a limitation, however figure 6 shows a plausible impact on longer term disease free survival

Figure 6: Modelled disease-free survival (note shorter time period than shown in figure 4)



Resource identification, measurement and valuation

The cost inputs largely remained unaltered, with the exception of the actual BCG treatment drugs and the specification of the regimen.

BCG Cost: A cost of £71.61 per instillation was used, based on OncoTICE 12.5mg powder for reconstitution for instillation (BNF 2021).

Treatment regimen: The regimens for both Synergo and BCG are taken from Tan (2019). For Synergo this includes 6 weekly installations of RITE at 2 x 20mg, followed by one instillation every 6 weeks for the 1st year and one every 8 weeks for the 2nd year. The regimen for BCG includes 6 weekly instillations, followed by maintenance 3 weekly instillations at 3,6,12,18,24 months)

Two experts said that this reflected their normal practice, one that BCG is normally completed at 12 months. The fourth stated that they would have additional doses at 30 and 36 months. The EAC have used the regimen from Tan (2019) as the base case, and included alternative regimens in sensitivity analysis. Table 19 lists the total treatments included in each year of the model

Table 19: Synergo and BCG treatment regimens

	Synergo Base case	BCG treatment		
		Base case	Sensitivity high	Sensitivity low
Year 0	14	13	13	13
Year 1	7	9	9	0
Year 2	0	0	6	0

Adverse events: Although Tan (2019) identify adverse events in both the Synergo and BCG arms of the trial, it is unclear how many of these led to additional health care costs, and for the small sub-group in the analysis the patient numbers are very low. The EAC have not identified an alternative source of data for adverse events. Patient information from Cancer Research UK is that side effects of BCG include:

- Irritated bladder
- Passing urine more often and more urgently
- Blood or debris in urine
- Flu like symptoms for 24 to 48 hours after treatment
- Discomfort and pain when passing urine

They also state that more rarely there could be systematic illness from BCG within the body, which may result in hospitalisation and intravenous antibiotics.

Most of the more common adverse events are treated conservatively, possibly with medication, and resolve over a short period of time. These are likely to have little cost impact, although they are unpleasant. However, some adverse events may result in patients not completing the BCG maintenance regimen. In Tan (2019) 5 Synergo patients did not complete 6 or more installations due to adverse events and 5 control arm patients were excluded due to adverse events.

The EAC have removed the adverse event costs from Synergo, as no evidence was identified to suggest that adverse events would be more costly with Synergo than BCG, and assumed that adverse event costs are equal. This change has minimal change in the life time horizon (reduction of £118 in lifetime cost incurred). The EAC explored the sensitivity to the cost of BCG procedures (which includes adverse event costs).

9.5 *Results from the economic modelling*

Base case result summary

For the submitted model comparing Synergo to MMC, both the original model and the EAC amended base case resulted in cost savings over both 5 year and life time horizons. Although the model results in a cost saving (£3,549 over lifetime horizon) per patient, for the clinical pathway that has been modelled, there are concerns about how well that pathway fits the normal use within the NHS.

The EAC model using Tan (2019) for Synergo vs. BCG for patients with no CIS may represent a more typical pathway, and results in an increased cost per patient over a lifetime horizon of £9,858.

Both models demonstrate a reduction in radical cystectomies and an increase in life years, although these changes are very small when using BCG as the comparator (for patients with no CIS).

Table 20: Summary of model results for Synergo vs. MMC and BCG

	Technology	Comparator	Cost saving per patient	QALYs*
Company submission, Synergo vs. MMC				
Short term (<=5 years)	£18,902	£20,456	£1,554	0.58
Longer term (post 5 years)	£17,639	£20,551	£2,912	1.17
Lifetime horizon	**£36,541**	**£41,007**	**£4,466**	**1.75**
EAC base case for Synergo vs. MMC				
Short term (<=5 years)	£19,746	£22,526	£2,780	0.66
Longer term (post 5 years)	£20,590	£21,358	£769	1.69
Lifetime horizon	**£40,335**	**£43,884**	**£3,549**	**2.35**
EAC model for Synergo vs. BCG (Tan 2019)				
Short term (<=5 years)	£34,438	£27,431	-£7,006	0.49
Longer term (post years)	£23,004	£20,153	-£2,852	0.30
Lifetime horizon	**£57,442**	**£47,584**	**-£9,858**	**0.79**
*QALYs are reported, but the EAC do not have confidence in the utility values used in the model				

Detailed results for Synergo vs. MMC (submitted model and EAC)

Despite numerous amendments to variables and the model structure (detailed in Appendix H), the final EAC results for Synergo vs. MMC (cost saving by £3,549 over a lifetime horizon) are not substantially different from the submitted model cost saving of £4,466 over a lifetime horizon (table 21). This has to be viewed in context of concerns about how well that pathway fits the normal use within the NHS.

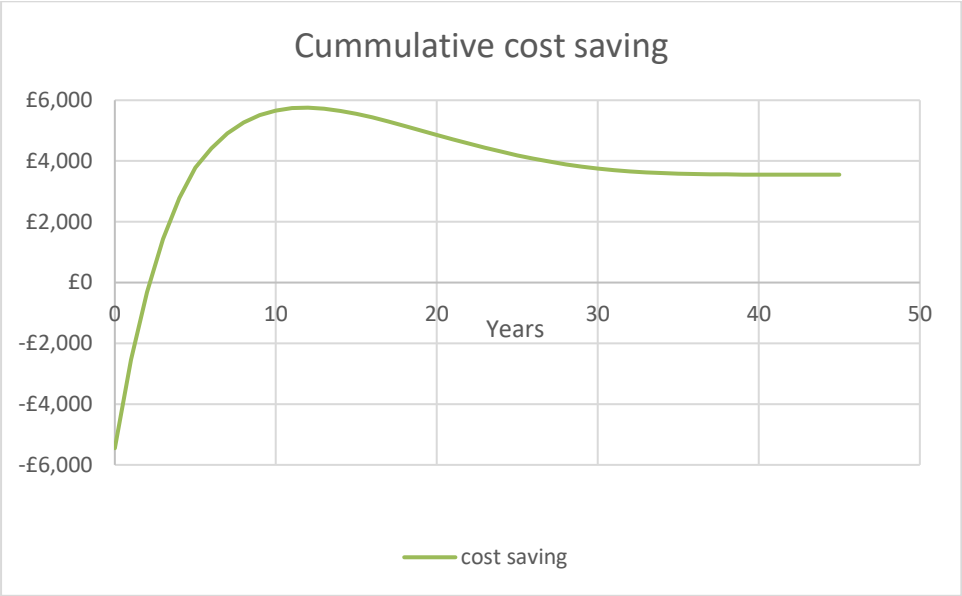
Figure 7 shows cumulative cost savings per cycle, with the initial cost of Synergo being countered by annual cost savings at each cycle until year 13. These annual cost savings are due to fewer radical cystectomies being performed and fewer patients incurring post-cystectomy costs in the Synergo arm (as shown in Appendix F). After year 13, the number of post-cystectomy

patients is similar in each arm, and there are a greater number of patients remaining in remission in the Synergo arm (and these accumulate annual costs for testing) There is a small annual cost incurred (between £0 and £148) in each cycle from this point onwards, leading to a gradual decrease in cumulative cost savings part this point. Over time there are fewer patients remaining in the model, and the impact decreases, as seen in figure 7.

Table 21: Summary of results for Synergo vs. MMC (Columbo 2011)

	Company Results			EAC Results		
Per patient results	**Technology**	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Remission	£12,762	£4,095	**-£8,667**	£12,885	£4,754	**-£8,132**
Recurrence	£6,972	£11,049	**£4,077**	£9,347	£14,212	**£4,865**
Post-cystectomy	£8,940	£17,431	**£8,491**	£9,776	£15,611	**£5,835**
Dead (palliative care)	£7,867	£8,432	**£565**	£8,327	£9,307	**£981**
Total	£36,541	£41,007	**£4,466**	£40,335	£43,884	**£3,549**
Total radical cystectomies	0.49	0.67	0.18	0.711	0.93	0.22
Total life years	12.93	11.77	1.16	11.62	9.47	2.15
Total QALYS	10.16	8.41	**1.75**	8.95	6.60	**2.35**
*QALYs are reported, but the EAC do not have confidence in the utility values used in the model						

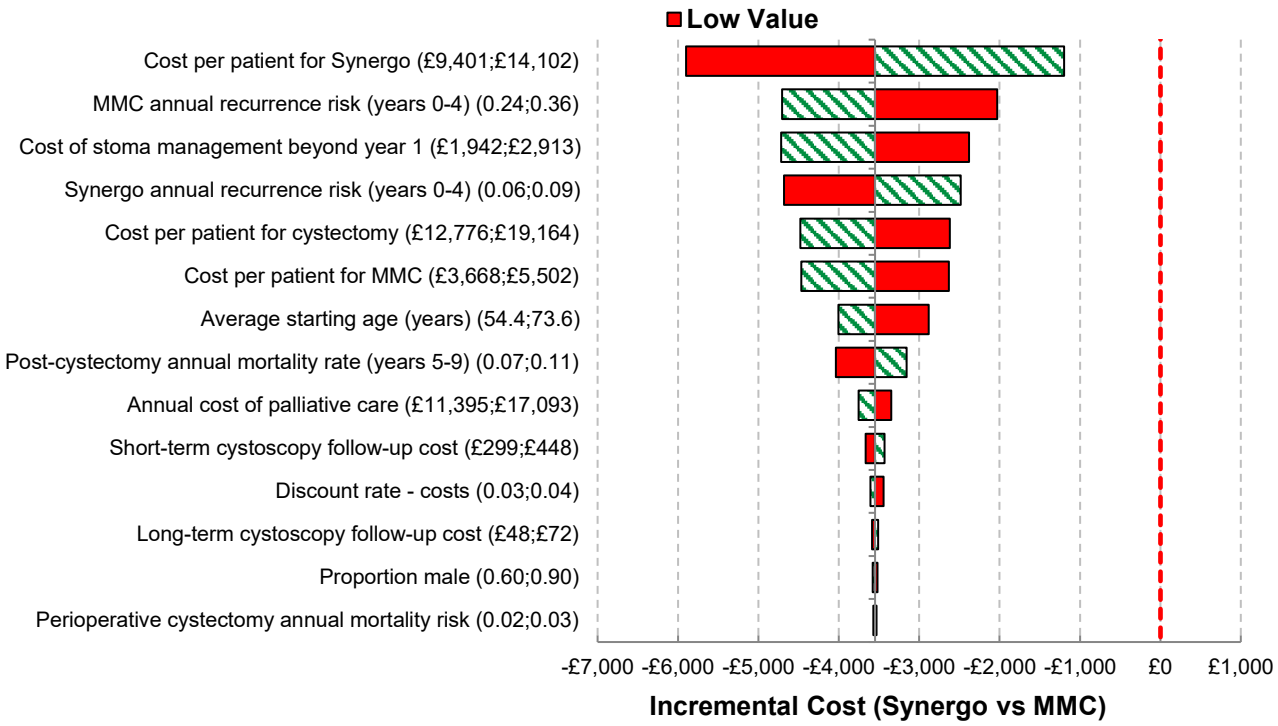
Figure 7: Cumulative cost saving for Synergo vs. MMC (Columbo 2011)



Sensitivity analysis results (Synergo vs. MMC)

The company submitted one-way sensitivity analysis using a 20% increase and decrease of variables. These found key drivers of the model to be the cost of Synergo, the risk of recurrence and the cost of stoma management. The EAC repeated the submitted one-way analysis using their amended parameters, as shown in figure 8. In the amended EAC base case, there remain no parameters that, when taken individually, result in the model being cost incurring at either the 5 year or lifetime time horizon. The key drivers have changed slightly after the EAC changes, with the cost of Synergo giving greatest variations, followed by the risk of recurrence, stoma management and cost of cystectomy.

Figure 8: One Way Sensitivity Analysis



The additional time for administering Synergo is included in the total Synergo cost, in the tornado diagram. The EAC completed additional two-way sensitivity analysis for the cost of additional treatment time and the cost of one year of stoma care (table 22). The company used a non-staff cost for additional time of £61 (based on £116 x 30 minutes), the EAC used a band 7 staff time of £71.55 (£61.33 x 70 minutes). The sensitivity analysis range includes the cost of both these costs for 70 minutes (£206.89, likely to include an element of double counting). This shows that where stoma care costs are greater than £2,000 per year, the model is cost saving for all included variations in additional time to administer Synergo.

Table 22: Two-way sensitivity analysis, showing cost saving per patient for variations in Stoma care and additional session time for Synergo. (Base case: Annual stoma care = £2,42.7, Additional time= £71.55, incremental cost saving, lifetime horizon = £3,549)

		Annual cost of stoma care after year 1						
		£500	£1,000	£1,500	£2,000	£2,500	£3,000	£3,500
Cost of additional time for Synergo (per session)	£50	-£1,163	£184	£1,532	£2,879	£4,226	£5,574	£6,921
	£75	-£1,463	-£116	£1,232	£2,579	£3,926	£5,274	£6,621
	£100	-£1,763	-£416	£932	£2,279	£3,626	£4,974	£6,321
	£125	-£2,063	-£716	£632	£1,979	£3,326	£4,674	£6,021
	£150	-£2,363	-£1,016	£332	£1,679	£3,026	£4,374	£5,721
	£175	-£2,663	-£1,316	£32	£1,379	£2,726	£4,074	£5,421
	£200	-£2,963	-£1,616	-£268	£1,079	£2,426	£3,774	£5,121
	£225	-£3,263	-£1,916	-£568	£779	£2,126	£3,474	£4,821
	£250	-£3,563	-£2,216	-£868	£479	£1,826	£3,174	£4,521

Detailed results for Synergo vs. BCG (patients with no CIS, Tan 2019)

The costs of Synergo are greater than BCG both in the short and long time horizons. In year one, the higher cost of Synergo is similar to the difference seen in the submitted model, however this is not balanced by sustained cost savings in the subsequent years. Due to the higher recurrence rates, patients in both arms move rapidly from remission to recurrence / cystectomy. There are only a small number of years where the number of additional Synergo patients in remission are sufficient to result in a cost saving for that year. This is shown in figure 9 and figure 10, where it can be seen that both the first and second years are cost incurring (due to treatment in second year), with only years 3 and 4 are cost saving.

Table 23: Summary of results for Synergo vs. BCG (Tan 2019)

	EAC Results, life time horizon, per patient		
	Technology	**Comparator**	**Cost saving per patient**
Remission	£16,438	£4,488	-£11,951
Recurrence	£15,650	£15,983	£333
Post-cystectomy	£15,989	£17,415	£1,426
Dead (palliative care)	£9,364	£9,699	£334
Total	**£57,442**	**£47,584**	**-£9,858**
Total radical cystectomies	0.96	0.98	0.02
Total life years	9.44	8.64	0.80
Total QALYS	6.54	5.74	0.79
*QALYs are reported, but the EAC do not have confidence in the utility values used in the model			

Figure 9: Cumulative cost saving, Synergo vs. BCG (Tan 2019)

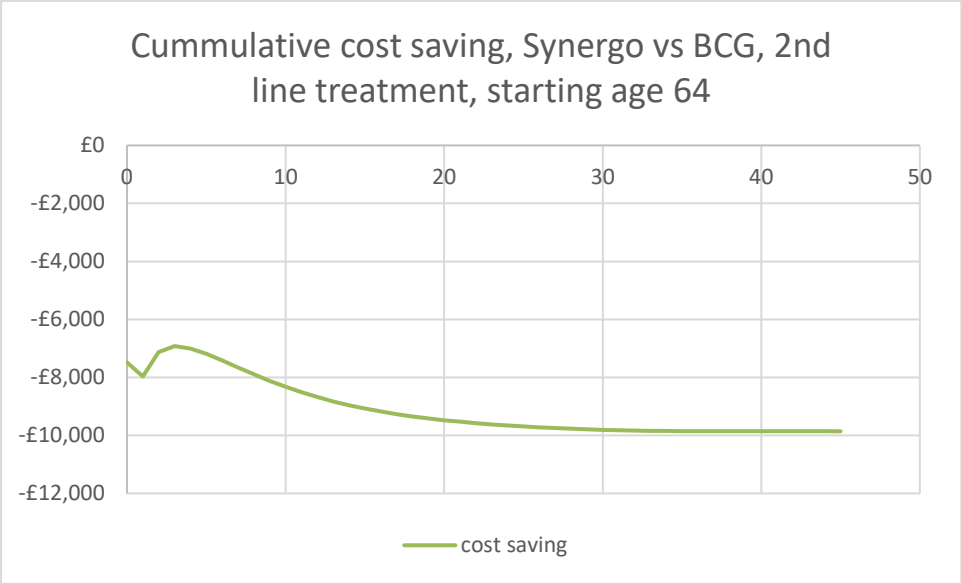
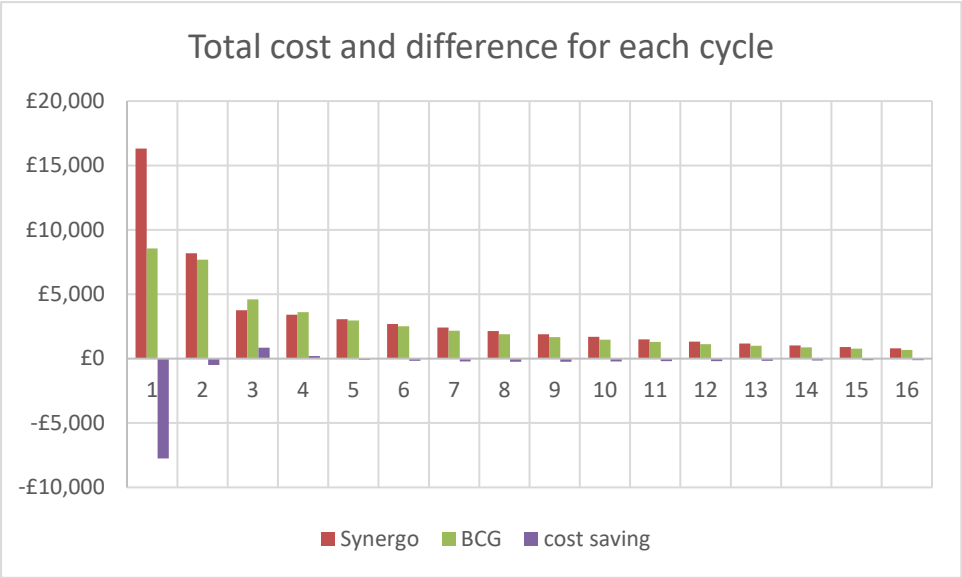


Figure 10: Annual costs for Synergo and BCG, plus cost saving, (Tan 2019)

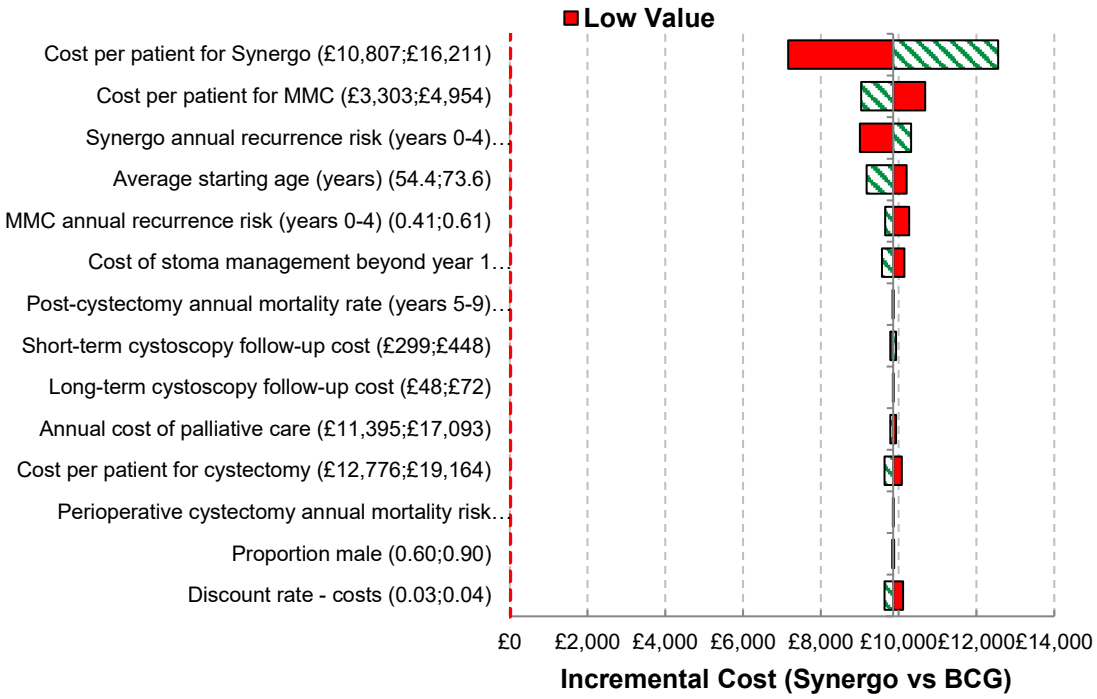


Sensitivity analysis (Synergo vs. BCG, Tan 2019)

The EAC repeated the same one-way sensitivity analysis, with the results shown in figure 11. None of the individual components brought the sensitivity analysis into cost saving (life time horizon). The key drivers were the costs of the treatment and the annual recurrence rates and the starting age. The variation due to cost of treatment will be slightly underestimated in this analysis, as this includes treatment costs in the first year only, and in this scenario the EAC modelled some treatment costs occurring in the next year. The cost of stoma became somewhat less important, as the difference in the number of people in post-cystectomy is much smaller.

Varying the BCG regimens had very little impact, the 3-year duration resulted in a cost incursion due to Synergo of £9,570 and the limit of 1-year treatment resulted in Synergo costing an additional £10,792 over a life time horizon. Note that this changed the costing of the regimen, but the clinical inputs remained the same. Any potential impact in outcomes due to different regimens was not modelled.

Figure 11: One Way Sensitivity analysis for Synergo versus BCG (Tan 2019)



Additional costs of Cystoscopy prior to Synergo

During discussions with clinical experts it was suggested that good practice would include a cystoscopy prior to the initial treatment with Synergo. The EAC have created an additional scenario to include this resulting in an additional cost of £261 for Synergo. The EAC base case for Synergo vs MMC changes from £3,549 to £3,288 cost saving per patient at a life time horizon. The EAC scenario for Synergo vs BCG (non CIS) changes from £9,858 to £10,119 cost incurring per patient at a life time horizon.

9.6 *The EAC's interpretation of the economic evidence*

The EAC made a number of amendments to the model structure and calculations as well as changes to the source data for annual stoma costs and additional wait time. These are summarised in table 24 with the direction of impact. Additional details are included in appendix H.

Table 24: EAC changes to submitted model, and impact

Description of change	Impact of change
Submitted model, before changes	**£4,466**
Changes in model calculations or interpretations of information, no changes in sources of information	
Correct calculations of disease free survival	Decrease in cost saving
Correct morality post RC	Large decrease in cost saving
Include costs for Synergo and MMC in whole population (Cycle 0)	Large increase in cost saving (was missing for more of MMC than Synergo)
Correct half cycle correction	Small decrease in cost saving
Inflation is standardised to 2020/21	Only small impacts
Correction to cystoscopy calculation	
EAC base case after corrections	**£3,300**
EAC change in sources of information	
Change in annual stoma costs	Increase in cost saving
Change in wait time	Decrease in cost saving
EAC base case	**£3,549**

The model, as submitted is reasonably robust to sensitivity analysis and EAC amendments. However, there are significant uncertainties on the relevance of the pathway.

The EAC amended the submission to use an alternative clinical source data (Tan, 2019) to model Synergo vs. BCG as 2nd line treatment for patients with no CIS. This model is cost incurring in its base case and in all one way sensitivity analysis. This is due to a smaller difference between recurrence rates, and the higher recurrence rates meaning patients move to cystectomy more quickly and no longer accumulate cost savings.

The models are driven by movement from disease free survival through to recurrence which results in radical cystectomy and stoma care. The clinical data from Tan (2019) with BCG as a comparator means that people progress more rapidly to radical cystectomy and that there is less difference between the progression between the two arms.

The validity of the economic models is largely an issue of how well they reflect either the current NHS pathway or an alternative suggested pathway. The modelling by both the EAC and company has been at least partially determined by the availability of clinical evidence.

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10 Conclusions

10.1 *Conclusions from the clinical evidence*

The available evidence suggests that radiofrequency induced chemohyperthermia delivered using Synergo is safe with adverse events limited to bladder pain and spasms during treatment and resolving afterwards. Serious side effects are rare and few patients stop treatment.

The clinical effectiveness of radiofrequency induced chemohyperthermia using Synergo is uncertain. There are a number of studies available reporting outcomes for patients treated with Synergo but comparative evidence is limited to 3 randomised trials. The usefulness and applicability of the results from these 3 trials is dependent on what is an appropriate comparator for Synergo which itself it dependent on the place in the clinical pathway for device assisted chemotherapy. When compared with standard MMC, long-term results from one trial (Colombo 2011) indicate that disease free survival was significantly better with Synergo ($p<0.004$) and no significant difference in overall survival ($p=0.558$). When comparing Synergo with BCG immunotherapy there was no difference in either recurrence free survival (Arends 2016) or disease-free survival (Tan 2019). The EAC noted that all 3 trials terminated early which is likely to have an impact on results.

The EAC has identified a number of key considerations specifically related to the clinical evidence for the committee to discuss include:

- The studies include people with both intermediate and high risk NMIBC and do not, in most cases, report results separately. The current clinical pathway has different treatment pathways for these risk groups and clinical expert input suggest that Synergo would not be used for intermediate risk NMIBC.

- One clinical trial compares Synergo to standard MMC and results show significantly longer disease-free survival with Synergo. Clinical expert input suggests that standard MMC would be used for intermediate risk

NMIBC only and devices assisted chemotherapy would not be an alternative in this group due to time and resource requirements.

- One UK clinical trial compared Synergo to BCG which is in line with where the clinical experts consider Synergo most likely to be used experts however it had some specific limitations which impact the certainty of the results.

10.2 *Conclusions from the economic evidence*

The overriding economic considerations are to determine what pathway should be modelled; what pathways are possible to model given the existing clinical evidence; and how much confidence can be placed in the results given the limitations of that evidence.

Current use of Synergo is as an alternative to BCG and radical cystectomy for people with high risk NMIBC, or for people with intermediate risk NMIBC who are being managed on the high-risk pathway. It may be offered as a first or second line treatment, and opinions vary as to where it is most appropriate.

The submitted model compared Synergo to MMC, using evidence primarily for intermediate risk NMIBC and no CIS (Columbo 2011). The model is restricted to where BCG treatment was unavailable or not suitable for that patient, as BCG treatment is not included in the model. Currently in the NHS, there are very few points in the pathway where a clinical decision between Synergo and MMC would be made, however it may be appropriate where other options of BCG or radical cystectomy are very limited.

The economic model for Synergo within this population and setting is cost saving in both the submitted and EAC variations of the model, and throughout all sensitivity analysis.

The EAC model comparing Synergo to BCG used evidence from a sub-group analysis of a larger study of 2nd line treatment primarily of high risk NMIBC (Tan 2019). The subgroup was of 33 patients with no CIS. The treatment decision of a 2nd course of BCG or Synergo was reflected in expert

engagement discussions, however the evidence relies on a small number of patients, and a mix of comparator treatments.

The economic model for Synergo compared to BCG as a 2nd line treatment for patients with no CIS, found that it was cost incurring, and this was consistent throughout all sensitivity analysis. The change from cost saving to cost incurring is primarily due to the shorter time to recurrence (at which point costs in both arms are the same). Therefore, fewer cost savings are accumulated prior to recurrence and these to not outweigh the additional cost of Synergo in the first cycle.

All models result in a reduction in radical cystectomies, an increase in total life years and an increase in QALYs, although these changes are much smaller for the Synergo vs. BCG model.

11 Summary of the combined clinical and economic sections

Synergo is a safe approach to treatment with adverse events limited to bladder pain and spasms during treatment and resolving afterwards. Serious side effects are rare and few patients stop treatment. The evidence for the clinical effectiveness and cost savings is not certain and may have limited generalisability due to the fact that there is no recognised pathway for device assisted chemotherapy. The certainty of the clinical and economic evidence may be dependent on a number of factors including stage/grade of tumour, presence/absence of CIS, previous treatments and reasons for using Synergo and MMC dose used.

Device assisted chemotherapy using Synergo is likely to be a beneficial addition to the current treatment options for NMIBC, giving patients more options to avoid radical cystectomy for longer however consideration should be given to the most appropriate place for Synergo to ensure most clinical and cost benefit.

12 Implications for research

The EAC identified a number of potential implications for research including

- Establish the most appropriate place in the current treatment pathway for device assisted chemotherapy through systematic review of the current evidence for device assisted chemotherapy as a treatment approach.

- A need to identify the most appropriate comparator for device assisted chemotherapy and Synergo specifically considering all other available treatment options including other device assisted chemotherapy options while recognising that the most appropriate comparator may differ for different risk groups.

- If considering BCG immunotherapy as the most appropriate comparator consideration should be given to what options are available for people who are intolerant or refractory to BCG and whether radical cystectomy is the only available option.

- A possible need to identify the most appropriate sequencing of treatments where device assisted chemotherapy is an option recognising that the current use of device assisted chemotherapy in the UK may not be the only appropriate place for use and the sequencing of treatment may depend on risk of recurrence and patient suitability or willingness to have alternative treatment options.

- A possible need to identify the risk group mostly likely to benefit from device assisted chemotherapy by ensuring any research studies recruit and report separately by risk group (intermediate or high-risk).

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14 Appendices

Appendix A: Clinical and Economic Evidence Identification

Appendix B: Data Extraction

Appendix C: Critical Appraisal

Appendix D: Excluded ongoing Studies

Appendix F: Markov model state diagrams

Appendix G: Model Stress Test

Appendix H: EAC changes to model

Appendix A: Clinical and economic evidence identification

Company search strategy, screening criteria and process for clinical evidence

A literature search was performed in 3 databases (PubMed, Embase, The Cochrane Library) to include the period from 1st Jan 2000 to 1st Feb 2021. The searches included a range of free text terms and, where appropriate, indexed terms to describe the condition, the intervention product and key components of the intervention product. The searches were restricted to literature published in the English language. The company stated that the published literature is continuously monitored for the presence of studies related to Synergo. The company also stated that it was not aware of any ongoing studies of Synergo other than those previously published or that they had sponsored. The company applied the following inclusion/exclusion criteria:

Inclusion criteria

Population: People with intermediate or high-risk non-muscle-invasive bladder cancer (NMIBC) who are a) BCG-unresponsive/resistant or b) indicated for BCG after failing previous instillations other than BCG but either

cannot tolerate it, do not wish to be treated with it, contra-indicated to it, or cannot be administered it due to shortage in supply.

Interventions: Radiofrequency-induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 System

Outcomes:

- Recurrence rates and time to recurrence
- Disease progression and changes to treatment indicative of advanced disease
- Rates of cystectomy
- Complete response rate for carcinoma in situ
- Disease-specific and overall survival
- Health-related quality of life
- Treatment tolerability
- Length of hospital stay
- Treatment delivery rates in inpatient or outpatient settings
- Device-related adverse events

Study design: Original clinical research.

Prospective and retrospective studies with one or more arms that report outcome data by target population.

Language restrictions: Publications in English only

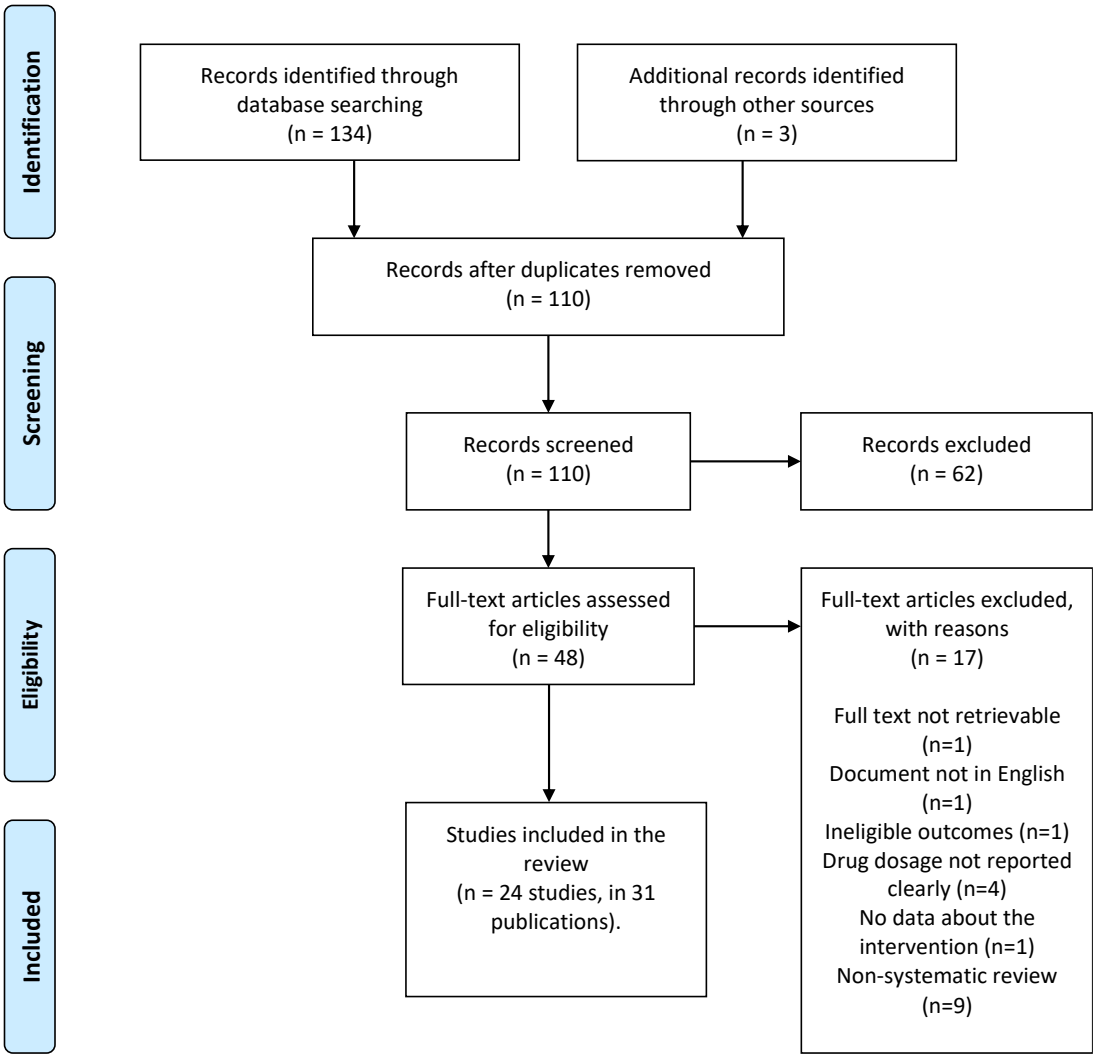
Exclusion criteria:

Study design: Insufficient detail of methods and results to enable data extraction, such as:

- dosage of the drug administered with the device not reported clearly or at all
- number of administered treatments not reported

Company study selection for clinical evidence

PRISMA 2009 Flow Diagram



Company search strategy for adverse events

The company reported that no adverse reports were identified from either the FDA Maude or MHRA databases.

EAC search strategy and study selection for clinical and economic evidence

The EAC conducted a single search for both clinical and economic evidence as directed by the scope. Ten bibliographic databases were searched to include the period from 1st January 2000 to 4th March 2021, using a range of

free text terms and, where appropriate, indexed terms, the searches were restricted to the English language. Two clinical trial registries were also searched for ongoing and unpublished trials; the company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices and the MAUDE database were searched for adverse events.

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
04/03/21	Cochrane Library CDSR CENTRAL	 0 54	
03/03/21	CRD (DARE, HTA, NHS EED)	0	
02/03/21	EMBASE	219	
02/03/21	Medline (ALL – includes Medline In Process & Medline Epub Ahead of Print)	114	
03/03/21	PubMed	22	
03/03/21	Scopus	274	
03/03/21	Web of Science	233	
05/01/21	company website: https://www.synergo-medical.com/	52	
			458
03/03/21	MAUDE adverse events https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm	0	
03/03/21	MHRA – search MDA & FSN in following: https://www.gov.uk/drug-device-alerts?keywords=&issued_date%5Bfrom%5D=&issued_date%5Bto%5D=	0	
03/03/21	Clinicaltrials.gov	0	11 (deduplicated against published results retrieved from database searches)
03/03/21	ICTRP	13	

EAC Search strategies

The Cochrane Library

#1 (synergo):ti,ab,kw (Word variations have been searched) 9
#2 ("radiofrequency-induced-thermo-chemotherapeutic-effect"):ti,ab,kw (Word variations have been searched) 0
#3 (RITE and chemotherap*):ti,ab,kw (Word variations have been searched) 6

#4 (thermochemotherapy or "thermo-chemotherapy" or "thermo chemotherapy" or thermotherapy or chemohyperthermia or hivec):ti,ab,kw (Word variations have been searched) 756
#5 (chemotherap* NEAR/3 (heat or heated or hypertherm*)):ti,ab,kw (Word variations have been searched) 486
#6 MeSH descriptor: [Hyperthermia, Induced] this term only 542
#7 MeSH descriptor: [Mitomycins] explode all trees 1299
#8 #6 and #7 25
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #8 1208
#10 MeSH descriptor: [Urinary Bladder Neoplasms] this term only 1498
#11 (NMIBC):ti,ab,kw (Word variations have been searched) 379
#12 ((bladder or intravesical) NEAR/5 (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or malignan*)):ti,ab,kw (Word variations have been searched) 4425
#13 #10 OR #11 OR #12 4428
#14 #9 AND #13 with Cochrane Library publication date Between Jan 2000 and Mar 2021, in Cochrane Reviews 0
#15 #9 AND #13 with Publication Year from 2000 to 2021, in Trials 54

CRD

1 (synergo) IN DARE, NHSEED, HTA 1
2 (radiofrequency-induced-thermo-chemotherapeutic-effect) IN DARE, NHSEED, HTA 0
3 (RITE and chemotherap*) IN DARE, NHSEED, HTA 0
4 (thermochemotherapy or "thermo-chemotherapy" or "thermo chemotherapy" or thermotherapy or chemohyperthermia or hivec) IN DARE, NHSEED, HTA 61
5 (chemotherap*) AND (heat or heated or hypertherm*) IN DARE, NHSEED, HTA 70
6 MeSH DESCRIPTOR Hyperthermia, Induced EXPLODE ALL TREES 226
7 MeSH DESCRIPTOR Mitomycin EXPLODE ALL TREES 42
8 #6 AND #7 0
9 #1 OR #2 OR #3 OR #4 OR #5 OR #8 126
10 MeSH DESCRIPTOR Urinary Bladder Neoplasms EXPLODE ALL TREES 198
11 (NMIBC) IN DARE, NHSEED, HTA 3
12 (bladder or intravesical) AND (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or malignan*) IN DARE, NHSEED, HTA 322
13 #10 OR #11 OR #12 322
14 #9 AND #13 4

EMBASE <1996 to 2021 February 26>

1 synergo.tw. (48)
2 "radiofrequency-induced-thermo-chemotherapeutic-effect".tw. (1)
3 (RITE and chemotherap*).tw. (15)

4 (thermochemotherapy or "thermo-chemotherapy" or "thermo chemotherapy" or thermotherapy or chemohyperthermia or hivec).tw. (3241)
5 (chemotherap* adj3 (heat or heated or hypertherm*)).tw. (5314)
6 Hyperthermia/ (14577)
7 Mitomycin/ (16442)
8 6 and 7 (115)
9 1 or 2 or 3 or 4 or 5 or 8 (8519)
10 bladder tumor/ (13028)
11 NMIBC.tw. (3206)
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13 10 or 11 or 12 (68875)
14 9 and 13 (255)
15 (case reports or editorial or letter).pt. (1503023)
16 14 not 15 (249)
17 limit 16 to (english language and yr="2000 -Current") (219)

PubMed

Synergo = 22

Scopus

(((TITLE-ABS-KEY (synergo)) OR (TITLE-ABS-KEY ("radiofrequency-induced-thermo-chemotherapeutic-effect")) OR (TITLE-ABS-KEY (rite AND chemotherap*)) OR (TITLE-ABS-KEY (thermochemotherapy OR "thermo-chemotherapy" OR "thermo chemotherapy" OR thermotherapy OR chemohyperthermia OR hivec)) OR (TITLE-ABS-KEY (chemotherap* W/2 (heat OR heated OR hypertherm*))) OR (TITLE-ABS-KEY (hypertherm* AND mitomycin))) AND ((TITLE-ABS-KEY (nmibc)) OR (TITLE-ABS-KEY ((bladder OR intravesical) W/2 (cancer* OR neoplasm* OR carcinoma* OR tumor* OR tumour* OR malignan*))))) AND (PUBYEAR > 1999) AND (LIMIT-TO (LANGUAGE , "English"))

Web of Science

12. (#10 AND #7) AND LANGUAGE: (English) Timespan=2000-2021 (233)
11. #10 AND #7 (274)
10. #9 OR #8 (71,376)
9. TS=((bladder or intravesical) NEAR/5 (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or malignan*)) (71,325)
8. TS=(NMIBC) (1660)
7. #6 OR #5 OR #4 OR #3 OR #2 OR #1 (9,966)
6. TS=(Hyperthermi* AND mitomycin) (837)
5. TS=(chemotherap* NEAR/3 (heat or heated or hypertherm*)) (4,757)

4. TS=(thermochemotherapy or "thermo-chemotherapy" or "thermo chemotherapy" or thermotherapy or chemohyperthermia or hivec) (5316)
3. TS=(RITE AND chemotherap*) (36)
2. TS=(radiofrequency-induced-thermo-chemotherapeutic-effect) (0)
1. TS=synergo (27)

Maude

1. Synergo = 0 hits
2. radiofrequency-induced-thermo-chemotherapeutic-effect = 0 hits
3. Chemohyperthermia = 0 hits
4. Thermochemotherapy = 0 hits

MHRA

1. Synergo = 0 hits
2. "radiofrequency-induced-thermo-chemotherapeutic-effect " = 0 hits
3. RITE = 0 relevant hits
4. Chemohyperthermia = 0 hits
5. Thermochemotherapy = 0 hits

Clinical Trials.gov

1. Synergo | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Bladder Cancer = 0 hits
2. RITE | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Bladder Cancer = 0 hits
3. radiofrequency-induced-thermo-chemotherapeutic-effect | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Bladder Cancer = 0 hits
4. thermochemotherapy | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Bladder Cancer = 0 hits
5. chemohyperthermia | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Bladder Cancer = 0 hits
6. Synergo OR RITE OR radiofrequency-induced-thermo-chemotherapeutic-effect OR thermochemotherapy OR chemohyperthermia | Completed, Suspended, Terminated, Withdrawn, Unknown status Studies | Studies With Results | = 0 relevant results

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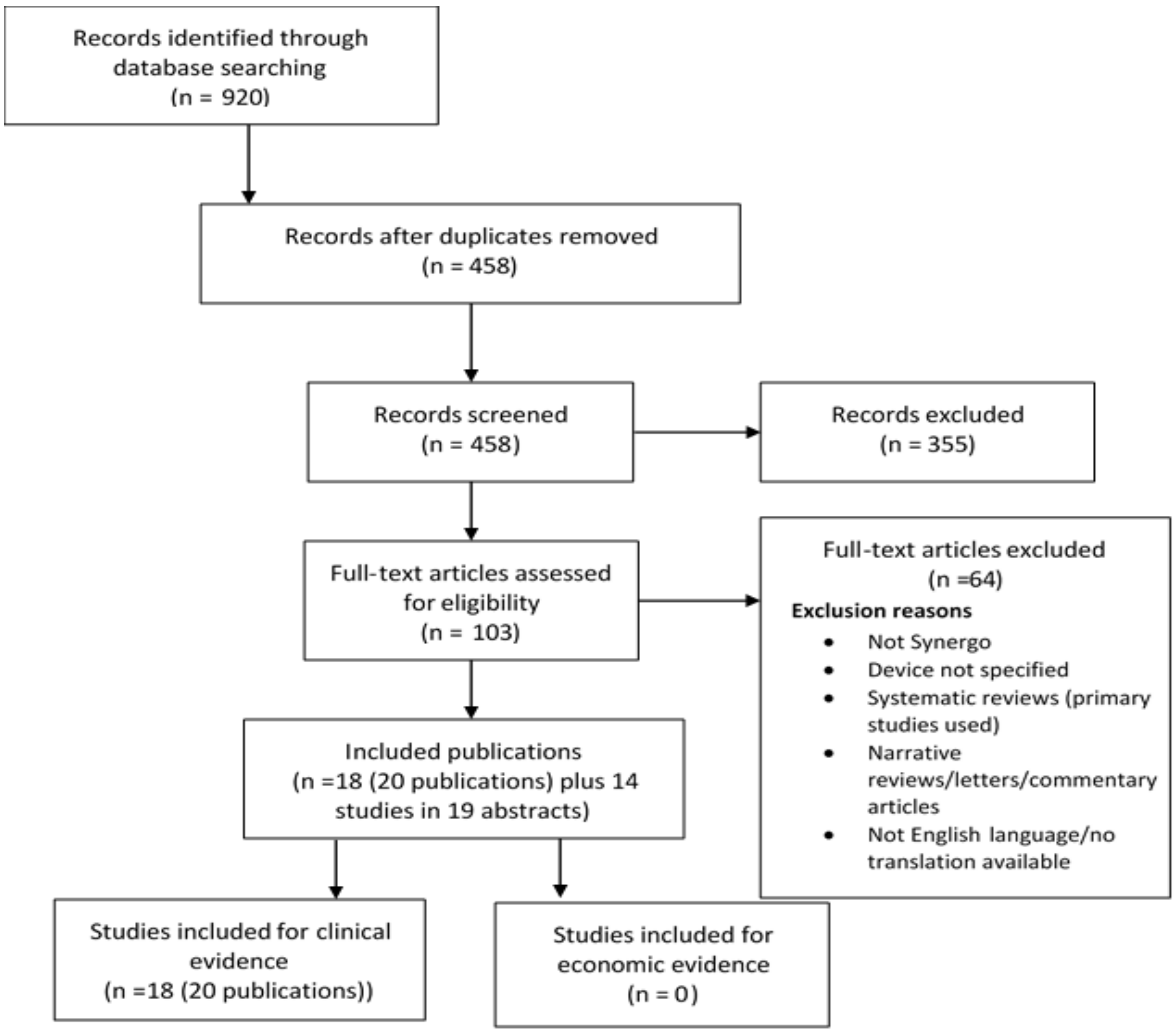
ICTRP

1. bladder cancer and synergo = 8 trials

2. bladder cancer and rite = 0 additional results
3. bladder cancer and radiofrequency-induced-thermo-chemotherapeutic-effect = 0 results
4. bladder cancer and thermochemotherapy = 1 additional result
5. bladder cancer and chemohyperthermia = 3 additional results
6. NMIBC and chemohyperthermia = 0 additional results
7. NMIBC and Synergo = 0 additional results

EAC study selection



Appendix B Data Extraction

Full Publications

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Arends 2016 **Country** Israel, Italy, the Netherlands, Austria, France, Belgium **Data collection** July 2002-December 2012 **Study Design** Randomised phase III trial	To compare intravesical chemohyperthermia (CHT) using mitomycin C (MMC) with intravesical bacillus Calmette-Guérin (BCG) as adjuvant treatment for intermediate and high-risk non-muscle invasive bladder cancer (NMIBC) **Primary Outcomes** • Recurrence free survival (RFS) in the intention to treat and per protocol analyses. **Secondary Outcomes** • Proportion of complete response (CR) in CIS patients • Disease progression to higher than stage T1 and/or metastatic disease • Safety	190 patients with intermediate and high-risk NMIBC according to 2001 European Association of Urology risk category definitions. **Inclusion** • Any pT1 or grade 3 urothelial carcinoma (UC) and/or carcinoma in situ (CIS) or multifocal pTa lesions and/or multiple recurrences of pTa lesions in the last 24 months. • Presumed transurethral resection of the bladder tumour (TURBT) • Resection of tumour bed and random biopsies in high risk patients • Positive cytology and/or CIS-positive biopsies were allowed in CIS patients.	**Sample Size** To test the null hypothesis of equal RFS probabilities in both groups after 24 months with 80% power at a 5% significance level. Expecting a drop-out rate of 20% resulted in target recruitment of 300 patients. **Randomisation** 1:1 allocation stratified by centre using permuted block method. **Statistics** Kaplan-Meier curves for each study arm with the null hypothesis tested using the log-rank test. Count and percentage for secondary outcomes	Intervention: Intravesical CHT with MMC using the Synergo system for 6 weeks followed by 5 maintenance sessions at 6 week intervals during the rest of year 1. Sessions comprised 2 30 minute treatments with 20mg MMC dissolved in 50ml distilled water combined with local hyperthermia at 42 ± 2^0C Control: BCG as a 1 year schedule, 6 weekly induction sessions and 3 weekly maintenance sessions at months 3, 6 and 12. **Follow-up** At least 24 months after randomisation • 3 month intervals including blood analysis, urinalysis, cytology, cystoscopy and biopsies of suspicious areas	***The trial was stopped early due to slow recruitment.*** 190 patients randomised • CHT=92; BCG=98 147 pure papillary tumours • CHT=71; BCG=76 43 concomitant CIS • CHT=21; BCG=22 184 patients for safety analysis • CHT=89; BCG=95 *Intention to Treat* 142 papillary NMIBC patients with at least one treatment given • CHT=68; BCG=74 • Median follow-up: 25.6 months (0.0-34 months) • 24 months RFS: 78.1% (95% CI 65.2%-	**Limitations** • Early closure due to slow recruitment – study is underpowered • No blinding of patients or physicians may introduce bias **Applicability** • Not a UK study however comparator and intervention are relevant **Funding/CoI** Medical Enterprises Europe BV provided financial support

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		Exclusion • Histology other than UC • Another primary malignancy • UC involving the urethra or upper urinary tract • Previous history of UC stage T2 or higher • Intravesical MMC treatments during previous 12 months • Any previous BCG therapy <48 months • Previous pelvic radiotherapy or systemic chemotherapy • Partial cystectomy • Bladder diverticulum>1cm • Residual urine >100ml • Bladder volume <150ml • urinary incontinence • urethral stricture impeding 20F • catheterisation • persistent haematuria • active intractable or uncontrollable	Fischer's exact test for comparisons		86.7%) in CHT compared with 64.8% (95% CI, 52.2%-74.9%) in the BCG group (p=0.08) *Per Protocol* 132 papillary NMIBC patients with at least 6 intravesical instillations as defined in the protocol • CHT=60; BCG=72 • Median follow-up: 25.3 months (3.9-34 months) • 24 month RFS was 81.8% (95% CI, 68.7%-89.8%) in the CHT group compared with 64.8% (95% CI, 52.2%-74.9%) in the BCG group (p=0.02) *Complete Response rate (CIS patients)* Complete response rate at 3 months was 88.9% in the CHT group and 85.7% in the BCG group (p=1). *Progression to muscle invasive disease* • 0 (0.0%) patients in the CHT group showed progression to	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		urinary tract infection (UTI), • active tuberculosis or BCG infection • patients with previous BCG life-threatening sepsis, known MMC or BCG allergy • known impaired immune response • positive HIV serology • receipt of systemic steroids or immunosuppressives • haematological disorders, • leukocytes <3500, platelets <100 000 • kidney or liver function disorders (>1.5 times upper normal limit) • pregnant/lactating women **Demographics** Mean age: CHT: 65.2 years BCG: 67.4 years Sex: CHT: 83.1% male BCG: 84.2% male Risk Group CHT: 29.2% high BCG: 32.6% high			muscle-invasive disease • 1 (1.4%) patients in the BCG group showed progression to muscle invasive disease *Safety* Adverse events (AE) were recorded for patients with at least one treatment (n=184) *CHT* 1540 treatments given to 90 patients 1431 AEs observed The most prevalent AEs during treatment were: • Bladder spasms (14.4%) • Bladder pain (14.1%) The most prevalent AEs after treatment were: • Dysuria (11.7%) • Nocturia (10.3%) • Urinary frequency (9.9%) *BCG* 1923 treatments given to 94 patients 1525 AEs observed	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		Risk Group without CIS CHT: 7.4% high BCG: 13.5% high Prior treatments: CHT: Chemo including MMC (52%), MMC (24%), BCG (24%) BCG: Chemo including MMC (44.4%), MMC (33.3%), BCG (22.3%) **Setting** Multicentre (11 centres in 6 countries) Risk groups were classified using 2001 guidance. A letter (Arends 2017) subsequently stated that 85 of the ITT patients (n=142) were high risk using the 2016 classification.			The most prevalent AEs were: • Urinary frequency (18%) • Dysuria (15%) • Nocturia (14.9%) • Haematuria (11.2%) • Fatigue (8.5%) The CHT group had significantly less • urinary frequency (OR 0.61, 95%CI 0.49-0.75) • nocturia (OR 0.79, 95% CI 0.63-0.98) • incontinence (OR 0.22, 95% CI 0.12-0.37) • Haematuria (OR 0.56, 95% CI 0.42-0.74) • Fever (OR 0.09 95% CI 0.04-0.10) • Fatigue (OR 0.17, 95% CI 0.11-0.28) • Arthralgia (OR 0.09, 95% CI 0.03-0.31) The CHT group had significantly more • Catheterisation difficulties (OR 16.7, 95% CI 5.1-54) • Urethral strictures (OR 2.3, 95% CI 1.3-4.1)	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Bladder tissue reaction (OR 5.8, 95% 4.0-8.3) • Bladder spasms (OR 15.5, 95% CI 9.7-25) • Bladder pain between sessions (OR 1.6, 95% CI 1.2-2.3) • Allergy (OR 2.7, 95% CI 1.6-4.6) 9 probably related serious adverse events were observed, 5 in CHT group (contracted bladder, urethral bleeding and fever) and 4 in the BCG group (retention, haematuria, UTI and fever)	
Arends 2014 **Country** Netherlands **Data collection** November 2001 to January 2013 **Study Design** Retrospective review of medical records	To report on a single centre experience of CHT **Outcomes** Recurrence Free Survival (RFS)	160 patients with NMIBC No inclusion/exclusion criteria reported **Demographics** • Median Age: 65 years (34 to 87) • High risk: 62.5%/Intermediate risk 37.5% (EAU criteria) • Male: 77.5% **Setting** Not reported – likely outpatients.	CHT using Synergo System *Statistics* • Kaplan-Meier to calculate RFS • Log rank test to compare subgroups • Cox proportional Hazards model to adjust for confounding variables • Chi-square test to assess association	6-8 weekly sessions followed by maintenance sessions at 6 weekly intervals during year 1 *Adjuvant* 20mg/50ml MMC or 25mg/50ml Epirubicin if allergic to MMC *Ablative* 40mg/50ml MMC or 50mg/50ml Epirubicin 2 30 minute cycles with bladder wall hyperthermia to a mean 42C±2C	• Indication for CHT was NMIBC refractory to regular intravesical treatment. • 80.6% had previous BCG therapy • 3.8% had no previous treatment • Mean number of treatments was 10.3 (2-37). • 10 patients discontinued CHT due to side effects • 12.5% of patients were treated with epirubicin	**Limitations** • Non-comparative • Retrospective • Limited outcome reporting **Applicability** • Not a UK study • Includes both intermediate and high-risk patients but results are not

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments

			between categorical variables
			• Generalized estimating equation (GEE) to estimate parameters with possible unknown correlation
					• A mean 5.9 TURBTs were done before CHT
					• 4.3% of patients progressed to muscle invasive disease
					• Initial CR rate 6 weeks after induction therapy was 77.5% (n=41) in the ablative group
					• No significant difference in CR rate comparing
					  • CIS/no CIS
					  • pTa/pT1
					  • low/high grade
					
					Recurrence Free Survival
					• All patients: RFS was 60% at 1 year and 47% at 2 years
					• Variables associated with decreased RFS (univariate analysis) were:
					  • Number of TURBTs: ≤2 (2 - year RFS 71%) vs.. >2 (2-year RFS 42%), p=0.014
					  • Recurrence frequency: highly recurrent (2-year RFS 36%) vs.
						presented by risk group
						• CHT is used as a treatment option for patients' refractory to treatments such as BCG which reflects one of the likely places in the treatment pathway in the UK
						
						Funding/CoI
						None declared

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					other (2-year RFS 72%), p<0.001 • Multivariable analysis indicated only recurrence frequency before CHT was independently associated with decreased RFS (HR 2.4, 1.30-44.43, p=0.005) • 1-year RFS for epirubicin was 64% vs. 59% for MMC • 2-year RFS for epirubicin was 55% vs. 46% for MMC • Difference was not significant (p=0.303) *Side Effects* • Common but mild and transient • 1,671 treatment sessions with a total of 1,979 adverse events • 96.6% (1912) were grade 1 or 2 • During treatment: pain (16.8%) and spasms (23.3%) were most common • After treatment: dysuria (22.6%) and	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					frequency/urgency (27.3%) were most common • GEE indicated that bladder spasms occurred more frequently in men (OR 2.36, 1.15-4.85); p=0.019)	
Brummelhuis 2021 **Country** Netherlands **Data collection** Nov 2001 – Jan 2020 **Study Design** Retrospective review of patient records	To assess treatment outcomes and effect of ablative dose **Outcomes** *CIS patients* Complete Response Durable response *Papillary patients* Recurrence free survival *All patients* Overall survival Relative survival Cancer specific survival	Medical records of 274 patients with histologically proven NMIBC (n=299 included in safety analysis) *Inclusion* At least 6 RF-CHT instillations *Exclusion* None reported **Demographics** Median Age: 66 years (60-74) Male/Female: 78.1%/21.9% Baseline histology: CIS with/without papillary tumour = 128 (46.7%) Papillary tumour only = 146 (53.3%) **Setting** Not reported	RF-CHT delivered using Synergo device *Statistical Tests* • Chi square to assess association between CIS and chemotherapeutic dose • Kaplan-Meier for survival estimates • Chi square to assess association between treatment duration and chance of recurrence	Six-weekly induction followed by maintenance regimen of 1 instillation every 6 weeks for year 1. One instillation every 8 weeks for year 2 and every 12 weeks thereafter. Treatment sessions comprised 2 30 min cycles with intravesical MMC (20 or 40g) or epirubicin (30 or 50mg) at 40.5-44°C. **Follow-up** 24 months	Median follow-up was 55.5 months (mean 24 months) 25 patients did not receive 6 instillations: • Suspected metastases at start of RF-CHT treatment • Stopped due to complaints caused by residual bladder tumour • RF-CHT catheter placement not possible • Local side effects 22 patients without concomitant CIS did not have papillary tumours resected before RF-CHT and received an ablative	**Limitations** • Non-comparative study • Retrospective review of patient records • Risk classification not reported **Applicability** • Not a UK based study • Some patients treated with epirubicin which may be reflective of UK practice however epirubicin not part of the current UK care pathway.

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					dose (40mg MMC or 50mg epirubicin) Patients with CIS at baseline: • 62.5% (n=80) received an ablative dose • 37.5% an adjuvant dose Previous Intravesical Treatment • BCG 85.4% • MMC 50.4% • RF-CHT 4.4% Reason for discontinuing BCG included: • BCG refractory disease (65%) • BCG intolerance (7.7%) • Reason not reported (27.3%) *Complete Response (CR)* • N=137 included in analysis • CR rate was 56% (CIS) and 52.4% (residual papillary tumour) at six months • Ablative doses were associated with non-statistically significant higher 6-month CR	• Mixed patient population with unclear risk classification so difficult to ascertain which patient group the evidence is most applicable to. **Funding/CoI** Nothing relevant to Synergo

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					rate (Adjusted OR 0.49, p=0.08) • Concomitant CIS at baseline was associated with non-statistically significant CR rate at baseline (Adjust OR=0.35, p=0.10) *Durable Response and Recurrence Free Survival (RFS)* Durable response rate of patients with concomitant CIS (n=70) was • 79.7% at 1 year • 66.5% at 2 years • 40.3% at 5 years For BCG refractory patients (n=52) • 79.2% at 1 year • 65.5% at 2 years • 38.7% at 5 years Recurrence free survival rates for patients with papillary disease • 77.9% at 1 year • 57.5% at 2 years • 37.2% at 5 years For BCG refractory patients (n=68) • 72.5% at 1 year • 54% at 2 years • 31.7% at 5 years	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Ablative dose significantly improved RFS and durable response rates compared with adjuvant dose (p=0.04) • Patients treated with ablative dose were significantly less likely to develop a recurrence (adjusted HR 0.94, p=0.81) • Prior BCG treatment increased the risk of recurrence (adjusted HR 2.07, p=0.04) *Progression* • 22 patients (8.5%) of all patients progressed to MIBC • 11 patients (4.3%) had distant metastases *Survival* • OS was 72.3% at 5 years and 51% at 10 years. In the BCG refractory subgroup OS 70.5% at 5 years and 43.9% at 10 years	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Relative survival (RS) was 80.6% at 5 years and 65.1% at 10 years. In the BCG refractory subgroup RS was 78.6% at 5 years and 73.1% at 10 years • Cancer specific survival was 86.6% at 5 years and 77.6% at 10 years. In the BCG refractory subgroup CSS was 85.7% at 5 years and 10 years. *Treatment after RF-CHT* • 80 (29.2%) received a radical cystectomy with/without neoadjuvant chemotherapy; 15 of these had progression to muscle invasive disease • 5 patients had systemic chemotherapy • 4 patients had chemoradiation with/without TURB • 12 patients had other intravesical therapy • Bladder preservation rate was 70.8%	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Radical cystectomy could be prevented for 2 years from last TURB in 76% and for 5 years in 61.1% of patients • OS rate for patients receiving radical cystectomy was 71% at 5 years and 42.6% at ten years *Outcome after RF-CHT Treatment* • After a median treatment period of 30.5 months (1-7 years), no significant recurrence occurred during treatment in 44 patients. • 12/24 patients who received treatment for less than 2 years developed recurrence compared with 3/20 patients treated for more than 2 years (p=0.02). *MMC versus Epirubicin* Multivariate analysis reports no significant difference in recurrence free survival and durable response for MMC vs.	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					Epirubicin (adjusted HR: 1.23 (0.71-2.14, p=0.46). *Tolerability and Safety* • 94.2% of treated patients experience at least 1 adverse event. • Spasms and pain were reported in 62.2% and 27.8% of patients during treatment • Dysuria and haematuria were observed in 53.1% and 29.9% of patients following treatment. • 30 patients experienced a severe (CTCAE grade 3) adverse event • 34 patients discontinued treatment due to side effects • Patients on the ablative dose reported significantly less pain or dysuria compared with adjuvant dose (19.5% v 34.8%, p<0.01; and 42.1% vs. 62.1%, p<0.01). • Incontinence was more reported more with ablative dose (10.5% vs. 2.5%, p<0.01).	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Colombo 2001 (Safety and tolerability study) **Country** Italy, Israel **Data collection** January 1996 and March 1998 **Study Design** Pilot feasibility study	To assess safety and tolerability of intravesical MMC, microwave induced hyperthermia with intravesical MMC and electromotive drug administration (EMDA) MMC. **Outcomes** Feasibility and tolerability	80 patients with superficial transitional bladder cancer (Ta-T1, G1-G2, recurrent, single small (<2cm) bladder tumours previously untreated by MMC) Inclusion/Exclusion Criteria not reported **Demographics** Not reported **Setting** Outpatients	*Analysis* • Subjective symptom before treatment (T1), immediately after last treatment(T2) and 7-10 days after treatment completion (T3) • Detailed, non-validated questionnaires • Scores reported as a mean value	Intravesical MMC (n=36): • 40mg in 50ml saline • 4, weekly sessions • Solution remained in bladder for 60mins with postural position changed every 10mins Synergo (TC) (n=29) • Synergo system • 40mg in 50ml distilled water • Local hyperthermia at a mean temp. of 42.5°C • 4 weekly sessions, mean session duration was 60mins EMDA (n=15) • Intravesical MMC solution according to EMDA procedure • 40mg MMC in 150ml of distilled water and 20mA of electric intensity • 4 weekly session, 20min duration **Follow-up** Not reported but results refer to early and late follow-up.	• TC and EMDA are both technically feasible • Short, intensive training required, particularly with TC • No adverse events related to technical equipment or errors • All treatment types well tolerated • No treatment sessions suspended • Most patients reported cystitis like symptoms • Local toxicity was higher in the TC group compared with EMDA and MMC • Local side effects with TC were mainly urgency and nocturia • No major complications were noted in early or late follow-up for any treatment *Complete Response* MMC: 27.7% TC: 66% EMDA: 40%	**Limitations** • Small sample size with limited numbers in each group • Not randomised • Limited outcomes • Limited follow-up time • Time period overlap with Colombo 2003 and 2011 • **Applicability** • Not a UK based study • Risk classification not reported but likely to be intermediate risk patients therefore limited applicability to high risk • Limited outcomes reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
						Funding/CoI Not reported
Colombo 2003 (short-term follow-up) **Country** Italy, Israel **Data collection** January 1994 to June 1999 **Study Design** Randomised Trial	To compare efficacy of hyperthermic MMC with standard intravesical MMC **Outcomes** • Response to treatment • Side effects and clinical complications	83 patients with primary/recurrent stage Ta and T1, grade G1 to G3 TCC of the bladder, treated by TURB. *Inclusion* • Intermediate (Ta-T1, G1-G2, multifocal primary or recurrent) • High risk (T1, G3 and CIS in association with papillary tumours) • Complete TURB possible • WHO performance status 1-2 *Exclusion* • Low risk bladder cancer • Residual tumour after TURB • Primary single, small Ta tumours • Transitional cell carcinoma of the prostate urethra • Solitary CIS	*Randomisation* • Randomised to either local microwave hyperthermia plus intravesical chemotherapy (HT-MMC) or intravesical chemotherapy alone (MMC) • Randomisation by sealed envelope process • No stratification *Sample Size* Study intended to detect a reduction in recurrence rate of 50% based anticipated reduction of at least 40% to 20%, with 80% power and a 5% type 1 error Sample size required was 158 (79 per group)	HT+MMC (n=42 randomised, n=35 analysed) MMC (n=41 randomised, n=40 analysed) Patients in both groups received • 8 weekly, 60 min treatment sessions followed by 4 monthly sessions **Follow up** Cystoscopy and cytology starting from end of induction phase and every 3 months for 2 years	**Interim analysis indicated superior of combined treatment (HT+MMC), study terminated early.** No significant difference between centres in relation to • Demographics • Baseline tumour characteristics • History or recurrence • Previous tumour size (>2cm) • Previous multifocal tumours (≥5cm) Significant difference between clinical centres in patients with recurrent tumours for • Previous tumour stage • Previous tumour grade *Response to Treatment* *Recurrence* Significant difference in recurrence rates between the treatment groups HT-	**Limitations** • Small sample size • Underpowered based on sample size calculations however study was terminated due to superiority of HT+MMC • No reporting of whether investigators were blinded • Time period overlap with Colombo 2001 **Applicability** • Not a UK study • Compares with standard MMC which may have limited applicability within the UK treatment pathway

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Distant/lymph node metastases • Urethral stricture • Large benign prostatic hyperplasia with residual urine >100ml • Bladder capacity <150ml • Treatment refractory UTI • Allergy to MMC • Pre-treatment in previous 3 months (local or systemic chemotherapy or radiation) **Demographics** *HT+MMC* Male: 83.3% Age >65: 40.5% *MMC* Male: 82.9% Age >65: 61% **Setting** Outpatients unit of 3 centres			MMC: 17.1% (6/35) MMC: 57.5% (23/40) (p=0.0002). Demographic factors (age and sex) had no effect on recurrence in either treatment group (p>0.05) No significant effect of prognostic factors (previous tumour size, previous multifocal tumours, previous grade/stage of tumour) on treatment groups (p>0.05). History of type recurrence (first episode, recurrent or high recurrent) demonstrated a significant effect on recurrence rates (p values not reported) Previous local chemotherapy did not impact recurrence rates (data not reported) Total number of treatment sessions had a significant effect with lower recurrence rates in patients who received full treatment compared with patients receiving less than	• Intermediate and high risk patients included

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					complete treatment (p<0.0001). *Disease Progression* 1 patient in the MMC group had recurrence at 3 month follow-up, developed metastasis and died. *Side Effects* • Pelvic pain was more common in the HT-MCC group (p=0.000) • Thermal reaction of the posterior wall was specific to the HT-MCC group • No patients stopped treatment due to pain • All occurrences were localised and transient *Clinical Complications* 1 complication was observed in the HT-MMC group (reduced bladder capacity with urge incontinence)	
Colombo 2011 (long term follow-up) **Country** Italy, Israel **Data collection**	To evaluate long-term efficacy of intravesical thermochemotherapy with mitomycin C (HT+MMC) vs. chemotherapy alone with mitomycin C (MMC) in patients with non-muscle	83 patients with primary/recurrent stage Ta and T1, grade G1 to G3 TCC of the bladder, treated by TURB.	As reported in Colombo 2003	As reported in Colombo 2003 **Follow-up** Median follow-up of tumour-free patients was 90 months (6-154)	***Study was stopped early due to significantly better efficacy of HT+MMC*** 75 patients (90.4%), completed the original study and were included in the analysis.	**Limitations** As Colombo 2003 **Applicability** As Colombo 2003 **Funding/Col**

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments

January 1994 to June 1999
 	
Study Design
Randomised Trial
	invasive bladder cancer (NMIBC) as an adjuvant treatment after complete transurethral resection.
	
	Outcomes
	Disease free survival
	Progression and radical cystectomy
	Bladder preservation rate
	Death
		Inclusion/exclusion as reported in Colombo 2003
		
		Demographics
		As reported in Colombo 2003
		
		Setting
		As reported in Colombo 2003
					• 65 patients (86.7%) had new data available
					• 10 patients (13.3%) had original data available
					
					Recurrence
					Per Protocol
					• Recurrent tumours were identified in 14/35 (40%) patients in the HT+MMC group compared with 32/40 (80%) in the MMC group (p<0.001)
					Intent to treat
					• Outcome data not available for 6/8 patients who left the study before first outcome evaluation (n=3) or first treatment (n=3)
					• Created a 'worst case scenario' with assumption that
					  ○ All HT+MMC patients were analysed as if tumour recurrence on day 0
					  ○ All MMC patients
						None declared

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					analysed as if they were tumour free for 10 years • Kaplan-Meier analysis on worst case scenario ○ DFS was significantly better with HT+MMC (p<0.004) Tumour Progression • Tumour progression requiring radical cystectomy (RC) at time of recurrence occurred in 5 patients; 2 in the HT+MMC group and 3 in the MMC group. • 4 additional patients had RC for recurrent high-risk NMIBC Bladder Preservation Bladder preservation rate was 86.1% in HT+MMC group and 78.9% in MMC group. Overall Survival No significant difference in overall survival between the groups (p=0.558)	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					There was no impact of demographic factors (gender, age) or tumour characteristics (previous tumour size, prior treatment with MMC or BCG, current tumour stage and grade) on DFS (p>0.05) Previous history of multiple tumour sites (<5 or ≥5) had no effect results for HT+MMC treated patients (p=0.77) but had a significant impact on results for MMC treated patients (p=0.001) with all patients with a history of ≥5 tumour sites experiencing tumour recurrence within the first 24 months of their treatment.	
Erturhan (2015) **Country** Turkey **Data collection** 2011 – unknown	To evaluate the results of thermochemotherapy in adjuvant treatment of primary high risk NMIBC **Outcomes** • Rate of recurrence	26 patients with NMIBC **Demographics** Mean age: 62.4 years (51-78) 24 (92%) Male 2 (8%) Female Ta GII; n=3 (11.5%)	**Statistical analysis** No detail reported. Kaplan Meier curves used for time to first recurrence free survival analysis	**Intervention** Single dose of intravesical mitomycin C (40mg) immediately after TURBT using the Synergo system SB-TS 101. Follow-up treatment consisted of once a week during the first 6	**Results** All patients completed six weeks plus six months treatment protocol, in addition to early single	**Limitations** • Was originally planned as an RCT but had to cancel the BCG arm due to global BCG shortage

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Study Design Initially planned to be a randomised study with BCG. However, the BCG arm of the study was cancelled due to global BCG supply problem	• Recurrence free survival • Progression • Adverse events	Ta GIII; n=4 (15.3%) T1 GIII; n=13 (50%) T1 GIII CIS (+); n=6 (23%) **Inclusion criteria** • Had TURBT after cancer diagnosis • Pathologically diagnosed with NMIBC • High-risk (T1 or Grade III or CIS (+) or multiple-recurrent >3cm Ta Grade I/II) **Exclusion criteria** • Previous bladder cancer or additional malignancy • Concurrent upper urinary system urothelial carcinoma • Not tumour free in the TURBT operation • Bladder capacity <150cc • Bladder diverticulum **Setting** Not reported		weeks and one a month for six months **Follow-up** Median follow-up time was 16.4 months (6-48 months)	dose intravesical mitomycin Recurrent urothelial carcinoma was identified in three patients (11.5%) – one developed Ta Grade II recurrence in bladder, the second a 0.5cm papillary lesion in right urethral orifice localisation and the third a 0.5cm lesion 1cm above urethral orifice. Both patients who developed recurrence in upper urinary system were initially T1 GIII and CIS (+) Recurrence free survival was 88.4%. There was no progression in any patient and therefore cystectomy was not required	• No in-depth baseline demographic information **Applicability** • Not UK based • Relevant outcomes and patient group **Funding/CoI** None reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					Dysuria and pain of procedure were the most commonly reported side effects/adverse events (42.3% and 38.4% respectively). No patient discontinued treatment due to side effects	
Gofrit (2004) **Country** Italy, Israel, Germany and The Netherlands **Data collection** Not reported	To evaluate the effectiveness of combined local bladder hyperthermia and intravesical chemotherapy for the treatment of patients with high-grade (G3) superficial bladder cancer. This included a prophylactic group and an ablative group **Outcomes** Prophylactic group: • Tumour recurrence • Tumour progression • Need for cystectomy Ablative group: • Complete ablation of tumour	52 patients with high-grade superficial bladder cancer **Prophylactic group** – n= 24. Protocol was recommended for patients who had G3 stage Ta or T1 tumours in the last transurethral resection specimen with neither visible tumour on the baseline video cystoscopy nor carcinoma in situ in the preceding random bladder biopsies **Ablative group –** n=28. Protocol was indicated for any remaining patients	**Statistical analysis** Kaplan Meier plots were drawn to assess recurrence free survival Statistical significance assessment was performed using Kaplan Meier survival analysis comparing two survival curves with the log-rank test	**Intervention** Both groups used Synergo unit SB-TS101: • Prophylactic group – 40g MMC after complete transurethral resection of all tumours • Ablative group – 80mg MMC when visible tumour is seen on video-cystoscopy or bladder biopsies were positive for carcinoma in situ (CIS) • EPI was given to 4 patients who were allergic to MMC (3 from ablative group) • Treatment regimen included eight weekly sessions, followed by four monthly sessions	In the entire study group, no cases of tumour progression to Stage T2 or bladder cancer-related mortality occurred Recurrence free survival rate for the whole study group was 71% after median follow-up of 15.2 months. Cystectomy was performed in 7 patients	**Limitations** • Doses are reported inconsistently throughout the study; 40mg and 80mg are reported in the abstract and treatment table but 40mg and 20mg are reported in the protocol **Applicability** • Not UK based **Funding/CoI** • Two authors are paid consultants to

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		Demographics Prophylactic group: Mean age 68 years 0 concomitant CIS and 0 CIS alone Prior BCG =12 Prior intravesical chemotherapy = 12 Ablative group: Mean age 69 years Two concomitant CIS and 1 CIS alone Prior BCG = 17 Prior intravesical chemotherapy = 11 **Setting** Not reported			Prophylactic group: • Fifteen (62.5%) were recurrence free after a mean follow-up of 35.3 months from first treatment session • 9 (39%) had tumour recurrence after a mean period of 10 months – 6 of these went on to develop Stage pTa tumour recurrence and three developed Stage Pt1 • 8 were treated with TURBT • 1 underwent radical cystectomy • Bladder was preserved in 23 (95.8%) patients • No statistically significant differences were found between patients with different tumour types, previously treated with BCG and those who were BCG naive and patients with numerous previous occurrences (>3) and	Medical Enterprises Europe B.V., the manufacturer of the Synergo device. • A relative of another author is in management at Medical Enterprises Europe B.V. • Funding not reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					those with fewer occurrences (<3) Ablative group: • 21 (75%) achieved complete response to therapy and 7 (25%) were classed as non-responders (<50% reduction in tumour size) • Four of the 7 non-responders underwent radical cystectomy and 3 underwent transurethral resection only • Of the 21 responders, 4 (19%) developed tumour recurrence after an average 13.7 months from the tumour eradication date. Two of these required cystectomy and two transurethral resection only. • After a mean follow-up of 20 months from eradication date, 17 (80.9%) were recurrence free • Bladder perseveration was seen in 78.6% of patients	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• No statistically significant differences were found between patients with different tumour types, previously treated with BCG and those who were BCG naive and patients with numerous previous occurrences (>3) and those with fewer occurrences (<3) The most common adverse events for both groups were posterior wall thermal reaction (15 (65.2%) in the prophylactic group and 18 (62%) in the ablative group) and dysuria for <48 hours (14 (60.1%) in the prophylactic group and 16 (55%) in the ablative group). Treatment was stopped in 2 patients after 4 or 5 sessions due to palmar rash.	
Kiss 2015 **Country** Switzerland **Data collection**	To evaluation combined microwave induced bladder wall hyperthermia and intravesical MMC in patients with NMIBC.	21 patients with histologically confirmed recurrent NMIBC *Exclusion*	Synergo system used *Statistics* • Adverse events and drops outs	**Curative Intent: N=11** 12 weekly sessions of 2 30min cycles (40mg MMC in 50ml sterile water) at 42±2°C	Median number of thermochemotherapy cycles: 6 (1-12) Adverse Effects: n=18 (86%)	**Limitations** • Non comparative study

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
2003-2009 **Study Design** Prospective, non-comparative cohort study	**Outcomes** Recurrence defined as • No recurrence – negative bladder wash cytology and negative cystoscopy at follow-up visits • Recurrence – biopsy-confirmed visible tumour or positive random biopsies Adverse events	• History of MIBC (T2 or higher) • Local or distant metastases • Variant histology • Residual urine >100ml • Urethral stricture • Pregnancy • Age <18 years • Active UTI **Demographics** • Median Age: 70 years (range 35-95) • 76% male • Multifocal disease n=19 **Setting** Urology Department	compared using X^2-test • Post void residuals compared using Mann-Whitney U-test • Descriptive results	Cystoscopy after 6 sessions to evaluate treatment response. **Prophylaxis against recurrence: N=10** 20mg MMC in 50ml sterile water at 42±2°C for 30mins in the same session, weekly for 6 weeks. **Analgesics** Standard analgesic treatment was paracetamol and metamizole sodium. An antimuscarinic was administered as required for bladder spasms. **Follow-Up** Median follow-up was 50 months	• No significant difference between curative/prophylactic groups (p=0.476) • Significant increase in number/severity if patients had more than 3 previous TURB and additional adjuvant bladder instillations (p=0.02). Pain Management • Pain and bladder spasms occurred in 12/21 (57%) patients • Additional pethidine hydrochloride up to 150mg administered in 7/21 patients • Thermochemotherapy administered under general anaesthetic in 2/21 (10%) patients. Completed treatments • Planned treatment was completed in 13/21 (62%), 7 in the curative group and 6 in the prophylactic group. • Planned therapy was abandoned in 8/21 (38%) due to serious adverse events	• Small number of patients included • Limited outcome reporting due to small patient numbers. **Applicability** • Not a UK study • Limited information to add to the body of evidence due to small numbers and narrative reporting • Some subgroup comparison suggesting differences in outcomes between patients being treated with curative intent and patients being treated prophylactically • Unclear how generalisable results from this study can be

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					6/21 patients showed no signs of tumour recurrence after a median 50 month (1-120 months) follow-up. Post-interventional recurrence rates were lowest in patients with an initial pTaG1 tumour stage and highest in pT1 initial tumour stage. 29% (6/21) patients underwent cystectomy for multifocal recurrence or progression to muscle invasive disease. 33% (7/21) patients died (2/7 died of metastatic disease) Median post-void residual urine was 10ml (0-90ml) before first treatment and 10ml (0-80ml) at first follow-up visit (p=0.613).	due to the small numbers/limited data. **Funding/CoI** None declared
Maffezzini 2014 **Country** Italy **Data collection** June 2006 to December 2010	To assess the activity of intravesical chemotherapy with local microwave hyperthermia in patients with NMIBC **Outcomes** • Disease free interval	42 consecutive patients with high risk NMIBC (EAU criteria) *Inclusion* • Risk of recurrence and progression calculated for each	Synergo system used *Statistics* • Categorical data summarised as n and % • Continuous data summarised as	• 40mg MMC in 50ml distilled water • Epirubicin used for patients with persistent intolerance to MMC • Bladder wall temp of 42.5±1.5°C	• 5 patients (11.9%) did not complete treatment schedule due to bladder spasms and were censored as negative and excluded from analysis	**Limitations** • Non-comparative • Not clear if retrospective or prospective

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Study Design Cohort study	• Treatment toxicity	patient – minimum score of 5 for recurrence and 7 for progression required • WHO performance status 0-2 • Adequate bone marrow function • Normal serum transaminase and bilirubin *Exclusion* • MIBC • Prostatic urethral tumours • Urethral strictures • Bladder diverticula **Demographics** • Median age at first event: 70 years (40-82) • Median age at enrolment: 74 years (40-82) • 64.3% males • Previous treatments: BCG 19%, Chemotherapy 45.3%, None 35.7% **Setting** Outpatients	mean (AD), median (range) • Chi square & Fischers exact tests to compare categorical data • Two sample paired t tests or Wilcoxon rank-sum tests for categorical data • Kaplan-Meier estimates for probability of recurrence • Multivariate Cox model to assess independent associations	• Solution continuously circulated. Replaced after 30 mins. • 4 weekly sessions, followed by 6 sessions delivered every 2 weeks and then 4 monthly sessions for a total of 14 sessions over 8 months • Treatment duration of 60min per session **Follow-up** *During Treatment* • Urinary cytopathology (UC) performed at 1 month, repeated at 4 months and treatment end • Cystoscopy and bladder biopsy at treatment end • Urine FISH at 1 months and treatment end *After Treatment* • UC and cystoscopy with biopsy when required starting 4 months after treatment end and every 4 months thereafter until recurrence • Median follow-up was 38 months (4-73 months)	(included in toxicity analysis) • 5 patients (11.9%) experienced treatment disruption due to disease recurrence (censored as recurrence) • 76.2% of patients (n=32) completed treatment • 2 patients were lost to follow-up after negative cystoscopy at 6 and 42 months (censored as negative) • 1 patient died of a concomitant disease (censored as negative) • Percentage of NED patients before the study was 14.95 (95% CI 5.5-28.8%) versus 88.8% (95% CI 73.7-94.8%) after treatment (p=<0.0001) • Patient EORTC scores (HR 41.1, p=0.01), multifocality (HR 17.7, p=0.02) and tumour stage (HR 8.5, p=0.02) were associated with higher risk of recurrence	• Small patient numbers **Applicability** • Not a UK study • Only high-risk patients are included so potentially limited generalisability to intermediate risk patients group **Funding/CoI** Not reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• After median follow up of 38 months, 57.1% of patients showed no evidence of disease and 30.9% had disease recurrence • 16.6% (7) of patients went on to recurrent radical cystectomy • Treatment was well tolerated • 12 patients had a history of allergy to MMC or developed intolerance during treatment • 2 responded to antiallergic medication and 10 were switched to epirubicin • No grade 3 or 4 toxicity was observed • Bladder spasms were associated with reduction in bladder capacity and caused treatment interruption in 5 patients	
Moskovitz (2005) **Country** Israel	Evaluate the efficacy of combined local hyperthermia and intravesical MMC in	32 patients with multiple or recurrent Ta or T1 TCC of the bladder	*Statistical analysis* Kaplan Meier plot was drawn to assess the risk of recurrence	**Intervention** Both groups used Synergo unit SB-TS101:	Prophylactic group:	**Limitations** • Non-comparative

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Data collection December 2000 – March 2004	patients with intermediate or high-risk recurrent TCC of bladder. This included a prophylactic group and an ablative group **Outcomes** Prophylactic group: • Tumour recurrence by biopsy Ablative group • Complete ablation of the tumour proven by multiple random biopsies or mapping TUR-T and urine cytology	**Prophylactic group** - n=22. Patients who underwent complete transurethral resection of all tumours confirmed by cystoscopy, biopsies and negative urine cytology. **Ablative group –** n=10. Patients in whom complete tumour eradication could not be achieved by a single TURBT as well as patients who are unable to undergo anaesthesia for medical reasons. **Demographics** Prophylactic group: • Mean age 69 years • 20 (91%) male • 5 (23%) intermediate risk; 17 (77%) high risk • 13 (59%) prior BCG • 10 (45%) prior intravesical chemotherapy Ablative group: • Mean age 68 years • 7 (70%) male • 10 (100%) high risk • 8 (80%) prior BCG		• Prophylactic group – 40g MMC after complete transurethral resection of all tumours • Ablative group – 80mg MMC in patients in those with viable tumours **Follow-up** Prophylactic group – up to mean 431 days Ablative group – mean 169.4 days	• Average number of treatments per patient was 10 sessions • 20 (91%) were recurrence free after a mean follow-up of 289 days from first treatment session • Two (9%) had tumour recurrence after a mean follow-up period of 431 days. No progression was seen in these patients. Ablative group • Average number of treatments per patient was 8.9 sessions • 8 (80%) patients achieved a complete response to treatment • Time to complete response was 104.5 days while follow-up was 200 days • 2 (20%) patients displayed partial response to treatment after four sessions. The most common adverse event in both groups was posterior wall thermal reaction (prophylactic	• Retrospective • Small patient numbers in each subgroup particularly the neo-adjuvant group • Unclear if patient overlap with Moskovitz 2012 **Applicability** • Not a UK study • Includes both intermediate and high-risk patients **Funding/CoI** Not reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• 8 (80%) prior intravesical chemotherapy **Inclusion criteria:** • Recurrent stage Ta and T1, grade G1 to G3 TCC of the bladder **Exclusion criteria:** • Low risk bladder cancer • Stage higher than T1 • Bladder tumour other than TCC • TCC involving the urethra or upper urinary tract • Urinary bladder diverticulum >1cm diameter • Undergone partial cystectomy • Any situation impeding a 20F catheterisation **Setting**: Not reported			group; 7 (21.2%), ablative group; 2(14.3%). Pain during treatment was also reported in 31 (7.8%) of total treatments.	
Moskovitz 2012 **Country** Israel	Evaluate the safety and efficacy of combined intravesical chemotherapy and	92 patients with intermediate or high-risk NMIBC **Demographics**	*Statistical Analysis* • Kaplan-Meier analysis for time dependent variables	Combined intravesical chemotherapy and hyperthermia using Synergo *Adjuvant (n=66)*	*Adjuvant Protocol* Median follow-up time was 23 months (mean, 32	**Limitations** • Non-comparative

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Data collection 2001 – no end date **Study Design** Retrospective Review of patient records	hyperthermia using Synergo **Outcomes** Adjuvant protocol • Tumour Recurrence • Bladder Preservation Rate Neo-adjuvant protocol • Response • Bladder preservation rate Treatment complication and adverse events	Mean age Adjuvant group – 68.2 years Neoadjuvant – 68.4 years Sex Adjuvant group: 86.4% male Neoadjuvant group: 76.9% male EAU Risk group Adjuvant group: 28.8% intermediate, 71.2% high Neoadjuvant group: 23.1% intermediate, 76.9% high **Setting** Outpatients	• Log-rank test for differences between groups	• 2x20mg in 60 mins • 6 weekly sessions (induction) • Six additional sessions at six weekly intervals (maintenance) *Neo-adjuvant (n=26)* • 2x40mg in 60 mins • 8 weekly sessions • Complete responders - Six additional sessions at six weekly intervals (maintenance) **Follow-up** • Cystoscopy and urine cytology every 3 months for first 2 years • Cystoscopy and urine cytology every 6 months years 3-5	months; range 3 months to 7 years) • 28% of patients (18/64) had tumour recurrence • Median time to recurrence was 13 months (mean, 19 months; range 2months to 7 years) • Estimated recurrence was 32.8% at 2 years • Median disease-free survival was 6.9 years • Disease progression rate was 4.7% (3/64) • Sex, recurrence history, EAU risk classification and previous intravesical treatments did not significantly impact on disease-free survival • Bladder preservation rate was 95.3% (61/64 patients) *Neoadjuvant Protocol* 24/26 patients were evaluable	• Retrospective • Small patient numbers in each subgroup particularly the neo-adjuvant group • Unclear if patient overlap with Moskovitz 2005 **Applicability** • Not a UK study • Includes both intermediate and high-risk patients **Funding/CoI** Not reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Complete response observed in 79% (19/24) • 84% (16/19) patients remained tumour free during mean 18 months follow up (2 months to 8 years) • Overall, durable response observed in 67% (16/24 patients) • Bladder preservation rate was 91.7% • Intention to treat analysis (included all 26 patients) reported an initial complete response of 73.1%, durable response rate of 61.5% and bladder preservation rate of 92.3% *Adverse Events* • 43.5% (40/92) experienced adverse events • Pain (29.3%) and bladder spasms (21.7%) were most common • Stenosis was observed in 5.5% (5/92) • Urethral stricture in 3.3%	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• 4.4% (4/92) patients withdrew before treatment completion	
Nativ 2009 **Country** Israel, Italy, Netherlands **Data collection** 2001 to 2008 **Study Design** Retrospective data review	Evaluate the efficacy of bladder wall hyperthermia combined with intravesical MMC in patients with recurrence after BCG **Outcomes** Disease free survival Recurrence rate	111 patients with biopsy proven urothelial cell carcinoma of the bladder, recurring after previous BCG therapy. *Exclusion* • CIS • Urethral stricture • Small bladder capacity • Bladder wall diverticulum • Nonpure urothelial cell carcinoma • Extravesical disease • Refractory UTI **Demographics** • Mean age 68 years (35-97 years) • 78% male • 26% stage T1 and 74% stage Ta • Average number of previous tumours was 5.3 • 77% high risk, 23% intermediate risk	*Analysis by four groups* • BCG refractory (did not achieve disease free status by 6 months) • BCG resistant (improved disease grade/stage by 3 months, resolution with further BCG treatment) • BCG relapse (early recurrence within 12 months; intermediate within 12 to 24 months; late >24 months). • BCG intolerant (toxicity resulting in early treatment termination) *Statistics* Descriptive statistics (mean/median)	Complete tumour resection followed by adjuvant (prophylactic) thermo-chemotherapy weekly for 6 weeks. 6 maintenance sessions at 4-6 week intervals 2 consecutive 30min cycles (20mg/50ml MMC) Bladder wall hyperthermia to 42±2°C. **Follow-up** Cystoscopy and urine cytology after the induction phase and every 3 months thereafter Median follow-up was 16 months	• 45% of patients experienced adverse events – most mild and transient • Pain and bladder spasm were most common (during treatment) • Haematuria, dysuria and transient incontinence after treatment • 6 (5.4%) patients withdrew due to adverse events (2 MMC allergy, 1 each pain, haematuria, difficult catheter insertion and incontinence. 105 patients included in efficacy analysis Median follow-up • Whole cohort: 16 months • Tumour-free: 21 months (2 to 74 months)	**Limitations** • Non-comparative study • Small patient numbers • Excludes patients with CIS **Applicability** • Not a UK study • Some subgroup analysis between different BCG treatment groups • Patients with CIS excluded – limits the generalisability of the results • EAU risk classification used and some comparison between

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		(EAU risk classification) **Setting** Outpatient setting	X^2 test to compare groups Kaplan-Meier analysis for recurrence and progression outcomes.		• Recurrence free probability was 85% at one year and 56% at two years • Average time to detection of recurrence was 16 months • 3 patients (3%) experienced recurrent muscle invasive disease; 1 had radical cystectomy and 2 were not eligible/refused and progressed to metastatic disease within 1 year • No significant differences between BCG treatment groups (p=0.38) • BCG refractory patients had a 56% recurrence rate at 2 years compared with other groups (p=0.06) • Significantly higher rate of recurrence at 2 years in patients with fewer than 10 treatments compared with patients completing maintenance (61% vs.. 39%, p=0.01)	intermediate and high risk patients. Potentially limited generalisability to UK due to differences in classification of intermediate risk. **Funding/CoI** Not reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Recurrence rate in patients with history of highly recurrent tumours (n=67) was 16.6% at 1 year and 50.2% at 2 years compared with 11.9% and 27.6% in other patients (p=0.09). • Recurrence in intermediate risk patients was 18% at 2 years compared to 49% in high risk (p=0.006) • No significant impact of disease stage, histological grade, sex, or prior MMC	
Sooriakumaran (2016) **Country** UK **Data collection** June 2006 to October 2013 **Study Design** Longitudinal cohort study (retrospective)	To assess predictors of response to hyperthermic MMC **Outcomes** • Time to progression survival (TTP) • Overall survival (OS) • Cancer specific survival (CSS) • Adverse events	97 patients with high risk NMIBC (EAU guidelines) *Exclusion* • Evidence of muscle invasion • HM as part of ablative strategy • <4 instillations • Disease progression during induction course **Demographics** • Median age: 73 years (IQR 12) • 83.5% male	Descriptive statistics for demographic and clinic-pathologic information CIS cases analysed separately from high grade (G3) cases Kaplan Meier plots, for TTP Long rank and Cox proportional hazards models for prognostic factors	Complete resection of any endophytic tumours. Full fulguration of areas suspicious of CIS. RITE (Synergo). Induction regimen: weekly 1-hour treatments for 6-8 weeks (temp 41-44^{o}C) with 40mg MMC in 50ml sterile water. Median 6 cycles (IQR range 6-7) was used. Patients with initial CR/PR had 2 year maintenance regimen (20mg in 50ml every 6 weeks for	72.2% (70/97) patients had initial complete response (CR) PR and nonresponse cases were pooled together to a no-CR category for analysis *Time to Progression Survival* • 61.9% (60/97) patients did not progress • 2 deaths attributed to bladder cancer (without progression) • 51.4% (18/35) patients who experienced	**Limitations** • Non comparative • Unclear if retrospective but likely **Applicability** • Includes only high risk patients therefore may have limited generalisability

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Prior treatments: BCG (69.1%), BCG + other (13.4%), other (8.2%), none (9.3%) • CIS: 75.2% • High grade (WHO grading system); 50.5% **Setting** Outpatients	Reverse Kaplan Meier method and descriptive statistics for OS and CSS	year one and every 8 weeks for year 2) **Follow-up** • 3 monthly cystoscopy plus biopsy of any abnormal mucosa, cold cup biopsy of bladder and prostate urethra and urine cytology in year 1 • 4 monthly rigid cystoscopy and biopsy of suspicious mucosa in year 2 • 6 monthly surveillance from year 3 onwards Median follow-up was 27 months (IQR 16-47 months) for TTP. Median follow up time was 31 months for OS Median follow-up time was 29 months for CSS	progression underwent radical cystectomy. • 8.6% (3/35) were treated with other treatments including BCG, chemoradiation and diverticulectomy. • 40% (14/35) progressed without receiving cystectomy, radiotherapy or BCG treatment being provided over the study period. In this group patients underwent endoscopic surveillance, surgical excision of extravesical disease or palliative treatments for MIBC. • In patients undergoing radical cystectomy, 66.7% (12/18) had CIS alone on final histology, 11.1% (2/18) had no evidence of malignancy and 22.2% (4/18) had high grade bladder cancer. • TTP was significantly worse in males compared with females (p=0.03)	to intermediate risk • EAU risk classification system used therefore may have excluded some intermediate risk patients that would be classified high risk in the UK. **Funding/CoI** None declared

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Initial CR was significantly associated with improved TTP survival (p<0.001) • CIS was statistically significantly associated with improved TTP compared with moderate grade (HR 0.17, p=0.02) and high grade (HR=0.42, p=0.019). *Response* • Initial response (assessed a median 12 weeks after first treatment) indicated 1 patient died between treatment completion on first check. • 17.5% (17/97) of patients died over the study period (7/17 of bladder cancer) • Mortality was lower in the CR group compared with no CR (survival: 88.6% versus 66.7%) *Adverse Events*	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• All self-limiting, none resulted in treatment stopping. • 7.2% (7/97) patients were hospitalised due to haematuria, urinary sepsis and transient non-specific abdominal pain. • 44.3% of patients suffered moderate to severe cystitis type symptoms (dysuria, nocturia and bladder spasm) • 24.7% (24/97) reported haematuria • 14.4% (14/97) experienced UTI • No allergic reactions or urethral strictures	
Sri (2020) **Country:** UK **Data collection:** June 2011 to June 2017	Retrospective study of a prospective cystectomy database to assess operative challenges and oncological outcomes in patients undergoing cystectomy for high risk NMIBC who received RITE-MMC, and contrast them with those that did not **Outcomes:**	138 patients who underwent radical cystectomy for HRNMIBC. **Inclusion criteria:** • All patients who underwent cystectomy for high risk NMIBC– including primary cystectomy, following BCG failure	**Statistical analysis** Kaplan-Meier curves were constructed to analyse all cause mortality, cancer specific mortality and time to recurrence between the RITE-MMC group and no treatment group.	**Intervention:** RITE-MMC group (40mg MMC)– • CIS patients received an 8 week induction cycle and no CIS patients received a 6 week induction cycle. • New referrals received a re-do TUR, urine cytology and upper tract imaging prior to induction. • Failure at induction would lead to a recommendation for radical cystectomy	**RITE MMC group:** • 6 (16.7%) patients developed recurrence over a mean follow-up of 37 months • 8 patients died with 4 of these attributable to recurrence **No RITE MMC:**	**Limitations** • Retrospective • Very limited baseline demographic information available • High risk of section bias **Applicability** • UK based

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
	Intraoperative difficulty • Operative time • Intraoperative blood loss • Length of stay • 90-day readmission	and those following intravesical treatment failure **Exclusion criteria:** • Any patient who would be deemed unsuitable or unfit for cystectomy **RITE MMC group** • n=36 • Patients who had radical cystectomy following BCG and RITE MMC failure • Median age 72 years **No RITE-MMC group** • n=102 • Patients who had primary radical cystectomy or radical cystectomy immediately post BCG failure • Median age 69 years		• All patients received maintenance instillation every 6 weeks for the first year followed by every 8 weeks for the second year • Annual upper tract imaging and urine cytology and cystoscopic surveillance offered every 3-6 months • Failure during maintenance	• 20 (19.6%) patients developed locoregional recurrence or metastatic disease over a mean follow-up time of 24.6 months • 38 patients died with 19 of these attributable to progression Kaplan Meier curve depicting time to recurrence for both groups was constructed. Log rank analysis suggested no statistical difference between groups (p=0.513) Survival curves demonstrating all cause mortality and cancer specific mortality was done for both groups. Log rank analysis showed no statistically significant difference between groups for all cause mortality (p=0.069) and cancer specific mortality (p=0.1269)	• Results have limited relevance as all patients have had radical cystectomy which is usually a main outcome measure. • The comparison group does not completely answer the question of the study. Needs to include a group where RITE-MMC is the first line treatment **Funding/CoI** None reported
Tan (2019) **Country**	To compare disease-free survival (DFS) time between radiofrequency-	104 patients with recurrence of intermediate or high risk	Sample size: 242 patients with 81 events per arm to	Intervention (n=48) • 6 weekly induction instillations of RITE using	***The trial closed early due to higher than expected***	**Limitations**

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
UK **Data collection** May 2010 to July 2013 **Study Design** Open label, phase III randomised controlled trial	induced thermo-chemotherapy effect (RITE) and institutional standard second-line therapy (control) in non-muscle invasive bladder cancer (NMIBC) **Primary Outcomes** • Disease free survival time • 3-month complete response for patients with biopsy proven carcinoma in-situ (CIS) at randomisation **Secondary Outcomes** • Progression free survival (PFS) time • Overall survival (OS) time • Disease-specific survival time • Recurrence free survival (RFS) time in non-CIS patients • Safety and tolerability	NMIBC according to European Association of Urology Guidelines following induction or maintenance BCG randomised to RITE (n=48) or control (n=56). **Inclusion** • Complete TUR of papillary lesions • Resection to confirm the absence of MIBC in patients with pT1 disease • Aged 18 years or older • WHO performance status ≤4 • Patients unfit or unwilling to have radical cystectomy **Exclusion** • Non-urothelial carcinoma • Low grade NMIBC recurrence • Treatment with intravesical chemotherapy ≤6 months • Prostatic urethra or upper tract disease • Known mitomycin-C (MMC) allergy	detect in increase in DFS from 45% to 60% at 24 months. Analyses based on Intention to Treat (ITT) Kaplan-Meier to assess time to event outcomes Primary Analysis: Treatment arms compared using log-rank test. Univariable Cox regression model for unadjusted Hazard Ratios Secondary Analysis: Multivariable Cox regression model with stratification factors for adjusted hazard ratios Pre-specified sub-group analysis to assess treatment effects separately within each stratification factor	the Synergo SB-TS 101 system. • 2 30 min cycles each with 20mg MMC (50ml sterile water) at 42±2^{0}C. • Dose reduction was not permitted • Maintenance RITE (40mg MMC in total; one instillation every 6 weeks for 1st year and one every 8 weeks for 2nd year) for patients who were disease free 3 months after treatment commencement Control (n=56) • 6 weekly instillations of BCG followed by maintenance therapy of 3 consecutive weekly instillations at 3, 6, 12, 18 and 24 months Or • Institutional standard of care defined at randomisation **Follow-up** Minimum 24 months at 3 monthly intervals (Physical exam, cystoscopy, urine cytology).	***CIS recurrence in RITE treated patients.*** Baseline characteristics were well balanced across treatment arms. Higher proportion of papillary disease with concurrent CIS randomised to RITE (25% vs.. 18%, p=0.38). At trial conception it was estimated that 22% of patients would have CIS at baseline however the actual proportion was 68%. High risk NMIBC was defined in 83% (RITE) and 89% (Control). *Intention to Treat* Analysis included 73 events: • 42 patients developed disease recurrence • 15 had recurrent CIS • 5 had disease progression • 11 died For patients without DFS events • Median follow-up time was 36 months	• Early study closure at interim analysis • Recruitment target not reached, study is underpowered **Applicability** • UK NHS setting • Patient population is applicable **Funding/CoI** Medical enterprises B.V. supplied the Synergo system at a discounted rate for the study

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Active/intractable urinary tract infection • Urethral stricture • Small bladder capacity (<250ml) • Significant urinary incontinence • History of pelvic radiotherapy **Demographics** RITE: 71% male, median age 77 years Control: 79% male, median age 76 years **Setting** 14 UK hospitals	Complete response rates compared using odds ratio and Fishers exact test		No significant difference observed between RITE and control • 24-month DFS rate was 35% versus 41% respectively (HR=1.33, 95% CI 0.84-2.10), p=0.23, adjusted p=0.49) No significant difference in the complete response rate of CIS at 3 months between RITE and control • 30% vs.. 47%, OR=0.43, 95% CI 0.18-1.28, p=0.15) In patients with baseline CIS, DFS was significantly lower in RITE-treated patients compared with control • 25% vs. 50% (HR=2.06, 95% CI 1.17-3.62, p=0.01) In patients without baseline CIS, DFS longer in RITE treated patients compared with control but the difference was not significant • 53% vs. 24% (HR=0.50, 95% CI, 0.22-1.17, p=0.11)	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• This treatment-subgroup interaction was statistically significant (p=0.007) *Per Protocol* • No significant treatment-subgroup interaction • Detrimental effect of RITE on patients with CIS at baseline was marked in those with concurrent papillary and CIS disease compared with those with CIS disease only. • No evidence of a differential treatment effect in CIS patients only (HR=1.53, 95% CI 0.77-3.05; p=0.22) Difference in DFS between RITE and control at 24 months • DFS: 89% vs.. 96%, p=0.04 No difference in PFS, OS, RFS between RITE and control at 24 months • PFS: 8 patients with progression; 83% vs. 87%, p=0.16 • OS: 30 deaths, 85% vs. 90%, p=0.18	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• RFS: 27 patients with recurrence, 23% vs.. 40%, p=0.98 *Safety* • 5 patients in each arm experienced adverse events resulting in stopped treatment including skin rash, urinary urgency and nocturia, inability to catheterise, and haematuria, persistent dysuria. • Most adverse events were grade 1-2, there were 2 grade ≥4 toxicities in the control arm • No difference in health related quality of life although RITE patients rated their health status higher than controls at 3, 6 and 9 month follow-up	
Van der Heijden (2004) **Country** Netherlands, Israel, Germany, Italy **Data collection**	To assess the efficacy of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder	90 patients with histologically confirmed Ta or T1 multiple or recurrent superficial transitional cell carcinoma of the bladder *Risk Classification* • EAU guidelines	Video cystoscopy & urine cytology every 3 months for 24 months *Statistics* • Kaplan-Meier plots to assess risk of recurrence	Microwave induced hyperthermic MMC using Synergo system SB-TS 101 6-8 weekly 60-minute sessions followed by 4-6 monthly sessions	Mean number of treatments was 10±2 Mean follow up 18 months (4-24 months) *Recurrence* • 14 patients had pathology proven	**Limitations** • Non-comparative • Retrospective

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
March 1994 to April 2003 **Study Design** Retrospective, non-comparative study	**Outcomes** • Pathology proven tumour recurrence • Side Effects	High Risk: T1, G3, multifocal or highly recurrent, CIS) Intermediate risk: Ta-T1, G1-2, multifocal, >3cm diameter *Inclusion* • Complete resection of all visible papillary tumours (Ta/T1) • WHO performance status 0 to 2 • Life expectancy of >24 months • Patients treated with 2x20mg MMC *Exclusion* • Bladder capacity <150ml • Concomitant malignancy • Extravesical TCC • Diverticle of the bladder • No follow-up cystoscopy/less than 6 treatments **Demographics** N=78 men/12 women Mean age 64.8 years (35-92) History of recurrent disease: n=76	• Log rank test to assess differences between groups	2x20mg MMC in 50ml distilled water (replaced at 30mins) 41°C to 44°C **Follow-up** 24 months	tumour recurrence, 5 with multiple lesions • No progression in stage/grade observed during follow-up • Risk of recurrence after 1-year follow-up was 14.3% (SE 4.5%) and 24.6% (SE 5.9%) after 2 years. • Significantly longer time to recurrence and a lower risk of recurrence for patients with intermediate risk TCC compared with high risk TCC. • Risk of recurrence in patients with previous BCG treatment was 23.1% (SE 7.7%) at 1 year and 41.2% (SE 9.9%) after 2 years *Side Effects* • 65 patients experience side effects • Side effects were local and transient (during treatment) • One case of severe, prolonged posterior wall thermal reaction with a lesion >2cm which took 3 months to heal.	**Applicability** • Not a UK based study • EAU guidelines used for risk classification **Funding/CoI** Not reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		No previous chemo: n=34 (16 with primary disease) **Setting** Outpatient setting			• Tissue reaction observed in 24% of patients • No significant difference between participating hospitals	
Van Valenberg (2018) **Country** Multicentre, international study. Details not reported. **Data collection** January 2000 to December 2016 **Study Design** Retrospective Observational Study	To examine the effect of intravesical radiofrequency induced chemohyperthermia (RF-CHT) in carcinoma in-situ (CIS) patients overall and based on previous therapy. **Primary Outcomes** Complete Response (CR) after 6 months **Secondary Outcome** • 2 year recurrence rate • Recurrence free survival (RFS) after CR • Progression Rate • Overall survival (OS) • Cystectomy-free survival (CFS) • Treatment tolerability	150 patients with histologically proven CIS with or without co-existing papillary Ta/T1 NMIBC tumours who had been treated with RF-CHT using mitomycin-C. *Inclusion* ≥6 RF-CHT instillations Pathology or combination of cytology and cystoscopy results available at 6 months (range 5-9 months) *Exclusion* Not reported **Demographics** • Age: mean age 69.4 years • Sex: Male 82% • BCG: mean 9.1 previous BCG-instillations at CR assessment **Setting**	**Complete Response** CR defined as absence of CIS, papillary high-grade tumour, stage T1 tumour or extra vesical evidence of urothelial carcinoma. Negative results proven by histopathologic examination or cystoscopy and urine cytology. Chi square test to compare between BCG-unresponsive, other BCG treated and treatment naïve patients. Kaplan-Meier (Mantel-Cox log rank tests) to assess RFS, OS and CFS	RF-CHT using Synergo SB-TS 101 system delivering mild hyperthermia (40.5-44ºC) to the bladder wall via direct non-ionising radiation. MMC dose was 40mg/50ml and the instilled solution was replaced after 30 mins giving a total dose of 80mg MMC in an hour. Patients treated for 4 to 8 weeks followed by maintenance instillations (1 instillation every 4-8 weeks). Schedules varied slightly at each centre. **Follow-up** • All patients: mean 35.8 months • BCG non-responders: mean 27.5 months • Other BCG treated patients: mean 38.5 months • Treatment naïve patients: mean 40.6 months	***Complete Response (CR)*** • Complete Response after 6 months was 66.2% • CR for BCG non-responders was 46% • CR for other BCG treated patients was 71.7% • CR for treatment naïve CIS patients was 83% • Significant difference in response rates when compared BCG non-responders with other BCG treated patients ($p<0.0001$) and treatment naïve CIS patients ($p<0.0001$) • CR response rate (all patients) increased with an increased number of RF-CHT instillations: 66.2% with a mean 8.2 instillations to 77.1% with a mean 10.3 instillations.	**Limitations** • Not a randomised trial • Non-comparative (all patients treated with Synergo) **Applicability** • Not a UK study although international so may include UK patients • Synergo used for all patients and subgroup analysis by previous treatments included **Funding/Col**

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		Multicentre, no other details reported.			• In BCG non-responders, CR rate increased from 46% (mean 7.6 instillations) to 57.6% (mean 9.8 instillations). • Higher doses (40mg) showed non-significantly higher CR rates compared with lower doses (20mg) 69.5% vs.. 51.6% (p=0.06). ***Recurrence Rate*** • In all patients with a CR, subsequent recurrence rate was 18.8% and RFS was 74.5%. • No significant difference between any treatment groups for RFS or recurrence rate ***Progression*** • Progression to MIBC (with/without lymph node or distant metastasis) was observed in 13.3% of patients. • 16% of progressions were in BCG non-responders, 13% in	Non-financial support received from Medical Enterprises Ltd.

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					other BCG treated and 10.6% in treatment naïve CIS patients (p=0.74). ***Bladder Preservation Rate*** • For all patients, the bladder preservation rates was 78.5% with a mean cystectomy free time of 99.9 months (95% CI86.7-113.1). • For BCG non-responders: bladder preservation was 71.4%, cystectomy free time was 45.2 months (95% CI 35.7-54.7) • For other BCG treated patients: bladder preservation was 84.1%, cystectomy free time was not reported • For treatment naïve CIS patients bladder preservation rate was 86.7%, cystectomy free time was not reported • Significant difference in bladder preservation rates when comparing	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					BCG non-responders with both other BCG treated and treatment naïve CIS patients (p=0.006). ***Overall Survival (OS)*** • OS was 78% at final follow-up • Mean survival time was 89.5 months (95% CI 74.7-104.8) • For BCG non-responders, OS was 76% and mean survival time was 79.7 months (95% CI 65.2-94.3) • No statistical significance observed between groups • Relative survival (as an approximation of cancer specific survival) was 89% after 3 years and 84% after 5 years of follow-up (95% CIs overlapped between observed OS and relative OS). ***Treatment Tolerability*** 13.4% of patients receiving any amount of RF-CHT instillations had to stop	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					induction and 17.8% had to stop maintenance due to adverse events. Adverse events included pain or spasms during instillation (7.8%), allergy (8.2%) and frequency or urge between instillations (7.5%).	
Volpe 2012 **Country** Italy **Data collection** January 2006 and December 2009 **Study Design** Non-comparative cohort study	To evaluate the effect of thermochemotherapy with MMC in high-risk bladder cancer patients who are non-responders to first line treatment **Outcomes** • Disease free survival Recurrence • Response Rates • Side Effects	30 patients with NMIBC unresponsive to chemotherapy/immunotherapy, suitable for radical cystectomy. *Exclusion* • Stage higher than T1 • Bladder tumour other than TCC • Urethra or upper urinary tract involvement • Urinary bladder diverticulum >1cm in diameter • Patients after partial cystectomy • Situation impeding a 20-Fr catheterisation **Demographics** Mean age: 55.4 years 28 male 2 female	*Statistics* Kaplan Meier curves to estimate DFS, compared with log rank test	• Prophylactic: 40mg MMC in 50ml distilled water (20+20) continuously pumped out of the bladder and reinstilled • Ablative: 80mg MMC in 50ml distilled water (40+40) continuously pumped out of the bladder and reinstilled • Solution changed after 30 mins • Bladder wall temperature of 42±2°C • Treatment duration 40mins effective heating **Follow-up** • Videocystoscopy and voiding urine cytology 45 days after the end of weekly and monthly sessions • Cystoscopy and urine cytology every 3 months for 2 years and every 6 months thereafter in responders	Mean follow-up was 14 months (±8.48 months) *Disease Free Survival (DFS)* • DFS for all patients was 77% at 12 months and 55% at 24 months • In patients treated only with BCG DFS was 100% at 12 months and 77% at 24 months • In patients previously treated with multiple agents DFS was 64% at 12 months and 46% at 24 months • Difference between the subgroups was statistically significant ($p<0.05$) • Prophylactic treatment: DFS was 87% at 12 months and 58% at 24 months • Ablative treatment: DFS was 85% at 12	**Limitations** • No comparator • Small sample size • Not clear if prospective or retrospective – likely retrospective **Applicability** • Not UK based • Limited to high risk patients who have not responded to previous treatment – may reflect the likely place in the UK clinical pathway as an option before radical cystectomy but will have limited

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		Prior treatments: BCG (n=13), multiple agents (n=17) **Setting** Outpatients			months and 48% at 24 months • Difference was not statistically significant (p=0.42) *Recurrence* • 56.7% (17/30) patients had a recurrence • 43.75% (7/16) patients in the prophylactic group and 46.25% (9/14) patients in the ablative group had a recurrence • Mean time to recurrence was 10.7 months (8 months in the prophylactic group and 12.5 months in the ablative group) • 17.64% of non-responders had progression to MIBC *Recurrence* • 42.85% (6/14) patients in the ablative group had a compete response *Side Effects* • Generally mild and transient	generalisability to intermediate risk population **Funding/CoI** None declared

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Primarily pain and bladder spasms during treatment • Posterior wall thermal reaction observed on cystoscopy • Most common adverse event was pain during treatment followed by haematuria and irritative symptoms • Mild skin allergy to MMC requiring antihistamine treatment which was greater in the ablative group	
Witjes (2009) **Country** Israel, Italy, Germany, Switzerland, Austria and the Netherlands **Data collection** March 1997 to June 2005 **Study Design** Retrospective Case Series	To study results of chemotherapy combined with intravesical hyperthermia in patients with mainly BCG-failing CIS **Outcomes** • Eradication of CIS • Tumour recurrence • Adverse Events	51 patients with CIS of the bladder (defined as non-papillary high-grade non-invasive urothelial cell carcinoma (UCC)) *Inclusion* • Biopsy proven, histologically confirmed CIS • WHO performance status 0-2 • Life expectancy >24 months *Exclusion* • Limited bladder capacity (<150mls)	Cystoscopy and Urine cytology every 3 months Biopsies of suspicious lesions *Statistical analysis* No details of statistical methods	RITE delivered using Synergo Weekly treatments for 6 weeks comprising 20mg MMC in 50ml sterile water replaced by a fresh identical solution after 30 mins for a total 40mg MMC in 1 hour Higher doses for patients with concomitant papillary tumours or wide areas of CIS (40mg twice, 80mg in 1 hours; weekly for 8 weeks) All patients received 6 maintenance instillations (one every 6 weeks)	49 patients were included in analysis • 45 (92%) had no CIS at 3 months (complete biopsy and cytology proven). • 2 additional patients had no CIS but had persistent papillary tumour • No difference in response between patients with/without concomitant papillary tumours (p=0.94) • No difference in response between	**Limitations** • Retrospective study • Non-comparative • Small sample size **Applicability** • Not a UK based study • Patient group is applicable but limited to CIS so generalisability to wider NMIBC

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Concomitant malignancy • Extravesical UCC • Diverticulum of the bladder • No follow-up cystoscopy • Fewer than 6 treatments. **Demographics** Mean age: 69.9 years (50-87 years) N=42 males Mean 3.2 previous TURs Previous Intravesical treatments: • BCG (n=34) • MMC (n=11) • Epirubicin (n=4) • Gemcitabine (n=3) • Keyhole-limpet hemocyanin (n=1) • Valrubicin (n=1) • Radiation (n=1) **Setting** Outpatient setting		**Follow-up** 24 months	BCG responders/non-responders (p=0.63) Complete responders were followed up for a mean 27 (3-77) months • 22/45 (49%) of patients had a recurrence • 5/45 had a cystectomy due to recurrent tumour • 1 patient (tumour free) had a cystectomy due to a contracted bladder • 17 patients had a pure CIS recurrence and were treated conservatively Safety • Side effects were mild and transient • Commonly included pain and bladder spasms during treatment • Irritative bladder symptoms for 1-2 days after • One patient stopped treatment due to haematuria, 1 treatment session was delayed for 1 week	patients may be limited. **Funding/CoI** One author received an honorarium as an advisor to MEL in the FDA Synergo registration procedure

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					and 1 session was shortened.	

Abbreviations: BCG, bacillus Calmette-Guérin; CIS, carcinoma in-situ; CSS, cancer specific survival; DFS, disease free survival; FISH, Fluorescence in situ hybridisation; MMC, mitomycin-C; NMIBC, non-muscle invasive bladder cancer; OS, overall survival; PFS, progression free survival; RFS, recurrence free survival; RITE, radiofrequency induced thermos-chemotherapy effect; TCC, transitional cell carcinoma; TTP, time to progression; TUR, transurethral resection; TURB, transurethral resection of the bladder; UTI, urinary tract infection

Abstracts

Study	Aims	Study Details	Results	EAC Comment
Ayres 2018 *Other Abstracts* • **Ayres 2012** • **Ayres 2017**	Report on 10-year experience of RITE	**Data Collection:** October 2006-August 2017 **Participants**: 135 patients with high risk NMIBC who failed BCG treatment **Treatment:** RITE delivered using Synergo (Induction and maintenance, 40mg MMC) **Follow-up:** Not reported in Ayres 2018) Median follow-up 47 months (38-58) reported in Ayres (2017)	***Results reported from Ayres 2018 as the most recent.*** • 5 patients did not complete induction due to significant side effects (pain, incontinence, severe rash) • Recurrence free survival was 63% at 1 year, 34% at 5 years and 24% at 10 years • Progression free survival was 92% at 1 year, 71% at 5 years and 62% at 10 years • 11 patients had progression to MIBC • 30 patients had radical cystectomy • Overall survival was 98% at 1 year, 63% at 5 years and 54% at 10 years • Cancer specific survival was 100% at 1 year, 79% at 5 years and 75% at 10 years	• Limited data reported due to being an abstract • Population is relevant to decision problem but only included high-risk NMIBC which may limit generalisability • RITE is used as an alternative to radical cystectomy for patients who are BCG refractory which represents the likely use of RITE in the NHS clinical pathway
Canepa 2016	To evaluate long term experience of treating NMIBC	**Data Collection:** 2004-2015	• Following induction 7.5% (n=11) patients stopped treatment due to recurrence (3 progressions and 8 recurrences)	• Limited data reported due to being an abstract

Study	Aims	Study Details	Results	EAC Comment
	with hyperthermic chemotherapy using Synergo	**Participants:** 146 patients' majority with high risk NMIBC (64 pts. with G3 (44%), 79 T1 (54%) and 22 CIS (15%). **Treatment:** intravesical thermo-chemotherapy MMC-C 40mg (HT-MMC). Induction of 4 weekly treatments with 2x40mg MMC followed by maintenance treatment (2x40mg, 3 session every 15 days, then 3 sessions every 21 days, then 3 sessions every 45 days) **Follow up:** Mean 39.2 months (2.4months to 7.9 years)	• Median number of treatments sessions was 11 • 37/146 patients reported a recurrence and 14/146 patients presented a progression • Recurrence free survival was 89.6% at 1 year, 79.2% at 2 years and 68.3% at 5 years • Progression free survival was 98% at 1 year, 96.2% at 2 years and 83.7% at 5 years • Side effects were primarily grade 1 and grade 2 • 10 patients experienced grade 3 side effects including bladder spasms/pain during treatment, dysuria and urgency.	• Reported in company submission in support of claimed benefits
Halachmi 2009	To evaluate recurrence and progression rates following TURT plus adjuvant CHT	**Data Collection:** Not reported **Participants:** 56 patients with T1G3 Transitional Cell Carcinoma **Treatment:** transurethral resection of tumour followed by adjuvant prophylactic intravesical MMC combined with hyperthermia **Follow-Up**	• 31.7% (n=16) had tumour recurrence of which 18.75% (3/16) progressed to invasive disease • Median time for recurrence was 8 months (Mean 10 months, range 2-31) • Kaplan-Meier estimated recurrence rate was 38.5% at 2 years and 47.3% at 4 years • 9% of patients dropped out due to adverse events	• Limited data reported due to being an abstract • Patients at high risk of recurrence are included which is relevant to the decision problem but may limit generalisability • CHT used in the adjuvant setting after TURT, not reported whether patients had previous treatments. CHT as first line treatment option may be appropriate in the UK setting.

Study	Aims	Study Details	Results	EAC Comment
		Median follow-up for tumour free patients was 18 months (mean 20 months, range 2-49)		
Hasner 2009	To evaluate if repetitive intravesical hyperthermia with MMC reduced recurrence and progression	**Data Collection:** August 2000 and August 2004 **Participants:** 23 patients with recurrent NMIBC after MMC or BCG **Treatment:** All patients underwent TUR Adjuvant (n=13): 2x20mg MMC Neo-adjuvant (n=10): 2x40mg MMC Simultaneous microwave induced intravesical hyperthermia at 42C **Follow-up:** Mean follow-up time was 57.6 months with prophylactic treatment and 66.3 months with neo-adjuvant treatment	**Adjuvant** • 38% (5/13) were tumour free (3 within 36 months before they died of other causes, 2 within 32 months and 1 within 11 months) • No tumour progressions observed **Neo-Adjuvant** • 30% (3/10) were tumour free (1 within 44 months, 1 within 60 months, 2 within 15 months with one recurrence each within 50.5 months without progression. • 1 recurred during treatment with progression and underwent cystectomy • 1 patient had iatrogenic perforation of urethra and rectum during catheter insertion and underwent cystectomy with neobladder • 1 patient died with bladder cancer • Adverse events included urethral strictures (22%) and bladder fibrosis (9%)	• Limited data reported due to being an abstract • CHT used in both adjuvant (prophylactic) and ne-adjuvant (ablative) setting which is likely an appropriate use in the UK setting • Some discrepancy in the numbers reported
Hiebeler 2020	Not reported	**Data Collection:** 2009-2015 **Participants:** 44 patients with intermediate or high-risk NMIBC **Treatment**	*Adjuvant (n=18)* • 2 patients were lost to follow-up • 87.5% (14/16) patients were tumour free after treatment completion • 2 patients had a recurrence (mean time 2.3 years) • No cystectomy performed	• Unpublished data • Limited data reporting as this is a translated abstract from an unpublished thesis • Translation has not been validated • Includes intermediate and high-risk patients

Study	Aims	Study Details	Results	EAC Comment
		Thermo-chemotherapy MMC using Synergo (41% adjuvant, 59% ablative) **Follow-up** Mean follow-up was 3.2 years	*Ablative (n=26)* • 90% were classified high-risk • 73% had history of recurrent disease • 1 year disease free rate was 83% and 5-year disease free rate was 70%	• Synergo used in an ablative and adjuvant setting
Kilb 2018	To evaluate RITE for high risk NMIBC	**Data Collection:** 2016-2018 **Participants:** 67 patients with high risk NMIBC (EORTC Classification), with 65.7% CIS rate. **Treatment:** 85% (n=53) treated with primary RITE as an alternative to BCG and 15% (n=14) as 2nd line alternative to radical cystectomy Induction phase: 8 treatments weekly (2x40mg MMC, 42C) using Synergo followed by bladder resection and maintenance treatment (6 weeks, 2x20mg, 42C) **Follow-up** Cystoscopy controls every 3 months for first 2 years and 6 months thereafter.	• Tumour persistence at week 11 after induction therapy (based on TURB results) was 14.9% (10/67) • Mean recurrence free time was 3.5 years • 10.4% of patients with recurrence progressed to MIBC, high risk recurrence occurred in 6% resulting in radical cystectomy and low risk recurrence in 1.5% with organ preservation • Death rate from bladder cancer was 1/67 • Adverse events resulted in incomplete treatments in 9% • Bladder preservation rate was 80.6% lasting >5 years in 53.8% (14/26)	• Limited data reported due to being an abstract •
Lüdecke 2015	To evaluate effectiveness of	**Data Collection:** Not reported	• Overall recurrence rate was 19.4% at 2 years • 41.7% BCG failure patients with BCG-resistance stay tumour-free	• Limited data reported due to being an abstract

Study	Aims	Study Details	Results	EAC Comment
	treatments for high risk NMIBC	**Participants:** 271 patients **Treatment:** Radiofrequency induced microwave hyperthermia with MMC (Synergo) 8 treatment, twice weekly (40mg MMC over 60 mins) followed by bladder resection 3 weeks after last session. Maintenance treatment in tumour free patients **Follow-up:** Mean follow-up was 2.2 years (28 days to 12.9 years)	• 66.7% recurrence free in early BCG-relapse patients over 2 years. • Recurrence-free rate of 81.6% in BCG naive high-risk NMIBC patients	• Included intermediate and high-risk patients but limited subgroup analysis
Lüdecke 2013(a)	Not reported	**Data Collection:** Not reported **Participants:** 138 patients with NMIBC **Treatment:** intravesical-chemotherapy with MMC (Synergo) **Follow-up:** mean follow-up was 2.9 years (3.6 months – 6.9 years)	• 52 patients treated in adjuvant indication and 86 patients treated in ablative indication (69 evaluable) • Overall recurrence free rate was 78.3% • 10 patients had recurrence without progression • 85.5% of the patients in ablative indication group reached CR, persisted for mean 26.1 months • 48 patients (69.6%) were tumour free study time • 8 patients (11.6%) needed a cystectomy • 3 patients (4.3%) progressed to metastatic disease and the other 5 demonstrated low-risk new tumours again treated transurethral • organ preservation rate was 76.8% (n=53)	• Limited data reported due to being an abstract • Included intermediate and high-risk patients but limited subgroup analysis • Unclear if any overlap with Lüdecke 2015

Study	Aims	Study Details	Results	EAC Comment
			• Side effects included allergy, UTI, spasm, difficulties with catheterisation and nocturia ascending from 1.4% to 5.6%.	
Lüdecke 2013(b)	To demonstrate the therapeutic efficacy of HTC	**Data Collection:** Not reported **Participants:** 69 patients with high-risk NMIBC **Treatments:** induction of 8 weekly treatments with 2x40 mg MMC • maintenance therapy every 6 weeks with 2x20 mg MMC in tumour free patients **Follow-up** Mean of 24.1 months	• All patients treated in ablative indication • 85.5% (59/69) patients reached complete remission at week 11 lasting a mean period of 26.1 months • 69.9% of patients were tumour free over whole study period • 11.6% (n=8) patients underwent radical cystectomy • Organ preservation rate was 88.4% (n=61) • patients (88.4%) achieved organ preservation despite high- and extremely high-risk disease. • Side effects requiring medical intervention included allergy, UTI, haematuria, detrusor spasm, difficulties with catheterisation and nocturia • Treatment was stopped in 3 cases because of allergy and urethral trauma not influencing the efficacy.	• Limited data reported due to being an abstract • Included intermediate and high-risk patients but limited subgroup analysis • Unclear if any overlap with Lüdecke 2015 and/or Lüdecke 2013(a)
Mizrahi 2020	To compare 2nd line treatments for BCG unresponsive NMIBC	**Data Collection:** 2008-2016 **Participants:** 68 patients with BCG unresponsive NMIBC **Treatments:** • Re-induction BCG (n=21) • Thermo-chemotherapy MMC using Synergo (n=23) • Early cystectomy (n=6)	• Response observed in 33.3% in the BCG group, 39.1% in the Synergo group • Immediate progression to MIBC observed in 19% in BCG group and 26.1% in Synergo group • 3 patients in each group progressed to metastatic disease during follow-up	• Limited data reported due to being an abstract • CHT used as 2nd line treatment option for patients who are BCG unresponsive, this is likely to represent an appropriate place in the UK clinical pathway • Does not report if patients are high risk, intermediate risk or both but appears to be both give statement 'BCG is the gold standard treatment for intermediate and high-risk NMIBC'

Study	Aims	Study Details	Results	EAC Comment
		Follow-up: Not reported		• Some discrepancy in the numbers reported
Pai 2014	To establish whether hyperthermic MMC is effective in patients with high risk NMIBC	**Data Collection:** June 2006 to August 2013 **Participants:** 100 patients with high risk NMIBC. (84 patients had failed BCG or were intolerant) **Treatment:** Induction regimen – weekly treatments for 6-8 weeks (41-44°C), followed by maintenance treatment for patients who responded. **Follow-up** Median follow-up was 34 months (3-88 months)	• Overall survival was 61.9% • 5-year disease specific survival was 85.2% • 5-year progression free survival was 46.9% • 20 patients had a radical cystectomy • 1 patient developed disease recurrence after cystectomy • 3 patients did not complete induction due to side effects	• Limited data reported due to being an abstract • No apparent overlap with any existing studies
Racioppi 2010	Not reported	**Data Collection:** January 2006 to December 2009 **Participants:** 24 participants with recurrent stage CIS, Ta and T1, grade G1 to G3 NMIBC **Treatment:** Prophylactic: 6 weekly sessions followed by 4 to six monthly sessions (total of 12 sessions)	• Patients classified as non-responders if <50% tumour size reduction not observed at 6 weeks • In the prophylactic group (n=8) 50% (n=4) were disease free and 50% (n=4) had recurrence with follow up 14.7 months, • In the ablative group (n=12), 42% were disease free (n=5) and 50% (n=6) had recurrence with follow-up 14.2 months. 1 patient lost to follow-up	• Limited data reported due to being an abstract • No apparent overlap with any existing studies

Study	Aims	Study Details	Results	EAC Comment
		Ablative: 8 weekly sessions followed by 6 monthly sessions Maintenance: 6 additional monthly sessions for responders **Follow-up** Prophylactic: 14.7 months for disease free survival Ablative: 14.2 months for disease free survival		
Racioppi 2019 *Other Abstracts* **Racioppi 2019(b)** **Ragonese 2016**	To compare patients treated 2nd line conservative intravesical device assisted therapy	**Data Collection:** Not Reported **Participants:** 142 patients with high risk NMIBC unresponsive to BCG **Treatments:** • Device assisted intravesical therapy (n=72) split between Synergo (n=42) and EMDA (n=30) • Radical cystectomy (n=70) **Follow-up** Median follow up was 59 months (±5.3)	All Patients High-grade disease-free survival • 51.4% in device assisted group (all patients) versus 84.3% in radical cystectomy group (p<0.05) Progression free survival • 69.4% in device assisted group versus 84.3% in radical cystectomy (p<0.05) Cancer specific survival • 94.4% in device assisted group versus 95.7% in radical cystectomy group Overall Survival • 91.7% in device assisted group and 88.6% in radical cystectomy group Synergo versus EMDA High-grade disease-free survival • 50% in EMDA versus 52.4% in Synergo subgroups (p<0.05) • Persistent/recurrent high grade NMIBC in 26.7% in EMDA and 26.2% in Synergo (p<0.05)	• Limited data reported due to being an abstract • EMDA outside the decision problem so may have limited applicability to the UK setting • Comparisons not made between Synergo and radical cystectomy which would be more relevant to UK practice

Study	Aims	Study Details	Results	EAC Comment
			• Progression to MIBC in 23.3% in EMDA versus 21.4% in Synergo (p<0.05) Stratification by CIS • High-grade disease-free survival was 36.4% for solitary/concurrent CIS and 57.9% with no CIS in EMDA versus 46.7% and 55.6% respectively in Synergo	
Roth (2011) *Other Abstracts* **Schneider (2011)**	To evaluate efficacy of chemotherapy with MMC combined with intravesical hyperthermia	**Data Collection:** 2003 to 2009 **Participants:** 21 patients with confirmed recurrent NMIBC **Treatments:** Thermochemotherapy (Synergo) weekly for 6 (prophylactic) or 12 weeks (therapeutic) weeks **Follow-up:** Median follow-up was 23 months (3-66 months)	• Median number of treatments was 6 per patients • Treatment abandoned in 8 patients due to side effects (pain (3), contracted bladder (2), allergic reaction (2), iatrogenic urethral perforation (1) • 4/13 patients completing treatment were tumour free, 4 had cystectomy due to multifocal recurrence, 5 died • Side effects were intensive and frequent including urinary urgency/frequency (52%), pain (36%) and gross haematuria (26%) • Overall, 29 patients showed no sign of recurrence at median follow-up	• Limited data reported due to being an abstract • Non-comparative • Same results in both abstracts (Roth 2011 and Schneider 2011)
Vendanayagam 2017	To assess efficacy of RITE MMC in patients with recurrent NMIBC (non-responsive or intolerant to BCG)	**Data Collection:** November 2011 to April 2015 **Participants:** 25 patients **Treatment:** RITE MMC using Synergo **Follow-up:** minimum follow-up period of 12 months	• Recurrence free survival rate was 76% at 12 months • Mean recurrence free survival time was 19.5 months	• Limited data reported due to being an abstract • Non-comparative

Appendix C Critical Appraisal Results

Study details

Reference	Arends, T. J., Nativ, O., Maffezzini, M., de Cobelli, O., Canepa, G., Verweij, F., Moskovitz, B., van der Heijden, A. G. and Witjes, J. A. (2016) 'Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guerin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non-Muscle-invasive Bladder Cancer', *European Urology,* 69(6), pp. 1046-52. NCT00384891

Study design

- X Individually-randomised parallel-group trial
- ☐ Cluster-randomised parallel-group trial
- ☐ Individually randomised cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Chemohyperthermia using mitomycin C	Comparator:	Bacillus Calmette-Guerin

Specify which outcome is being assessed for risk of bias	Recurrence-free survival (24 months)
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 2 24 mo RFS, CHT (95% CI): ITT = 78.1% (65.2–86.7), PP = 81.8 (68.7–89.8) 24 mo RFS, BCG (95% CI): ITT = 64.8 (52.2–74.9), PP = 64.8 (52.2–74.9)

Is the review team's aim for this result…?

- X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

✓ Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
✓ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Study details

Reference	Colombo R, Da Pozzo LF, Salonia A, et al. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. J Clin Oncol. 2003;21(23):4270-4276. doi:10.1200/JCO.2003.01.089 Colombo, R., Salonia, A., Leib, Z., Pavone-Macaluso, M. and Engelstein, D. (2011) 'Long-term outcomes of a randomised controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC)', BJU International, 107(6), pp. 912-8.

Study design

X Individually-randomised parallel-group trial

☐ Cluster-randomised parallel-group trial
☐ Individually randomised cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	Hyperthermia and intravesical chemotherapy with Synergo	Comparator:	Intravesical chemotherapy only

Specify which outcome is being assessed for risk of bias	Time to first occurrence (Colombo 2003)
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Exp: 6/35 (17.1%); Comp: 23/40 (57.5%) recurrences (p=0.0002)

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Study details

Reference	Tan, W. S., Panchal, A., Buckley, L., Devall, A. J., Loubiere, L. S., Pope, A. M., Feneley, M. R., Cresswell, J., Issa, R., Mostafid, H. and et al. (2019) 'Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guérin or Institutional Standard in Patients with Recurrence of Non–muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guérin Therapy (HYMN): a Phase III, Open-label, Randomised Controlled Trial', European urology, 75(1), pp. 63-71. NCT01094964

Study design

X Individually-randomised parallel-group trial
☐ Cluster-randomised parallel-group trial
☐ Individually randomised cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	radiofrequency-induced thermo-chemotherapy using Synergo. Treatment comprised two 30-min cycles, each with 20 mg MMC.	Comparator:	either six consecutive weekly BCG instillations (50 ml normal saline) followed by maintenance therapy (three consecutive weekly instillations at 3, 6, 12, 18, and 24 mo) or institutional standard of care defined at randomisation.

Specify which outcome is being assessed for risk of bias	Disease free survival time

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	RITE v control: 35% versus 41%, respectively (HR 1.33, 95% confidence interval [CI] 0.84–2.10], p = 0.23; adjusted p = 0.49)

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial

☐ Trial protocol

☐ Statistical analysis plan (SAP)

X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

☐ "Grey literature" (e.g. unpublished thesis)

☐ Conference abstract(s) about the trial

☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

☐ Research ethics application

☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)

☐ Personal communication with trialist

☐ Personal communication with the sponsor

JBI Critical Appraisal Checklist for Case Series

Citation: Brummelhuis, Iris S G et al. “Long-Term Experience with Radiofrequency-Induced Hyperthermia Combined with Intravesical Chemotherapy for Non-Muscle Invasive Bladder Cancer.” Cancers vol. 13,3 377. 20 Jan. 2021, doi:10.3390/cancers13030377

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal:

Paper files of 25/324 patients were missing so weren’t included, a minimal number not included. More men included. Some of the results reported do not have p values or are not significant.

JBI Critical Appraisal Checklist for Case Series

Reviewer Michal Pruski Date 13/04/2021

Author Colombo et al. Year 2001 Record Number_____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	☐	☐	X	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	☐	☐	X	☐
• Did the case series have complete inclusion of participants?	☐	☐	X	☐
• Was there clear reporting of the demographics of the participants in the study?	☐	X	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	X
• Was statistical analysis appropriate?	☐	☐	☐	X

Overall appraisal:

No exclusion criteria were mentioned. Note that clinical information and follow-up results were reported via a non-validated questionnaire. No statistical analysis.

JBI Critical Appraisal Checklist for Case Series

Reviewer Michal Pruski Date 13/04/2021

Author Erturhan Year 2015 Record Number_____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	☐	☐	X	☐
• Did the case series have complete inclusion of participants?	☐	☐	X	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	X
• Was statistical analysis appropriate?	☐	☐	X	☐

Overall appraisal:

Uncertainty about patient inclusion and no detail about statistical analysis.

JBI Critical Appraisal Checklist for Case Series

Reviewer Michal Pruski Date 13/04/2021

Author Gofrit Year 2004 Record Number_____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	☐	☐	X	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	☐	☐	X	☐
• Did the case series have complete inclusion of participants?	☐	☐	X	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	X	☐	☐
• Was statistical analysis appropriate?	☐	☐	X	☐

Overall appraisal:

The report uses the somewhat unclear phrase of 'virtually all the patients' rather than simply stating all or stating the exclusion criteria. While they report the statistical strategy for the KM survival analysis, they do not do it for other aspects (see e.g. second column on p. 468 on the same level as the 'Results' heading on the first column) and they do not define what they take 'statistically significant' to mean.

JBI Critical Appraisal Checklist for Case Series

Reviewer Michal Pruski Date 13/04/2021

Author Kiss et al. Year 2015 Record Number_____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	☐	☐	X	☐
• Did the case series have complete inclusion of participants?	☐	☐	X	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	X
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal:

Aside of some ambiguity regarding the completeness of patient inclusion, there were no major concerns.

JBI Critical Appraisal Checklist for Case Series

Reviewer____Helen Morgan_____Date_14/04/2021

Citation: Maffezzini, Massimo et al. “Intravesical mitomycin C combined with local microwave hyperthermia in non-muscle-invasive bladder cancer with increased European Organization for Research and Treatment of Cancer (EORTC) score risk of recurrence and progression.” Cancer chemotherapy and pharmacology vol. 73,5 (2014): 925-30. doi:10.1007/s00280-014-2423-y

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal:

Included more men and more smokers, small sample.

JBI Critical Appraisal Checklist for Case Series

Reviewer____Helen Morgan_____Date_14/04/2021

Citation: Moskovitz, B et al. “Thermo-chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients.” Annals of oncology : official journal of the European Society for Medical Oncology vol. 16,4 (2005): 585-9. doi:10.1093/annonc/mdi124

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal:

Included more men, small sample.

JBI Critical Appraisal Checklist for Case Series

Reviewer____Helen Morgan_____Date_14/04/2021

Citation: Moskovitz, Boaz et al. "10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer." Future oncology (London, England) vol. 8,8 (2012): 1041-9. doi:10.2217/fon.12.90

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal:

Included more men, small sample.

Reviewer_ _ _ _ Helen Morgan _____ Date_14/04/2021

Citation: Sooriakumaran, Prasanna et al. "Predictive Factors for Time to Progression after Hyperthermic Mitomycin C Treatment for High-Risk Non-Muscle Invasive Urothelial Carcinoma of the Bladder: An Observational Cohort Study of 97 Patients." Urologia internationalis vol. 96,1 (2016): 83-90. doi:10.1159/000435788

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal:

Included more men.

JBI Critical Appraisal Checklist for Case Series

Author_____Sri _____ Year_____2020___ Record Number_____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	☐	☐	X	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	☐	☐	X	☐
• Did the case series have complete inclusion of participants?	☐	☐	X	☐
• Was there clear reporting of the demographics of the participants in the study?	☐	☐	X	☐
• Was there clear reporting of clinical information of the participants?	☐	☐	X	☐
• Were the outcomes or follow up results of cases clearly reported?	☐	☐	X	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	X	☐
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal: Include X Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____Retrospective comparison of a cystectomy data base. Limited reporting of outcomes and patient information so limited applicability.

JBI Critical Appraisal Checklist for Case Series

Reviewer____Helen Morgan_____Date_13/04/2021

Citation: van der Heijden, A G et al. "Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder." European urology vol. 46,1 (2004): 65-71; discussion 71-2. doi:10.1016/j.eururo.2004.01.019

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Limited detail i.e. 9 European hospitals but sufficient			
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal: More men included.

JBI Critical Appraisal Checklist for Case Series

Reviewer_____Helen Morgan_____Date_13/04/2021

Citation: van Valenberg, F Johannes P et al. "Intravesical Radiofrequency-Induced Chemohyperthermia for Carcinoma in Situ of the Urinary Bladder: A Retrospective Multicentre Study." Bladder cancer (Amsterdam, Netherlands) vol. 4,4 365-376. 29 Oct. 2018, doi:10.3233/BLC-180187

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal: More men included.

JBI Critical Appraisal Checklist for Case Series

Reviewer_____Helen Morgan_____Date_13/04/2021

Citation: Volpe, A et al. "Thermochemotherapy for non-muscle-invasive bladder cancer: is there a chance to avoid early cystectomy?." *Urologia internationalis* vol. 89,3 (2012): 311-8. doi:10.1159/000341912

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
• Was statistical analysis appropriate?	X	☐	☐	☐

Overall appraisal:

More men included. Small sample size.

JBI Critical Appraisal Checklist for Case Series

Reviewer____Helen Morgan_____Date_13/04/2021

Citation: Alfred Witjes, J et al. “Intravesical hyperthermia and mitomycin-C for carcinoma in situ of the urinary bladder: experience of the European Synergo working party.” World journal of urology vol. 27,3 (2009): 319-24. doi:10.1007/s00345-009-0384-2

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	X	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	X	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	X	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	X	☐	☐	☐
• Did the case series have complete inclusion of participants?	X	☐	☐	☐
• Was there clear reporting of the demographics of the participants in the study?	X	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	X	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	X	☐	☐	☐
• Was statistical analysis appropriate?	limited detail but narrative presentation of results with p values			

Overall appraisal:

More men included. Small sample size as noted by authors but data collected over several years and from several centres indicating CIS is not very common.

Appendix D Ongoing Studies

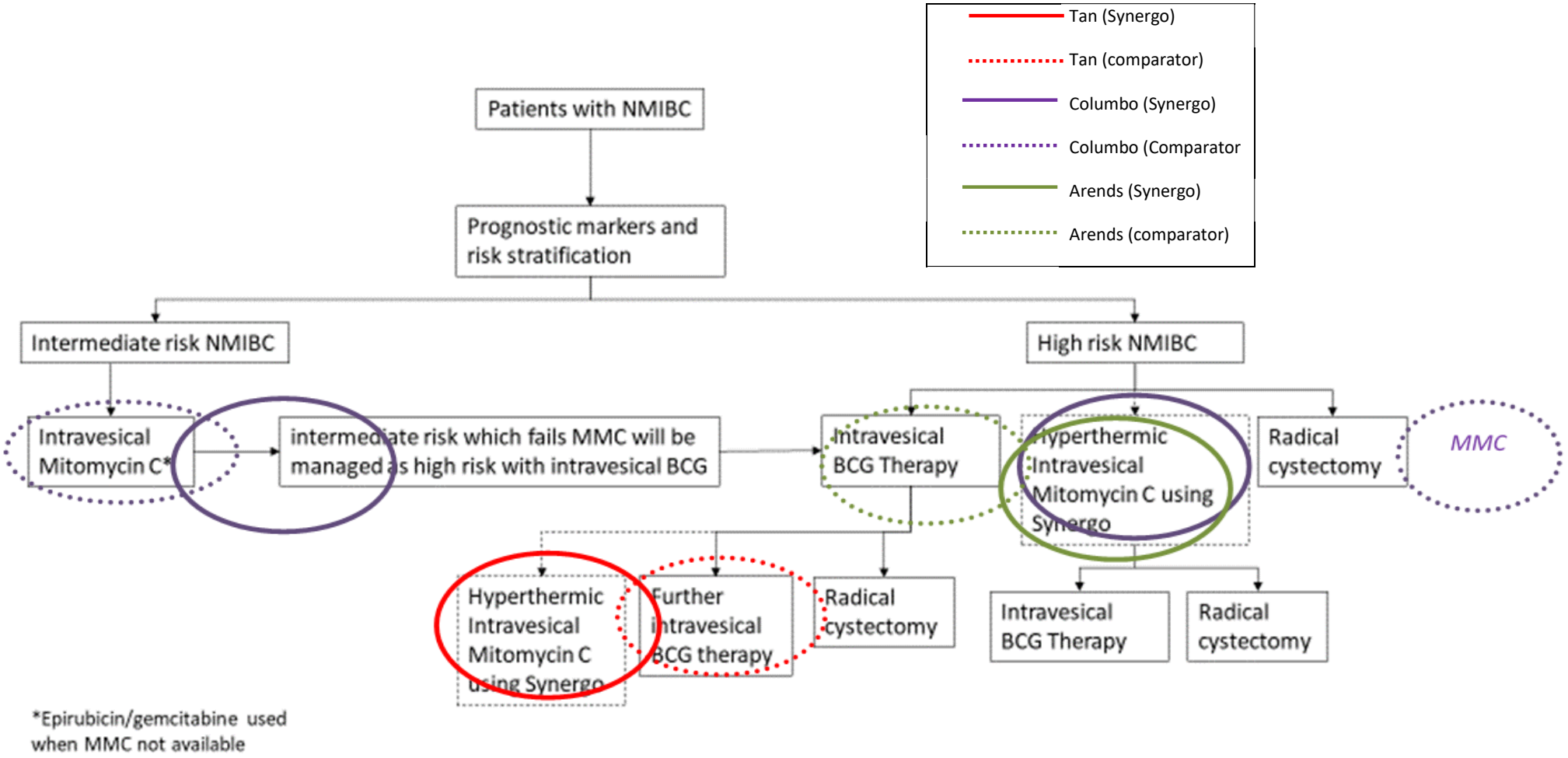
The following potentially relevant studies were identified but excluded from the main report as they do not use Synergo or in the case of one study using Synergo, no details of the study happening are reported.

Trial ID	Title	Recruitment Status	Target size	Intervention	Condition	Primary outcome
NCT00491296	Changes in Prostate Specific Antigen Levels During Synergo Therapy-Intravesical Chemotherapy Instillations Combined With Hyperthermia	Unknown Based on dates reported, this study never started	25	Synergo	Bladder cancer	Not reported
NCT03694535	Intravesical Thermochemotherapy With Mitomycin-c	Completed	44	Elmedical	High risk NMIBC	• Recurrence • Progression rate • Side effects
eudract_number:2015-005151-27	Randomised prospective clinical trial to evaluate the rate of early recurrence in bladder cancer in non-muscle invasive between the chemohyperthermia (QH) with mitomycin-C prior to transurethral resection of bladder in ambulatory surgery program and post resection treatment with mitomycin C in normothermia.	Not reported	Not reported	Not reported	Bladder cancer	• Tumour recurrence post urethral resection • Adverse events • Predictive factors for treatment response and hospitalization • Quality of life and sexual health
eudract_number:2016-001186-85	HIVEC HR: USE OF CHEMOHYPERTHERMIA WITH INTRAVESICAL MITOMYCIN (HIVEC) FOR THE TREATMENT OF PATIENTS WITH NMIBC AND HIGH RISK (HR)	Not reported	Not reported	Not reported	High risk NMIBC	• Disease free survival 4 months follow up of TURBT followed by HIVEC compared with TURBT followed by standard BCG therapy • Time to progression of HIVEC vs.. BCG • 2. Cancer specific survival of HIVEC vs. BCG • 3. Adverse Events of HIVEC vs. BCG • 4. QoL of HIVEC vs.. BCG
Trial NL5636 (NTR5751)	A Phase III randomised trial of intravesical chemotherapy vs.. chemohyperthermia in intermediate risk non-muscle invasive bladder cancer	Not reported	Not reported	Not reported	Intermediate risk NMIBC	• Recurrence rate • Tumour progression • Acute toxicity • Functional bladder capacity • Quality of life

2013-002628-18	HIVEC (Hyperthermic IntraVEsical Chemotherapy) FOR PATIENTS WITH INTERMEDIATE RISK NMIBC COMPARED WITH STANDARD INTRAVESICAL INSTILLATION OF CHEMOTHERAPY AS ADYUVANT TREATMENT. A COMPARATIVE, PROSPECTIVE, RANDOMISED STUDY.	Not reported	Not reported	Combat	Intermediate risk NMIBC	• Disease free survival • Recurrence Rate • Time to Progression • Safety
2014-005001-20	CHEMO-RESECTION WITH HYPERTHERMIC INTRAVESICAL INSTILLATION (HIVEC-R) VS. STANDARD TREATMENT IN PATIENTS WITH NMIBT: COMPARATIVE, PROSPECTIVE AND RANDOMISED STUDY OF EFFICACY AND TOLERABILITY	Not reported	Not reported	Combat	NMIBC	• Disease free survival • Response rate • Tolerability • Quality of Life • Cost Effectiveness
ISRCTN23639415	A Phase II, Open Label, Multicenter Randomised Controlled Trial Comparing Hyperthermia Plus Mitomycin To Mitomycin Alone, In Patients with Intermediate Risk Non-Muscle Invasive Bladder Cancer	No longer recruiting	Not reported	Combat	Intermediate risk NMIBC	• Disease free survival
NCT02471547	Intravesically Heated Thermo-chemotherapy With Mitomycin-C Prior to TURBT	Unknown	300	Elmedical	Bladder cancer	• Recurrence rates
CTRI/2020/03/024351	Comparative study of intravesical bacille calmette guerin vs. hyperthermic intravesical chemotherapy (HIVEC)with mitomycin-c in superficial urinary bladder carcinoma following TURBT	Not yet recruiting	90	Not reported	NMIBC	• Adverse Events • Recurrence

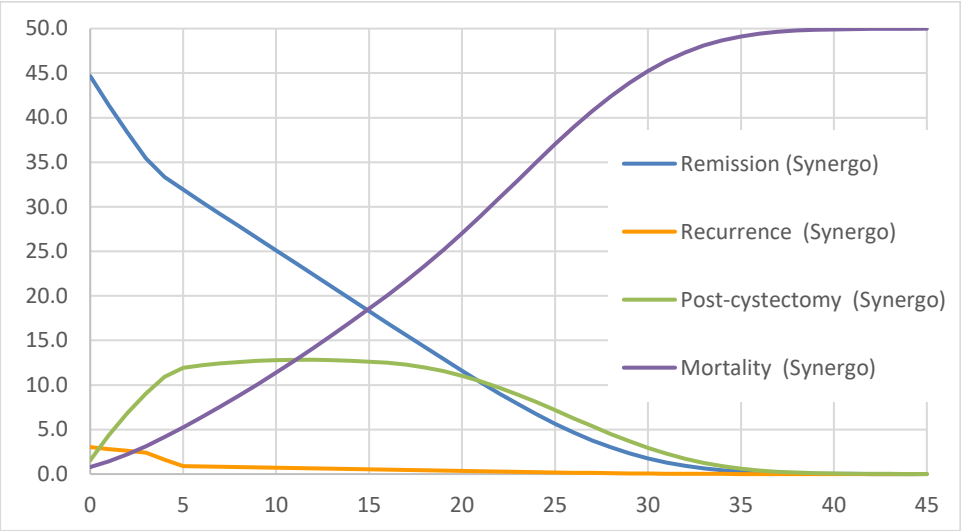
Appendix E Patient pathway for economic model

The available studies with comparative clinical evidence to populate the model do not fit exactly into the NHS pathway described by experts. The diagram below attempts to show their approximate position, but should be considered with the text in the assessment report, as the actual situation is more nuanaced.

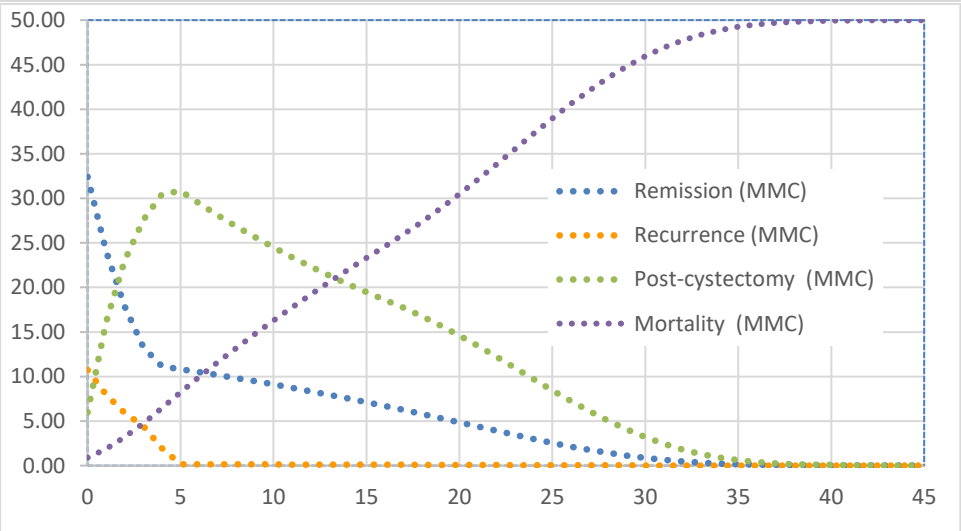


Appendix F Markov state diagrams

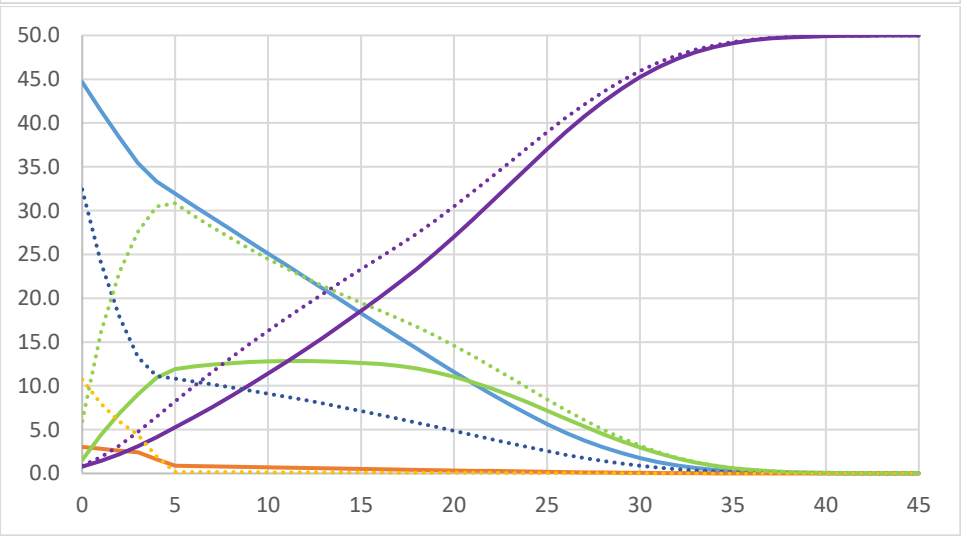
Submitted model for Synergo vs. MMC, Columbo 2011. Including half cycle correction



Synergo arm of model

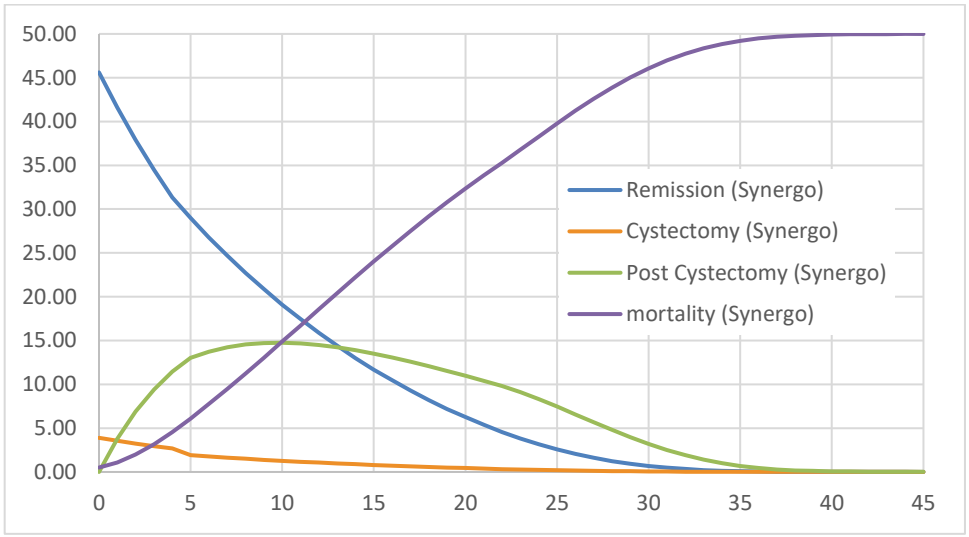


Comparator arm of model

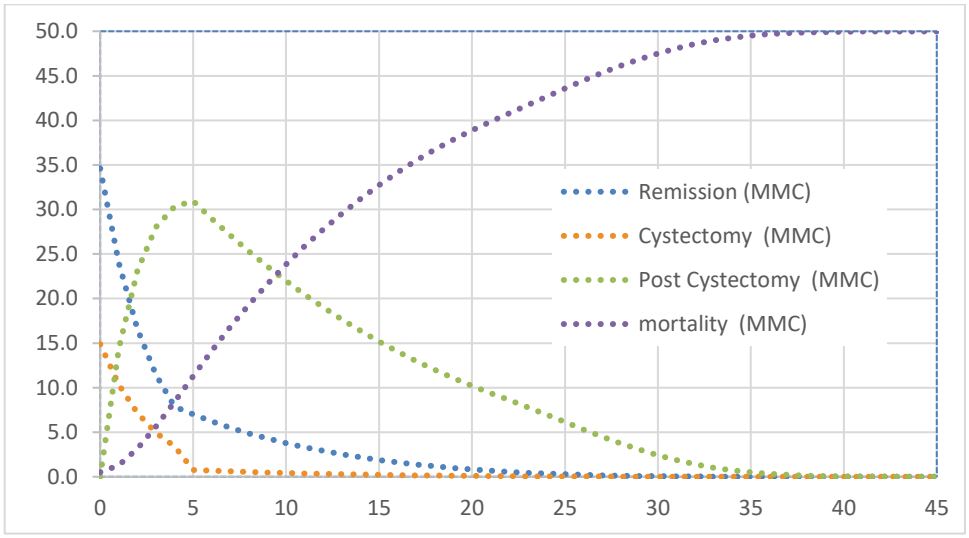


Both arms of model

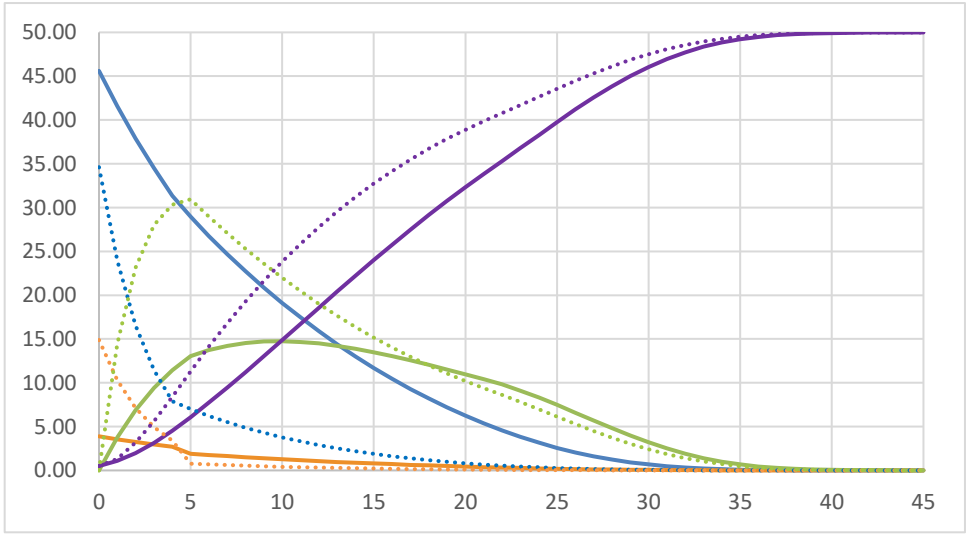
EAC base case for Synergo vs. MMC, Columbo 2011. Including half cycle correction



Synergo arm of model

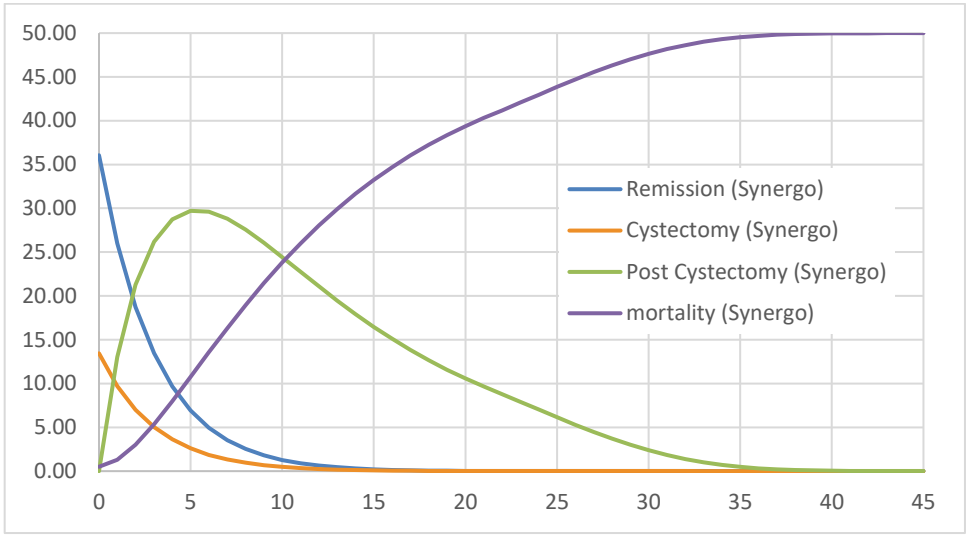


Comparator arm of model

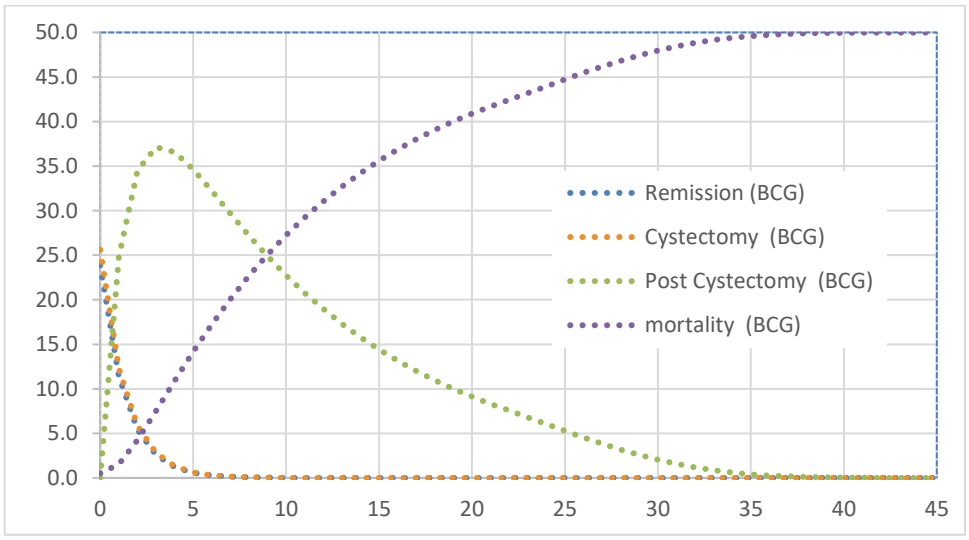


Both arms of model

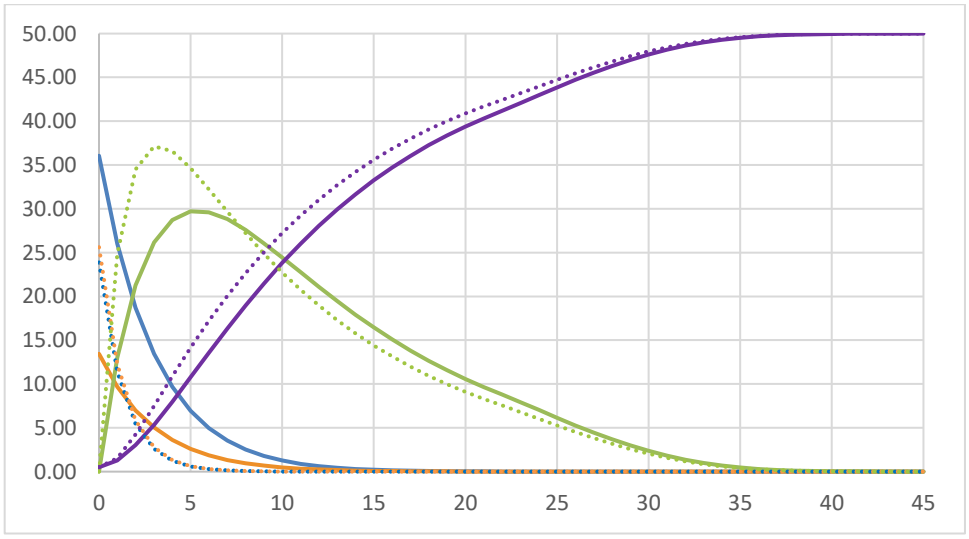
EAC base case for Synergo vs. BCG 2nd line treatment, Tan 2019. Including half cycle correction



Synergo arm of model



Comparator arm of model



Both arms of model

1.

Appendix G Stress testing submitted model

Stress testing: Columbo 2011, submitted model				
Scenario	**Cost of synergo**	**Cost of Comparator**	**Cost difference**	**Notes**
Base case	£36,541	£41,007	-£4,466	This is the life time horizon
The number of patients equal to1.	£36,541	£41,007	-£4,466	0 patients results in an error, 1 patient
The number of patients equal to 1000.	£36,541	£41,007	-£4,466	
Cost of Synergo device = 0	£36,229	£41,007	-£4,778	Very small impact, most of device cost is in the consumables
Cost of Synergo device and consumables= 0	£30,620	£41,007	-£10,387	Has a greater impact, there is still a cost for adverse events and for additional waiting time
Cost of Synergo device, consumables, adverse event and wait time= 0	£29,825	£41,007	-£11,181	Limitation on cost saving, as over a lifetime most of the costs are not derived from the direct treatment, but from impact of other treatments and costs. 5 year cost saving has risen to £8,269 at this point, but still £12,187 associated with synergo. At this [point chemo costs are same for each, but it is cystectomy, reintervention and stoma that are driving changes.
Total synergo cost = 0 plus MMC cost =0	£28,280	£39,608	-£11,328	MMC cost is zero, but appointment costs still required. The MMC and treatment costs are the same for each branch, so changing costs changes both.
Cystectomy = £0	£31,683	£33,212	-£1,529	Has a big impact on the cost saving, and is cost incurring at 5 years. Less impact on the overall cost of either strategy.
Starting age=20 – did not work, so do age=50	£38,875	£42,811	-£3,936	Expect to see reduced mortality, and reduced cost due to mortality (mortality table only runs from 50
Starting age = 90	£26,883	£27,723	-£840	Less time to accumulate costs or savings
Cost of palliative care = 0	£28,674	£32,574	-£3,901	Reduced cost saving and reduced costs, less people die in the Synergo arm
Survival risk same for both arms (set to synergo values)	£36,541	£29,825	£6,715	Cost incurring, as there are the costs of synergo, without clinical benefits.
Stoma care =£0 (for year 1 and after)	£26,731	£22,181	£4,551	Costs reduced, and cost incurring as there are fewer longer term costs incurred. Biggest costs are recurrence for MMC and remission for Synergo

Appendix H: EAC Changes to the Model

Worksheet	Cell	Description	Incremental change
Mortality	K34	changed to be take 1-J34, so calculating mortality not survival	-£2,660
LT Markov (Synergo)		Include costs for Synergo in all first cycle population plus cost for Cystectomy	
	AC16	change cylce 0 post-cystectomy to include costs for synergo and cystectomy - for non adjusted costs, makes no difference as 0 people in state, but if half-cycle correction puts people in this state for cycle 0 then they never accumulate costs of synergo or cystectomy	-£2,660
	AH16	Include costs for Synergo in all first cycle post cystectomy population plus cost for Cystectomy	-£1,812
	AI16	include Synergo costs in Dead state, cycle 0	-£1,629
LTMarkov (MMC)		Include costs for MMC in all first cycle population plus cost for Cystectomy	
	AC16	change cylce 0 post-cystectomy to include costs for MMC and cystectomy - for non adjusted costs, makes no difference as 0 people in state, but if half-cycle correction puts people in this state for cycle 0 then they never accumulate costs of MMC or cystectomy	-£1,629
	AH16	Include costs for MMC in all first cycle post cystectomy population plus cost for Cystectomy	-£4,113
	AI16	include MMC costs in Dead state, cycle 0	-£4,194
LT Markov (Synergo)	Q13:T13	Add in values for start of cycle 0 (all in remission)	
	Q16:T16	change to be mean of row 13 and row 16	
	Q17:T61	change to be mean of same row and row above (instead of below)	-£4,731
LT Markov (MMC)	Q13:T13	Add in values for start of cycle 0 (all in remission)	
	Q16:T16	change to be mean of row 13 and row 16	
	Q17:T61	change to be mean of same row and row above (instead of below)	-£3,964
		Update all costs to be consistent at 2020/21	
EAC inflation		EAC inflation spreadsheet was created using PSSRU indices to show inflation more transparently. Cost cells are linked through to this sheet so that the source data is clearly visible. All changes are only small (some were inflated to 2021/22)	
Costs	E23	day case (1st) changed from £411 to £402 plus linked	
	E24	day case (subsequent) changed from £238 to £233 plus linked	
	E63	cystectomy changed from 12538 to 12267 plus linked	
	E64	reintervention changed from 29601 to 2834	-£3,866
	D79:G93	EAC added component costs and rates of adverse events for greater transparency. Also linked through to inflation as needed, but not change in total calculated value	
	E34	adverse events linked to EAC calcs	
	E127:128	adverse events linked to EAC calcs	-£3,866
	G77	palliatve care costs - changed to £14244	
	E67	updated from to 2244 to 2198 and linked	-£3,857

	E64	error corrected in reintervention inflation changed to 2897	-£3,863
	E138	calculation added and inflation corrected 35.80 changed to 35.02	-£3,743
	E134	inflation corrected, changed from 48.74 to 47.69	-£3,740
	E136	value unchanged, linked to inflation sheet	
	E137	changed to calculate 4 x E134 (this also changes inflation update)	-£3,738
	E35	inflation corrected changed from 61 to 59.28 (but more changes may be required)	
Clinical	G33	Change from E24-E28 to (E24-E28)/E24 this gives appropriate graph, otherwise assumes starts from 1	-£4,055
		Graphs added to show clinical data and state populations, no change to actual model	-£4,055
Costs	J76	changed from £267 to £261	-£4,080
Clinical	F33:F44	change calculation to have denominator of 4 (not 5) as it is a 4 year period	-£2,953
	G33:G34	change calculation to take difference from year 4 to 9, not year 5 to 9 - previously missing the change between year 4 and 5	
Costs	E71	linked to telephone costs correctly inflated (instead of £36)	-£2,951
	E67	linked to EAC stoma costs of £2,244 (also changes E71)	-£3,347
Costs	F34:G35	Add wait time and cost separately to show calculation more clearly	
	G34:35	Make 70 min wait time and change to band 7 time from PSSRU	
	E35	link to G34 and G35 (change from £59.28 to £71.55	-£3,199
Costs	F76	changed to reference cell J76 not I76, as cytoscopy is only annual after 4 years	-£3,512
	I76	11 visits over 5 years, not 13 (see assessment report)	-£3,549
Change to incorporate Tan clinical data, and reflect an alternative part of the pathway			
Tan source data sheet		Additional sheet	
Clinical	E20:F28	deleted	
	E21:F21	set to Synergo - 53.5, BCG = 23.8 (values from Tan source data sheet)	
	E33:E34	changed to take difference from year 0 to 2	
	F33:F34	changed to calculate annual probability over 2 years	
	H33:H34	changed to be equal to F33:34 as no data longer than 2 years	£4,677
	graph	clinical graph and additional EAC columns to populate it were removed	
Tan source data sheet		graph added to show DFS over years, and EAC extrapolation added to graph	
Costs	E23	row added with cost for one dose of BCG (£71.61) BNF2021	
	F41:G42	new number of cycles, including cycles in year 2	£6,185
	G44:G46	link to BCG cost (E23) rather than MMC cost (E22)	
	F48:G49	add calculations to make live - cycles x subsequent admin costs	£7,009
Long term Markov (Synergo)	AF17:AF18	change remission for year 1 and 2 to include maintenance costs (Cost F57:58)	

Long term Markov (MMC)	AF17:AF18	change remission for year 1 and 2 to include maintenance costs (Cost G57:58)	£8,630
costs	F48:G49	Correction to take correct cycle row	£7,619
Costs	E35	Adverse events for Synergo =0 (same for both arms)	£7,501
Costs	F48	Include additional time in year 1 calculation	
	F51	Add consumables and adverse events to Synergo year 1	£9,858

Cedar

Healthcare Technology Research Centre

GID- MT553 Synergo for non-muscle-invasive bladder cancer

Addendum: additional health economic information

Authors: Megan Dale
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Date: 18th May 2021

Version: V1.0

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Contents

1 EQ-5D-5L values for QALY calculations

In the assessment report the EAC queried the validity of the calculated QALYs, due to the uncertainty about the source of EQ-5D-3L values used by the company. The EAC have contacted the author of the paper cited (Cox 2020), who responded that EQ-5D-3L measures were used as part of the questionnaire for collection of EORTC data during the BOXIT trial (Kelly 2019) , using a paper form sent to participants at baseline, and at 8 weeks, 12 weeks, 6 months, 12 months, 24 months and 36 months post baseline.

Although the use of EQ-5D-3L was not reported in the main BOXIT trial, the EAC accept this explanation and the subsequent use of QALY values in the company submission.

Cox et al. report a mean health state value of 0.846 for patients with no event, 0.763 for patients with a grade 3 recurrence and 0.747 for patients with MIBC progression (62 % of which had a radical cystectomy). From the graph of EQ-5D-3L scores over time, for the 29 patients who experienced MIBC progression at some point during the trial, the mean health state value varies from approximately 0.82 at baseline, to 0.6 at 24 months, and back to 0.7 at 36 months.

The company submission uses health state values of 0.85 for the remission state based on Cox (2020), and 0.65 for post-cystectomy based on a decrement of 0.2 from Mason (2018), which was accepted by the EAC.

2 Sensitivity analysis of existing models to number of treatments

The number of treatments was not included as a separate item in the one-way sensitivity analysis. Therefore, the EAC investigated the impact by re-running each model with 12 and 21 treatments for Synergo (with and without a similar change in the comparator).

With 21 treatments for Synergo, spread over 2 years (14 in year 1, 7 in year 2) and no change in MMC, the EAC scenario for Synergo vs MMC changes from £3,549 cost saving to £3,858 cost incurring per patient at a life time horizon. If MMC is also changed to 21 treatments, then the incremental cost incurred by using Synergo is reduced to £1,665 per patient at a life time horizon.

With 12 treatments for Synergo and no change in BCG, the EAC scenario for Synergo vs BCG (non CIS) changes from £9,858 to £5,957 cost incurring per patient at a life time horizon. If BCG is also

changed to only 12 treatments, then the incremental cost incurred by using Synergo is £6,891 per patient at a life time horizon.

The EAC consider this as an additional sensitivity analysis only. We have accepted the company's interpretation of the Colombo trial as requiring 12 treatments in the first year, and none in subsequent years. There is however variation in reported Synergo regimens, and this additional analysis shows the model to be more sensitive to a plausible variation in numbers of treatment than is apparent from the submitted one-way sensitivity analysis that takes the cost of Synergo as a whole cost and varies it by 20%.

3 Comparison of Synergo vs RC for patients with high-risk NMIBC, 2nd line treatment, no CIS

Discussions with some experts have led to an additional scenario being modelled. It has been suggested that BCG is less likely to be used as a second line treatment for high risk NMIBC currently than when the study reported in Tan (2019) was carried out. The EAC have modelled this in a relatively simple and exploratory analysis by using the model based on Tan (2019) in which patients have high risk NMIBC with no CIS. In the comparator arm, the costs for BCG are removed and the Markov modelling altered to assume that all patients start the model in the cystectomy state. They then progress in the next cycle to post-cystectomy and remain in that cycle until death. All other model assumptions, including the assumption that 100% of patients will take up radical cystectomy, are unaltered. There is half life correction applied to mortality, however all patients receive cystectomy in the first cycle and then all patients who are alive move to the post-cystectomy state in the second cycle without half life cycle correction for this movement.

Table 1: Results for additional modelling of Synergo vs RC (high risk NMIBC, 2nd line treatment, no CIS)

Costs (per patient)	Synergo	RC	Cost Saving
Remission	£16,438	£0	-£16,438
Recurrence	£15,650	£15,890	£240
Post-cystectomy	£15,989	£19,372	£3,383
Dead (palliative care)	£9,364	£10,000	£636
Total	£57,442	£45,262	-£12,180
Radical Cystectomies	0.96	1	0.04
Life years	9.44	8.13	1.32
QALYS	6.54	5.28	1.26

In this model the Synergo arm is unchanged (from Synergo vs BCG (no CIS)). In the comparator arm it can be seen that there are no costs for remission (prior to cystectomy). The Recurrence/Cystectomy costs are all incurred in the first cycle, as all patients start the model with this procedure. Post cystectomy, all patients incur annual stoma costs, but have a slightly higher mortality rate than patients in the Synergo arm who are in remission. Therefore, fewer costs are accumulated over the model time horizon.

Although the incremental cost incurred has increased in this scenario, there is also an increase in the gain of life years (and possibly QALYs). The majority of patients in both arms will experience radical cystectomy, however those in the Synergo arm may delay it somewhat, with a small proportion (4%) avoiding cystectomy altogether.

4 Consideration of economic impact for less than 100% take up of RC for patients with recurrence, in all models.

An assumption in the submitted company model is that all patients who experience recurrence after the initial modelled treatment will be offered, and accept radical cystectomy. Discussions with experts suggested that not all patients are suitable or willing to have radical cystectomy, even if no other treatments are possible.

To explore this scenario the EAC have carried out additional sensitivity analysis to understand the potential impact. The changes made to the model are:

- Create an additional variable that allows the uptake of radical cystectomy to be varied.
- Create an additional variable that allows a separate mortality risk if there is no radical cystectomy following recurrence.
- The cost of the radical cystectomy procedure (and re-treatment for a percentage of procedures) is applied only to the proportion of the patients that proceed with radical cystectomy. Other costs in that state remain unchanged.
- Mortality for the post-cystectomy group is changed to apply different risks to the proportion of the group who have or do not have radical cystectomy. These are added to give an overall risk which is applied to the whole group.

This is an exploratory investigation and limited by:

- The EAC have not systematically searched for, or identified data for the mortality risk if radical cystectomy is not suitable, or accepted, when it would otherwise have been clinically appropriate
- The EAC have not systematically searched for, or identified data for the uptake of radical cystectomy (either not suitable, or unacceptable), when it would otherwise have been clinically appropriate
- An additional state has not been added into the model for patients who do not have radical cystectomy following recurrence

- The annual costs for years following recurrence (£2,427) are assumed to be the same for both those patients who have RC (and have stoma costs) and those patients who do not proceed with RC (as they are presumed to need some level of additional care).
- Mortality is unaltered in the recurrence / cystectomy state (only changed in the post-cystectomy group).

This analysis does not change the base case of either model, but gives a two-way sensitivity table that demonstrates the direction of impact if these variables are changed. For both models it can be seen that if there is a reduced uptake of radical cystectomy, any cost savings are decreased (or costs incurred increased). As the estimated mortality risk for patients who do not proceed with radical cystectomy increases, the direction of impact is similar.

It is important to note that in this scenario, although the model becomes less cost saving (or more cost incurring), this is due to an increased mortality of the patients within the model. There is an increase in life years and QALYs due to Synergo as mortality risk for patients who do not proceed with radical cystectomy increases, and as the uptake of radical cystectomy decreases (unless mortality risk is assumed to remain constant).

Table 2 Additional sensitivity analysis for Synergo vs MMC

Annual mortality risk for patients with recurrence who do not proceed with radical cystectomy :	Percentage of patients with recurrence who proceed with radical cystectomy						
	40%	**50%**	**60%**	**70%**	**80%**	**90%**	**100%**
9%	£1,229	£1,616	£2,002	£2,389	£2,776	£3,162	£3,549
10%	£971	£1,399	£1,827	£2,257	£2,687	£3,117	£3,549
20%	-£469	£112	£721	£1,363	£2,043	£2,769	£3,549
30%	-£1,203	-£605	£40	£748	£1,545	£2,464	£3,549
40%	-£1,641	-£1,053	-£411	£311	£1,155	£2,195	£3,549
50%	-£1,934	-£1,359	-£730	-£14	£844	£1,957	£3,549
60%	-£2,144	-£1,584	-£968	-£265	£591	£1,748	£3,549

Table 3 Additional sensitivity analysis for Synergo vs BCG (Tan, 2019, patients with no CIS)

Annual mortality risk for patients with recurrence who do not proceed with radical cystectomy	Percentage of patients with recurrence who proceed with radical cystectomy						
	40.0%	**50.0%**	**60.0%**	**70.0%**	**80.0%**	**90.0%**	**100.0%**
8.8%	-£9,901	-£9,894	-£9,887	-£9,879	-£9,872	-£9,865	-£9,858
10.0%	-£9,972	-£9,954	-£9,935	-£9,916	-£9,897	-£9,878	-£9,858
20.0%	-£10,340	-£10,286	-£10,224	-£10,153	-£10,071	-£9,973	-£9,858
30.0%	-£10,513	-£10,456	-£10,388	-£10,305	-£10,197	-£10,055	-£9,858
40.0%	-£10,615	-£10,561	-£10,494	-£10,408	-£10,293	-£10,124	-£9,858
50.0%	-£10,684	-£10,633	-£10,569	-£10,484	-£10,367	-£10,184	-£9,858
60.0%	-£10,734	-£10,686	-£10,625	-£10,543	-£10,426	-£10,236	-£9,858

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Synergo for non-muscle-invasive bladder cancer

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem from scope

1 The technology

Synergo treats non-muscle-invasive bladder cancer (NMIBC) using radiofrequency-induced thermo-chemotherapeutic effect (RITE). Device assisted chemotherapy with Synergo is designed to improve the delivery and efficacy of chemotherapy with the aim of reducing tumour recurrence and disease progression. It offers an additional treatment option for NMIBC in addition to BCG therapy and radical cystectomy. It delivers controlled radiofrequency radiation (non-ionising microwave radiation), which heats the superficial layers of the bladder wall, and simultaneously flushes the bladder with a chemotherapy drug (thermochemotherapy). The drug solution is continuously pumped out of the bladder, cooled, and recirculated to prevent overheating. A miniature antenna in the catheter emits radiofrequency radiation directed at the bladder wall tissue, at a depth which does not generate heat on the external surface of the bladder avoiding injuries to surrounding organs.

The technology is an intravesical irrigation system combined with an energy delivering unit. The system has a radiofrequency generator that delivers radiofrequency energy at 915 MHz (the lower limit of microwave electromagnetism). It also includes a drug circulating unit and a microprocessor with application-specific software. The user interface consists of a computer, monitor with touch screen, and barcode reader. The software monitors and records treatment parameters in real time during the treatment session. Synergo is CE marked as a Class IIb medical device.

2 Proposed use of the technology

2.1 Disease or condition

Non-muscle-invasive bladder cancer (NMIBC) is a type of cancer in which the cancerous cells are contained within the most superficial layer of the bladder wall (uroepithelium) and do not involve the underlying muscle layer. NMIBC is classified as stage Ta when the tumour is confined to the uroepithelium. It is classified as stage T1 when there is spread into the connective tissue layer

between the urothelium and the muscle wall. It is also graded on the characteristics of the tumour from G1 (or papillary urothelial neoplasm of low malignant potential [PUNLMP]; least aggressive and slow growing) to G3 (or high grade papillary urothelial carcinoma; most aggressive and fast growing). Carcinoma in situ is a nonpapillary (flat) form of tumour consisting of early, high-grade cancer cells confined to the superficial layer of the bladder wall.

2.2 Patient group

Synergo is intended for use in people with intermediate- or high-risk non-muscle-invasive bladder cancer whose disease has not responded to intravesical BCG therapy, or in whom intravesical BCG therapy is not available, intolerable or cannot be delivered safely.

2.3 Current management

People with suspected bladder cancer are usually offered a transurethral resection of bladder tumour (TURBT). This procedure is intended to remove all visible papillary tumours, where feasible, and obtain a sample for biopsy. The outcome of TURBT is used to stratify cancers according to risk (low-, intermediate- or high-risk), based on the size and number of tumours detected and the histological stage and grade of the cancer. Treatment for people with a confirmed diagnosis of NMIBC is guided by this risk classification. In patients with low-risk non-muscle-invasive bladder cancer, TURBT alone may be sufficient. In patients with intermediate- or high-risk cancers, additional treatment is usually offered:

- Intermediate-risk cancer: intravesical chemotherapy (usually mitomycin C). People in whom their disease has not responded to intravesical chemotherapy may be considered for intravesical BCG therapy and treated as if high-risk cancer.
- High-risk cancer: a choice of intravesical BCG or radical cystectomy (surgery to remove the whole bladder). People for whom their disease has not responded to the first line intravesical BCG therapy or in whom cannot tolerate BCG therapy may be considered for cystectomy. Further intravesical therapy may be considered in some of these people if radical

cystectomy is unsuitable or declined by the person or if the bladder cancer that recurs is intermediate- or low-risk.

The following publications have been identified as relevant to this care pathway:

- NICE Guideline [NG2]: Bladder Cancer: Diagnosis and Management
- Interventional Procedures Guidance [IPG628]: Intravesical microwave hyperthermia and chemotherapy for non-muscle invasive bladder cancer
- Interventional Procedures Guidance [IPG638]: Electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer
- European Association of Urology (EAU) Guidelines: Non-muscle-invasive Bladder Cancer

2.4 Proposed management with new technology

There are currently no NICE clinical guidelines verifying the position of device-assisted hyperthermic chemotherapy options like Synergo in the NHS clinical pathway for bladder cancer. Expert advice indicates that the technology is being used as an alternative to further intravesical therapy or cystectomy in people with high-risk NMIBC in whom:

- their disease has not responded to recent BCG therapy or recurs following treatment
- intravesical BCG therapy is declined, not available, intolerable or cannot be delivered safely (contraindicated)

People receiving Synergo therapy are typically treated as an outpatient in specialist centres. There is no need for general anaesthesia during treatment, but local anesthetic lubricating gel may be used to insert the treatment catheter. Synergo is administered by healthcare professionals such as bladder cancer nurse specialists or consultant urologists in secondary and tertiary care settings.

2.5 Company claimed benefits and the decision problem

Details of the company's claimed benefits and the decision problem are described in Appendix E.

The company did not propose any changes to the decision problem. The company noted however that that no robust evidence is available comparing Synergo with other device-assisted hyperthermic chemotherapy options. The company included limited evidence comparing Synergo with electromotive drug administration (EMDA). The EAC agreed with the company and made no changes to the decision problem.

3 The evidence

3.1 Summary of evidence of clinical benefit

In total, the company included 31 publications (24 studies) in their clinical submission. Of the 24 studies included, 19 were used to inform the clinical evidence base. This comprised of 16 published studies (3 comparative and 13 non-comparative) reported in 20 publications (17 full text publications and 3 abstracts). As well as 3 additional studies reported as abstracts only (6 abstracts in total). Five systematic reviews were also identified by the company but were not used to inform the clinical evidence base because the primary studies were used instead.

The EAC undertook their own literature search and identified a total of 19 studies (from 20 full publications). This comprised of the 16 studies submitted by the company, as well as 3 additional full text studies (see table 1 for details). The rationale for the selection of these studies is in section 4.1 and 4.2 of the EAC assessment report. The EAC's search also identified 14 studies reported across 19 abstracts and included the 3 abstract only studies submitted by the company. Studies reported as abstracts were not included in the EAC's evidence review but details of the studies can be found in Appendix B of the EAC assessment report.

Table 1 summary of included studies

Studies included by both EAC and company	
Publication and study design	16 studies reported across 17 full text publications: • 3 RCTs (Arends 2016; Colombo 2003 and Colombo 2011; Tan 2019) • 1 prospective comparative study (Colombo 2001) • 3 prospective non-comparative studies (Kiss 2015; Erturhan 2015; Maffezzini 2014) • 9 retrospective non-comparative studies (Arends 2014; Briummelhuis 2021; Gofrit 2004; Moskovitz 2005; Moskovitz 2012; Nativ 2009; van der Heijden 2004; van valenberg 2018; Witjes 2009)
Studies in company submission excluded by EAC	
Publication and study design	8 studies submitted by the company were excluded by the EAC: • 5 systematic reviews were excluded because the primary studies were included instead (Colombo 2016; Lammers 2011; Soria 2015; van valenberg 2016; Witjes 2019) • 3 prospective non-comparative studies presented as abstracts only (6 abstracts in total) were excluded due to the volume of evidence available and some uncertainties around potential overlap of study data (Ayres 2018 [also Ayres 2017, Ayres 2012 and Ayres 2010]; Kilb 2018; Luedecke 2015)
Studies not in company submission included by EAC	
Publication and study design	3 additional studies were included by the EAC: • 1 retrospective comparative study (Sri 2020) 2 retrospective non-comparative studies (Volpe 2012; Sooriakumaran 2016)

The EAC focussed on 5 comparative studies (3 RCTs, 1 prospective cohort study and 1 retrospective cohort study) in their clinical evidence review (see table 2 for details). The EAC judged 1 of the RCTs to have low risk of bias (Arends et al. 2016), while the other 2 trials had some concerns with bias from deviations from intended interventions and selection of the reported result (Colombo 2003 and 2011; Tan 2019). The other two comparative studies were included but were deemed to be of low methodical quality with a high risk of bias (Colombo 2001 and Sri 2020). See table 7 in section 5.2 of the EAC assessment report.

The full-text non-comparative studies were considered to be of low to medium methodological quality. This was due to several factors including retrospective analyses, small patient numbers, lack of comparators, limited outcomes reported, unclear reporting of risk classifications and in some cases, uncertainty around whether there is patient overlap between studies The EAC did not include data from abstracts in its main report due to volume of evidence and potential overlap of study data, but details of these are reported in Appendix B of the EAC assessment report. Neither the company nor the EAC did a meta-analysis.

The 3 pivotal RCTs have Synergo positioned differently in the clinical pathway. Two of the RCTs compared Synergo with BCG therapy in intermediate- and high-risk NMIBC patients (Arends et al. 2016 and Tan et al. 2019), while one (Colombo et al. 2003 and 2011) compared Synergo with MMC alone.

Tan et al. (2019) was a UK-based RCT and was judged by the EAC to best reflect the current use of the technology in the NHS; that is as an alternative 2nd line treatment option to further BCG therapy in people with intermediate- or high-risk NMIBC who experience disease recurrence following previous BCG therapy. The EAC noted however that the study had several issues which limits the quality and certainty of the results. Limitations specific to Tan et al. (2019) were that not all people in the comparator arm were treated with BCG. The comparator in the trial was BCG or 'institutional standard of care' meaning some people were treated with MMC alone or MMC-EMDA. There was also a higher number of people in the Synergo arm that had concurrent papillary and CIS tumours. Also, the trial did not report on the type of BCG failure prior to enrollment. There is no information on the proportion of people who were BCG refractory, resistant or intolerant in either arm of the study, although the numbers receiving less, or more than 6 instillations are reported.

Arends et al. (2016) was a non-UK trial which assessed the use of Synergo as a first-line treatment option for people with intermediate- or high-risk NMIBC.

The trial also included intermediate-risk patients who would not normally be offered BCG as a first-line treatment option.

Colombo et al. (2003 and 2011) was a non-UK based trial with 10-year follow-up data. It compared Synergo with intravesical MMC alone in people with primary or recurrent intermediate- and high-risk NMIBC. The EAC considered this trial to reflect the current use of Synergo within the NHS least accurately. This is because there are very few points in the proposed pathway where a clinical decision between Synergo and MMC would be made. The EAC noted however this clinical decision may be appropriate in situations where BCG or radical cystectomy are unavailable or unsuitable.

The main outcomes reported across the trials were rates of recurrence, disease progression and survival. Compared with BCG therapy, there was no difference in either recurrence free survival (Arends et al. 2016) or disease-free survival (Tan et al. 2019). When compared with MMC alone however, long-term results from Colombo et al. (2011) report that disease free survival was significantly better with Synergo ($p<0.004$) with no significant difference in overall survival ($p=0.558$).

The EAC noted several limitations that impact the quality, certainty and relevance of the available RCT evidence:

- All 3 trials terminated early. Colombo et al. (2003 and 2011) was stopped early due to significantly better efficacy with Synergo, while Tan et al. (2019) closed early due to a higher-than-expected CIS recurrence rate in the Synergo arm. Arends et al. (2016) stopped early due to slow recruitment.

- All trials offered an adjuvant regimen only (2x 20mg MMC) meaning that 68% of people in the Tan et al. (2019) trial and 22% in Arends et al. (2016) with CIS may have been untreated, and in practice would receive a higher ablative dose (2x 40mg MMC). Colombo et al. (2011) included only 1 patient with CIS so most people in this trial are likely to have been treated with an appropriate regimen. Whether the ablative

regimen using Synergo is more effective than other treatment options in people with CIS cannot be determined from the evidence currently available.

- All studies include people with both intermediate and high-risk NMIBC and in most cases the results were not reported separately. Currently, in the UK, Synergo is used to treat only high-risk NMIBC, therefore the extent to which results can be generalized to any specific risk group is uncertain.

The EAC also included 2 non-randomised comparative studies in their evidence review. One was a retrospective cohort study which included people who underwent radical cystectomy for high-risk NMIBC (Sri et al. 2020). It compared outcomes between people who underwent either primary cystectomy or cystectomy immediately after BGC failure (102 people) with those who underwent cystectomy for failed BCG followed by subsequent treatment with Synergo (36 people). The study reported no significant difference in the time to recurrence or mortality (all-cause and cancer specific) between the 2 groups. Results suggest that Synergo as a 2nd line treatment option does not compromise oncological outcome compared to people undergoing cystectomy who did not receive Synergo treatment. The study, however, included a limited number of people treated with Synergo and the EAC considered it to have a high risk of selection bias. The other comparative study included by the EAC was a prospective pilot feasibility study which had a small sample size and was mainly aimed at assessing feasibility and safety (Colombo et al. 2001).

See table 2 for full study details and outcomes of the comparative studies included in the EAC clinical evidence review.

Fourteen non-comparative studies reported on the use of Synergo. Only 2 were considered prospective studies (Erturhan 2015 and Kiss 2015) and 2 included UK centres (Sooriakumaran 2016; Van Valenburg 2018). There was a high level of heterogeneity in patient characteristics, treatment schedule and follow-up time among the single-arm studies. Median follow-up ranged from 6

months to 6 years. Recurrence was reported in 13 studies as recurrence-free survival, probability of recurrence or number of patients with a recurrence during follow-up. Recurrence rates varied depending on whether an ablative or adjuvant regimen was used, whether patients had received previous BCG treatments and whether patients had concomitant CIS (see table 10 of the EAC assessment report for a full summary of results). Complete response for ablative regimen ranged from 43% to 92% (reported in 9 studies). Disease progression ranged from 0% to 38% (reported as an outcome in 10 studies), bladder preservation rates ranged from 71% to 96% (reported in 5 studies).

Five studies (Brummelhuis 2021, Gofrit 2004, Moskovitz 2005, Moskovitz 2012, Volpe 2012) reported results separately for adjuvant and ablative regimens. Six studies (Brummelhuis 2021, Nativ 2009, Sooriakumaran 2016, van der Heijden 2004, van Valenberg 2018, Witjes 2009) reported outcomes separated by whether patients had previous BCG treatment or not and by reason for stopping BCG. Two studies (Arends 2014, Brummelhuis 2021) reported limited results by whether patients were treated using MMC or epirubicin.

Table 2 Summary of key comparative studies

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	EAC Comments
Arends et al. 2016 ***Design***: RCT ***Location***: 11 centres from 6 countries (Israel (3), Italy (3), the Netherlands (1), Austria (1), France (2), Belgium (1)) ***Setting***: Outpatients **Funding:** Medical Enterprises Europe BV provided	***Participants***: 190 patients with intermediate and high-risk NMIBC according to 2001 European Association of Urology risk category definitions	***Intervention***: RITE with MMC using Synergo system (n=92) *Adjuvant regimen* comprising 2x20mg MMC in 50ml distilled water, local hyperthermia 42±2C for 6 weekly sessions (induction) followed by 5 maintenance sessions at 6-week intervals in year 1. ***Comparator***: BCG Immunotherapy (n=98) *Regimen* BCG as a 1-year schedule, 6 weekly induction sessions and 3 weekly maintenance	***Primary*** • Recurrence free survival (RFS) in the intention to treat and per protocol analyses. ***Secondary*** • Proportion of complete response (CR) in CIS patients (defined as negative biopsy and/or cytology at 3 months) • Disease progression to higher than stage T1 and/or metastatic disease • Safety Follow-up: At least 24 months after randomization	24-month RFS (ITT): • Synergo: 78.1% (95% CI 65.2%-86.7%) • BCG: 64.8% (95% CI, 52.2%-74.9%) p=0.08 3-month complete response rate (CIS patients only): • Synergo: 89% • BCG: 85.7% p=1.00 No patient experienced progression to muscle invasive disease in the Synergo group compared with 1 patient in the BCG group.	• Study is underpowered due to early closure (slow recruitment) • Study population, comparator and outcomes are all applicable to decision problem although this study does not include UK patients. • Some consideration to whether patients classified as intermediate risk would be managed as high risk in the UK.

financial support		sessions at months 3, 6 and 12. BCG was retained in the bladder for 120 mins.			
Colombo 2001 ***Design:*** Pilot feasibility study (prospective non-randomised, comparative) ***Location:*** Italy ***Setting:*** Outpatients **Funding:** not reported	***Participants***: 80 patients with superficial transitional bladder cancer (Ta-T1, G1-G2, recurrent, single small [<2cm] bladder tumours previously untreated by MMC)	***Intervention:*** Device assisted MMC (hyperthermic or electromotive) *Hyperthermic Regimen* Synergo system with 40mg MMC in 50ml distilled water, local hyperthermia at a mean temp. of 42.5C for 4 weekly sessions, mean session duration was 60mins *Electromotive (EMDA) regimen* Intravesical MMC solution according to EMDA procedure with 40mg MMC in 150ml of distilled	Feasibility and tolerability of the different treatment approaches ***Follow-up*** Not reported	CR (complete response) MMC: 27.7% Synergo: 66% EMDA: 40%	• Unclear whether the study included high risk NMIBC or just intermediate risk • Safety and tolerability only, therefore results likely to have limited applicability • Not a UK based study and unclear how applicable the comparison between hyperthermic MMC and standard intravesical MMC is to the UK setting

		water and 20mA of electric intensity for 4 weekly sessions, 20min duration ***Comparator:*** Standard intravesical MMC *Regimen:* 40mg in 50ml saline for 4 weekly sessions			
Colombo 2003 Colombo 2011 ***Design:*** RCT ***Location:*** Italy, Israel ***Setting:*** Outpatients **Funding:** none declared	***Participants:*** 83 patients with primary/recurrent stage Ta and T1, grade G1 to G3 TCC of the bladder, treated by TURB.	***Intervention:*** RITE with MMC using Synergo system (n=42) *Adjuvant Regimen:* Synergo system with 2x20mg MMC in 50ml distilled water, local hyperthermia at a mean temp. of 42C±2C ***Comparator:*** Standard intravesical MMC (n=41)	Short-term (Colombo 2003) • Response to treatment • Side effects and clinical complications Long-term (Colombo 2011) • Disease free survival • Progression and radical cystectomy • Bladder preservation rate	Recurrence Short term results (2003) • Synergo: 17.1% (6/35) • MMC: 57.5% (23/40) p=0.0002 Long-term results (2011) *Per Protocol* • Synergo: 14/35 (40%) • MMC: 32/40 (80%) Disease progression Short-term results (2003)	• Not a UK based study and unclear how applicable the comparison between hyperthermic MMC and standard intravesical MMC is to the UK setting • Adjuvant regimen of hyperthermic MMC is used (Prophylactic) which is applicable to UK setting.

		Regimen 2x20mg MMC in 50ml distilled water Patients in both groups received 8 weekly, 60 min treatment sessions, followed by 4-monthly sessions.	• Death ***Follow-up*** 2 years	• 1 patient in the MMC group had recurrence at 3-month follow-up, developed metastasis and died. Long-term results (2011) Tumour progression requiring radical cystectomy (RC) at time of recurrence • Synergo: 2 patients • MMC: 3 patients • 4 additional patients had RC for recurrent high-risk NMIBC <u>Disease Free Survival</u> • DFS was significantly better with Synergo ($p<0.001$) <u>Overall Survival</u> • No significant difference in overall survival between the groups ($p=0.558$) <u>Organ Preservation</u> • Synergo: 86.1% • MMC: 78.9%	
Tan 2019	***Participants:*** 104 patients with recurrence of	***Intervention:*** RITE with MMC using Synergo system	Primary Outcomes	<u>RFS in the per-protocol population only</u> Synergo: 23%	• UK based study comparing hyperthermic MMC

Design: RCT ***Location:*** UK ***Setting:*** Outpatients **Funding:** Cancer Research Campaign Clinical Trials Centre **Funding:** Cancer Research Campaign Clinical Trials Centre. Medical enterprises B.V. supplied the Synergo system at a discounted rate for the study.	intermediate or high risk NMIBC according to European Association of Urology Guidelines following induction or maintenance BCG. randomised to RITE (n=48) or control (n=56)	*Adjuvant Regimen:* • Synergo system with 2x20mg MMC in 50ml sterile water, local hyperthermia at 42±2C for 6 weekly induction instillations • Dose reduction was not permitted • Maintenance treatment was one instillation every 6 weeks for 1st year and one every 8 weeks for 2nd year for patients who were disease free 3 months after treatment commencement. ***Comparator:*** BCG Immunotherapy ***or*** institutional standard	• Disease free survival time (DFS) • 3-month complete response for patients with biopsy proven carcinoma in-situ (CIS) at randomisation Secondary Outcomes • Progression free survival (PFS) time • Overall survival (OS) time • Disease-specific survival time • Recurrence free survival (RFS) time in non-CIS patients • Health related quality of life • Safety and tolerability ***Follow-up***	BCG: 40% p=0.98 <u>PFS in the per-protocol population only</u> Synergo: 83% BCG: 87% p=0.16 <u>24-month DFS (patients without DFS events)</u> Synergo: 35% BCG: 41% HR=1.33 (95% CI 0.84-2.10) p=0.23, adjusted p=0.49 <u>24-month DFS (with baseline CIS)</u> Synergo: 25% BCG: 50% HR=2.06, (95% CI 1.17-3.62) p=0.01 <u>24-month DFS (without baseline CIS)</u> Synergo: 53% BCG: 24% HR=0.50, (95% CI, 0.22-1.17)	with BCG immunotherapy which is likely to be applicable to the UK setting based on discussions with clinical experts • Comparator also included 'institutional standard of care' as an option, patients received either BCG (n=33), MMC alone (n=10) or MMC with EMDA (n=13) • No subgroup analyses are included for the different treatment types

		of care defined at randomisation *BCG Regimen:* 6 weekly instillations of BCG (50ml saline) followed by maintenance therapy of 3 consecutive weekly instillations at 3, 6, 12, 18 and 24 months	24 months	p=0.11 <u>3-month CR</u> Synergo: 30% BCG: 47%, OR=0.43, (95% CI 0.18-1.28, p=0.15)	
<u>Sri 2020</u> ***Design:*** Retrospective comparative case review ***Location:*** UK ***Setting:*** Not reported **Funding:** none reported	***Participants:*** 138 patients (36 treated with intervention, 102 not treated) who underwent radical cystectomy for high risk NMIBC as primary treatment or following treatment failure	***Intervention:*** RITE with MMC using Synergo system • Synergo system used (40mg MMC at 42C±2C • CIS patients received an 8 week induction cycle and no CIS patients received a 6 week induction cycle. • New referrals received a re-do TUR, urine cytology and	• Intra-operative difficulty • Operative time • Intraoperative blood loss • Length of stay • 90-day readmission ***Follow-up*** 24 months (median)	<u>Recurrence</u> • 20 patients (19.6%) developed locoregional recurrence or metastatic disease in the no MMC group • Mean time to recurrence was 24.6 months • 6 patients (16.7%) developed recurrence in the Synergo group • Mean time to recurrence was 37 months <u>Survival</u> No significant difference between groups for all-cause mortality	• Results have limited relevance as all patients in this cohort had a radical cystectomy as primary treatment or following treatment failure • The question of whether treatment with radiofrequency-induced chemohyperthermia has an impact on outcomes for patients who go on to radical cystectomy may

		upper tract imaging prior to induction. • Failure at induction would lead to a recommendation for radical cystectomy • All patients received maintenance instillation every 6 weeks for the first year followed by every 8 weeks for the second year ***Comparator:*** No RITE (primary cystectomy or cystectomy following BCG failure)		(p=0.069) or cancer specific mortality (p=0.129) <u>Organ Preservation</u> Synergo was not correlated with 90-day hospital readmission	have more relevance to the wider clinical pathway than for Synergo specifically

Conclusions on the clinical evidence

In conclusion, the EAC considered the clinical effectiveness of Synergo to be uncertain based on the available clinical evidence. Based on expert advice some of the limitations of the published evidence are not unexpected due to the small numbers of eligible patients, no clear comparators, and the learning curve associated with using Synergo and the need for specialist centres experienced in delivering treatment. Further expert advice around the feasibility of running RCTs in this population and setting highlighted a number of issues, including slow recruitment, geographical considerations and the need for people to travel as well as ethical considerations around the most appropriate comparator to include.

Overall, the EAC noted that the efficacy of Synergo may be dependent on several factors including stage/grade of tumour, presence/absence of CIS, previous treatments and reasons for using Synergo and MMC dose used. It noted however, that the procedure appears safe with most side effects limited to during treatment and resolving afterwards.

3.2 Summary of economic evidence

Neither the company nor the EAC identified any published economic studies relevant to the decision problem.

De novo analysis

The company submitted a Markov model with a one-month cycle and a life-time horizon. The model was based on an NHS and personal social services perspective with a 3.5% discount rate. It comprised of 4 health states: remission, recurrence (which is treated with radical cystectomy in all cases), post-cystectomy and death. See figure 3 of the EAC assessment report for a depiction of the company's Markov model structure.

The population modelled was a subset of the scope population. It included both people with intermediate- and high-risk NMIBC, in whom BCG is either unavailable or unsuitable. The model compared MMC delivered using

Synergo with use of MMC alone. BCG was not included in the model as a comparator or as part of the clinical pathway because the company considered comparative evidence between Synergo and BCG was not appropriate for use. The population age was 64 years.

The EAC identified several limitations in the submitted model relating to the current use of Synergo in the NHS. The use of Synergo as an alternative to MMC alone is not currently part of the clinical pathway as outlined by the clinical experts.

The company model made several assumptions which are discussed in section 9.2 of the assessment report. Overall, the EAC considered the assumptions were appropriate for the modelled scenario but noted that most were a product of the available clinical evidence and the resulting position in the clinical pathway. The EAC did not make any changes to the assumptions in the submitted model but noted the following considerations:

- The model assumes that all patients receiving radical cystectomy will have a urinary stoma. In practice, some people receiving radical cystectomy could have continent urinary diversion, although expert advice it that most people would have a urinary stoma.
- Model results are unlikely to be generalisable to people with CIS treated with an ablative regimen. This is because the modelled treatment was adjuvant, and the study population used to inform the clinical parameters included only one patient with carcinoma in situ (CIS).
- The model includes treatment over year 1. In clinical practice a full treatment plan may include reduced treatment cycles in year 2 and 3.

See table 13 of the EAC assessment report for a full list of model assumptions.

Model parameters

The main clinical parameters used in the company's model include the annual risk of recurrence, mortality, treatment after recurrence and adverse events. A full description of the parameters is outlined in section 10.2.3 of the EAC assessment report.

Clinical parameters for risk of recurrence and adverse events were sourced using data from Colombo et al (2011). Risk of recurrence was derived using the 10-year Kaplan Meier graph from the study. Values for reintervention following cystectomy as well as mortality risk with radical cystectomy (annual and 30-day risk) were sourced from Afshar (2018). Values for population wide mortality risk came from National life tables UK (ONS, 2017 to 19). The proportion of people receiving a stoma after cystectomy was assumed to be 100%. The EAC stated that this agreed with advice sought from experts which confirmed that most people who have a cystectomy will receive a stoma.

The EAC agreed with the data sources used for the clinical parameters but made the following changes to the values in the model:

- Risk of recurrence:
    - 0-4 years: EAC corrected calculation to take risk over 4 years, instead of 5 (values increased from 24.6% and 6.3% to 29.8% and 7.8% for MMC alone and Synergo, respectively)
    - 5-9 years: EAC amended to calculate difference in survival between 5 and 10 years as a percentage of those in cohort at 5 years (value increased from 1.4% and 9.7% to 2.7% and 6.1% for MMC alone and Synergo, respectively).

  These changes decrease cost saving.
- Annual mortality risk after radical cystectomy: EAC corrected calculation to ensure that the value used was for mortality rather than survival. This change resulted in a large decrease in cost savings.

The company reported QALYs in their economic submission but the EAC did not have confidence in the utility values used in the model, specifically those used for people with NMIBC in remission which were taken from Cox et al. (2020). Cox et al. (2020) stated that values were derived using the EQ-5D-3L tool administered as part of the BOXIT trial, reported in Kelly (2019). However, the EAC were unable to find any information to suggest that EQ-5D-3L was used as part of the BOXIT trial in either Kelly (2019) or the trial registration site, although Cox et al (2020) provides methods and analysis of the utility scores.

Costs and resource use

The cost and resource use parameters included in the company model include: the cost of intravesical MMC and costs associated with the administering treatment (both arms); additional costs associated with the use of Synergo, including device costs (annual lease, training and consumables), costs of adverse events and additional time needed to administer treatment; costs associated with radical cystectomy, including the cost of stoma care; cost of follow-up in recurrence free patients; cost of palliative care.

The full base case cost values and sources are shown in table 15 of the EAC assessment report, and a summary of procedure specific costs is shown in figure 16. The EAC made the following changes:

- Inflation: where applied the EAC corrected errors for inflation, standardising to 2020/21 costs. This change had a small impact on cost savings.

- Annual stoma costs: the EAC calculated costs of products from NHS supply chain instead of using the annual UK cost per patient reported by the East of England NHS Collaborative Hub (2019). This change increased cost saving.

- Additional time for administering Synergo: the EAC increased additional time from 30 to 70 minutes and changed the source of information to PSSRU 2020. This change decreased cost saving.

- Annual follow-up costs: the EAC decreased the number of follow up visits over the first 5 years from 13 to 11 for high-risk patients based on based on NICE guidance NG2 (see table 16 of the EAC assessment report).

- Palliative care: EAC used an outpatient palliative care code (non-medical specialist palliative care; £101) from NHS reference costs (2018/19), inflated to 2020/21.

See table 17 of the EAC assessment report for full details of the cost and resource use parameters used in the company and EAC base case model.

Results

Both the company and the EAC estimate cost savings from the use of Synergo in people with intermediate- and high-risk NMIBC in whom BCG is either unavailable or unsuitable. The company and EAC base case results are presented in table 5 below.

Table 5 company and EAC base case results over a lifetime horizon (Synergo versus MMC alone; Colombo et al. 2011)

	Company Results			EAC Results		
Per patient results	**Technology**	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Remission	£12,762	£4,095	**-£8,667**	£12,885	£4,754	**-£8,132**
Recurrence	£6,972	£11,049	**£4,077**	£9,347	£14,212	**£4,865**
Post-cystectomy	£8,940	£17,431	**£8,491**	£9,776	£15,611	**£5,835**
Dead (palliative care)	£7,867	£8,432	**£565**	£8,327	£9,307	**£981**
Total	£36,541	£41,007	**£4,466**	£40,335	£43,884	**£3,549**
Total radical cystectomies	0.49	0.67	0.18	0.711	0.9322	0.22
Total life years	12.93	11.77	1.16	11.62	9.47	2.15
Total QALYS	10.16	8.41	**1.75**	8.95	6.60	**2.35**

Sensitivity analysis

The company's one-way deterministic sensitivity analysis (DSA), which varied each base case parameter by ± 20%, found the key drivers of the model to be the cost of Synergo, the risk of recurrence and the cost of stoma management.

After the EAC changes to the model, the key drivers were found to be the cost of Synergo, followed by the risk of recurrence, stoma management and cost of cystectomy. Results of the EAC's one-way deterministic sensitivity analysis (DSA) are shown in figure 8 of the EAC assessment report.

Additional economic modelling done by the EAC

The EAC presented an additional model that was felt to better reflect the current NHS use of the technology. In this additional analysis, Synergo was modelled as an alternative 2nd line treatment option to further BCG therapy in people with intermediate- or high-risk NMIBC who experience disease recurrence following previous intravesical therapy. The EAC amended the base case model, using Tan et al. (2019).

The EAC used results from the subgroup analysis of patients without CIS from Tan et al. (2019) (n=33). This is because these patients were considered to have been treated with the appropriate dose (adjuvant regimen). Most people in the trial had CIS present (68%) and in clinical practice would typically receive a higher dose (ablative regimen) which was not offered in the trial. People with CIS were likely to have been undertreated in the trial. This model is therefore only applicable to people without CIS receiving an adjuvant regimen. Data was extracted from the Kaplan Meier graph for disease free survival over 2 years and the annual risk of recurrence was calculated. The length of follow up in Tan et al. (2019) was a limitation however, figure 6 of the EAC assessment report shows the plausible impact of Synergo on longer-term disease-free survival by extrapolating the modelled disease-free survival curves over a 10-year period.

The EAC noted that the comparator arm in the Tan et al. (2019) trial was either a second course of BCG or institutional standard care (MMC alone or EDMA). Information on the distribution of each treatment is provided for the total population but not for the subgroup of people without CIS. The EAC used the comparator arm data from the trial for the clinical inputs, but only costed for BCG therapy (6 weekly instillations, followed by maintenance therapy to year 2). Except for costing for BCG therapy (£71.61 per cycle; BNF 2021). instead of MMC alone, all other costs were unchanged. The EAC removed the adverse events costs for Synergo from the additional model because the cost of adverse were assumed to be similar for Synergo and BCG therapy. Mortality parameters remained unchanged.

The EAC model using Tan et al. (2019) for Synergo versus BCG resulted in an increased cost per patient over a lifetime horizon of £9,858. In this analysis, the costs of Synergo were greater than BCG both in the short and long-time horizons and were not balanced by sustained cost savings in the subsequent years. The EAC noted that Synergo was only cost saving in years 3 and 4 (see figures 9 and 10 of the EAC assessment report). The change from cost saving in the base case to cost incurring in the additional analysis was mainly due to the use of clinical data from Tan et al. (2019) which reported higher recurrence rates and a smaller difference in rates between Synergo and BCG arms. This meant that, compared to the base case model, patients in both arms progressed more rapidly from remission to recurrence (radical cystectomy) where the costs are the same in both Synergo and BCG arms. Results from the EAC's additional modelling are presented in table 6 below.

Table 6 EAC additional modelling results over a lifetime horizon (Synergo versus BCG in people with no CIS; Tan et al. 2019)

	EAC Results, life time horizon, per patient		
	Technology	**Comparator**	**Cost saving per patient**
Remission	£16,438	£4,488	-£11,951
Recurrence	£15,650	£15,983	£333
Post-cystectomy	£15,989	£17,415	£1,426
Dead (palliative care)	£9,364	£9,699	£334
Total	**£57,442**	**£47,584**	**-£9,858**
Total radical cystectomies	0.96	0.98	0.02
Total life years	9.44	8.64	0.80
Total QALYS	6.54	5.74	0.79

The EAC's one-way DSA found the key drivers of the Tan et al (2019) model were the costs of the treatment, the annual recurrence rates and the age of people entering the model. None of the changes to the individual parameters moved the estimates into cost-savings (over a lifetime horizon).

A summary of the short term, long-term and lifetime cost estimates for Synergo versus MMC alone or BCG are shown below in table 7 below.

Table 7 summary of results for Synergo versus MMC alone or BCG

	Technology	Comparator	Cost saving per patient	QALYs
Company submission, Synergo vs MMC				
Short term (<=5 years)	£18,902	£20,456	£1,554	0.58
Longer term (post 5 years)	£17,639	£20,551	£2,912	1.17
Lifetime horizon	**£36,541**	**£41,007**	**£4,466**	**1.75**
EAC base case for Synergo vs MMC				
Short term (<=5 years)	£19,746	£22,526	£2,780	0.66
Longer term (post 5 years)	£20,590	£21,358	£769	1.69
Lifetime horizon	**£40,335**	**£43,884**	**£3,549**	**2.35**
EAC model for Synergo vs BCG in people with no CIS (Tan 2019)				
Short term (<=5 years)	£34,438	£27,431	-£7,006	0.49
Longer term (post years)	£23,004	£20,153	-£2,852	0.30
Lifetime horizon	**£57,442**	**£47,584**	**-£9,858**	**0.79**

Estimates changed from cost saving in the EAC base case (versus MMC alone) to cost incurring in the additional analysis using Tan et al. (2019) data (versus BCG). The EAC noted that this is mainly due to the shorter time to recurrence, at which point costs in Synergo and BCG arms are the same. This means that when Synergo was modelled as a 2nd line alternative to BCG, fewer cost savings were accumulated before recurrence and therefore were unable to offset the additional cost of Synergo in the first cycle. Both models demonstrate a reduction in radical cystectomies and an increase in quality and length of life, although these changes are very small when using BCG as the comparator (for patients with no CIS).

Further advice from experts suggested that good practice would include an additional cystoscopy prior to initial treatment with Synergo. This would result

in an additional cost of £261 for Synergo. In this scenario, cost savings were reduced from £3,549 to £3,288 per patient (lifetime horizon) in the EAC base case (vs. passive intravesical mmc). The EAC analysis for Synergo vs. BCG (no CIS) changes from £9,858 to £10,119 cost incurring per patient (lifetime horizon).

Conclusions on the economic evidence

The EAC concluded that the economic modelling is limited by the availability of evidence to represent the most relevant pathways for NHS use. When modelled as an alternative to passive intravesical MMC in people for whom BCG treatment was unavailable or not suitable, Synergo was cost saving by £3,549 per patient over a lifetime horizon. However, this does not currently reflect a common treatment decision in the NHS.

When modelled as a second-line treatment alternative to further BCG therapy, Synergo was cost incurring by £9,858 per patient over a lifetime horizon. However, this modelling was based on data from a small subgroup of 33 people with no CIS and relies on a mix of comparator treatments. Another limitation in the data is that the Tan et al. (2019) trial enrolled a heterogenous group of people who may have been BCG refractory, resistant or intolerant. Further advice from clinical experts suggests that people who are 'BCG unresponsive' (that is T1 disease after induction BCG or high-grade Ta and/or CIS after induction BCG plus 3 further BCG instillations) would not be offered further BCG therapy and therefore does not reflect current clinical decision-making. In this scenario, the most appropriate comparator would be cystectomy which could not be modelled in this analysis using Tan et al (2019).

4 Ongoing research

The company did not identify any ongoing or planned studies in their submission. The EAC searched ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) and identified 1 study (NCT01955408) in which Synergo was included as an intervention (please

see section 8.2 of the EAC assessment report for full details). The study aimed to assess the severity of overactive bladder symptoms in patients after Synergo treatment for bladder cancer. The EAC note that although this study is reported as being complete, no results have been posted and the last verified update on the trial registration was October 2017.

5 Issues for consideration by the Committee

Clinical evidence

- Synergo is currently being used in the NHS as a second line treatment option for people with high-risk NMIBC in whom their disease has not responded to recent BCG therapy. It can also be used when NMIBC recurs following treatment; or when intravesical BCG therapy is declined, not available, intolerable or cannot be delivered safely. Three RCTs were identified for Synergo for NMIBC. They each positioned Synergo differently in the clinical pathway. The trial considered to best represent the current use of Synergo in the NHS (Tan et al. 2019) had significant limitations.

- Two RCTs comparing Synergo to BCG therapy showed no difference in either recurrence-free survival or disease-free survival. Compared to MMC alone, long-term results showed disease-free survival was significantly better with Synergo.

- Several single-arm studies report on recurrence, complete response (ablative regimen), disease progression, bladder preservation and overall survival with Synergo. While these studies provide non-comparative evidence, many include subgroup analyses such as comparisons between adjuvant and ablative regimens, or comparing outcomes based on previous BCG treatment and reasons for stopping (non-responders, treatment intolerant and treatment naïve).

- Synergo is considered an additional treatment option for people with high-risk NMIBC before making the decision to have a cystectomy or in

whom cystectomy is not an available option. Colombo et al. (2011) reported that cystectomy was more likely with MMC alone, although the results were not statistically significant. The reported bladder preservation rate over 10 years were 86.1% and 78.9% with Synergo and MMC alone, respectively. Bladder preservation rates reported in non-comparative studies ranged from 71% to 96% (reported in 5 studies).

- No comparative study looked at high-risk NIMBC alone and no distinction can be made between the results of the different risk groups. There is no evidence to assess the impact of risk group on the effectiveness of Synergo for treating NIMBC.

- It was reported that some of the RCTs experienced slow recruitment and all 3 were stopped early for various reasons. There was also a lack of clarity on the most appropriate comparators, patient populations and treatment regimens. Due to the small numbers of people expected to be treated with Synergo and it being offered in specialist centres, further research in the form of an RCT is not expected to be feasible. Also, due to the high risk of disease progression in a BCG-unresponsive population may mean there are additional ethical considerations if considering an RCT.

Cost evidence

- The company model is limited to a comparison between MMC with Synergo compared to MMC alone. It was considered the only appropriate comparison, due to the available evidence base. This is in a small subset of the scope population which does not fully reflect how the technology is currently being used in the NHS.

- The company analysis shows Synergo to be cost saving compared to MMC treatment. The model showed a reduction in radical cystectomies and an increase in life years with Synergo. The main drivers of the model were the cost of Synergo, risk of recurrence and the cost of

stoma management. Additional analysis shows Synergo to be cost incurring when compared to BCG therapy. However, the evidence used to populate the model has substantial limitations that could impact the robustness of the analysis.

- Additional analysis was done comparing Synergo to BCG therapy in people with intermediate- and high-risk NMIBC without CIS, to better reflect the current NHS use in people with high-risk NMIBC. However, the data was based on subgroup data from the Tan et al. (2019) trial which has substantial limitations. The evidence relies on a small number of patients without CIS (n=33), and a mix of comparator treatments (BCG, MMC alone and EMDA).

- People with high-risk NMIBC who were BCG non-responsive would not be offered further BCG therapy and that in this clinical scenario and the most appropriate comparator would be cystectomy which has not been modelled.

6 Authors

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NICE Medical Technologies Evaluation Programme

May 2021

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- O'Connell S, Knight L, Morgan H et al., MT553 Synergo for non-muscle-invasive bladder cancer External Assessment Centre report, April 2021.

B Submissions from the following sponsors:

- Medical Enterprises Europe B.V

C Related NICE guidance

- Bladder cancer: diagnosis and management. NICE guideline 2 (2015). Available from: https://www.nice.org.uk/guidance/ng2
- Electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer. NICE interventional procedures guidance 638 (2019). Available from: https://www.nice.org.uk/guidance/ipg638
- Intravesical microwave hyperthermia and chemotherapy for non-muscle invasive bladder cancer. NICE interventional procedures guidance 628 (2018). Available from: https://www.nice.org.uk/guidance/ipg628

D References

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Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Professor Sanjeev Madaan
Consultant Urological Surgeon & Lead Cancer Clinician, Darent Valley Hospital, Dartford.

Benjamin Ayres
Consultant Urological Surgeon, St Georges University Hospital NHS Foundation Trust.

Toby Page
Consultant Urologist, Newcastle upon Tyne Hospitals Trust.

Param Mariappan
Consultant Urological Surgeon & Honorary Clinical Senior Lecturer, NHS Lothian & University of Edinburgh.

Ahmed Ali
Consultant Urological Surgeon, Frimley Health NHS Foundation Trust.

Angela Elliott
Urology Clinical Nurse Specialist (CNS) – Bladder Cancer Nurse, Frimley Health NHS Foundation Trust.

Chris Backhouse
Macmillan Urology Cancer CNS, St Georges University Hospitals NHS Foundation Trust.

For full details, please see the expert adviser questionnaire (EAQ) responses which are included in the committee pack.

Appendix C: Comments from patient organisations

Advice and information were sought from patient and carer organisations. The following patient and carer organisations were contacted:

- Action Bladder Cancer UK
- Bladder & Bowel UK
- Fight bladder cancer
- Macmillan cancer support
- Tenovus cancer care

A response was received from Fight Bladder Cancer, please see the response in the committee pack for full details.

Appendix D: Decision problem from scope

Population	People with intermediate or high-risk non-muscle-invasive bladder cancer (as determined by NICE guideline NG2).
Intervention	Radiofrequency-induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 System
Comparator(s)	Intermediate and high-risk: •Other device-assisted chemotherapy options (hyperthermic or electromotive drug administration) Intermediate-risk: •Passive intravesical chemotherapy High-risk: •Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy •Cystectomy
Outcomes	The outcome measures to consider include: •Recurrence rates and time to recurrence •Disease progression and changes to treatment indicative of advanced disease •Rates of cystectomy •Complete response rate in papillary non-muscle-invasive bladder cancer •Complete response rate for carcinoma in situ •Disease-specific and overall survival •Health-related quality of life •Treatment tolerability • Length of hospital stay •Treatment delivery rates in inpatient or outpatient settings •Rates of failed treatment delivery due to device-related issues •Adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which can include scenarios in which different numbers and combinations of devices are needed when relevant.
Subgroups to be considered	Where evidence allows the following subgroups may be considered: •People in whom previous intravesical therapy has failed •People with papillary tumours only •People with carcinoma in situ, with or without papillary tumour (ablative therapy)

	• Subgroups based on risk group (intermediate or high), stage and grade of cancer • Intravesical agent used	
Special considerations, including those related to equality	Bladder cancer is more common in men than in women, and most cases happen in people aged 60 and over. Women diagnosed with bladder cancer are more likely to present at an advanced stage and have worse prognosis and outcomes than men. Bladder cancer is more common in white people than in black or Asian people. Age, sex and race are protected characteristics under the Equality Act. People with cancer are considered to have a disability under the Equality Act.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	Yes*
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	*Synergo is contraindicated in pregnancy. Pregnancy is a protected characteristic under the Equality Act 2010.	
Any other special considerations	Special consideration is needed when treating people with metallic or magnetic implants (such as pacemakers and prostheses). For people with implantable cardiac devices, it is advised to obtain approval and follow-up from a cardiologist before treatment with Synergo. Awareness to excessive sensitivity is needed in cases of metallic prostheses in the pelvic region.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Synergo for non-muscle-invasive bladder cancer

1 Technology

1.1 Description of the technology

Synergo uses radiofrequency-induced thermo-chemotherapeutic effect (RITE) to improve how chemotherapy is given to treat non-muscle-invasive bladder cancer. It delivers controlled radiofrequency radiation (non-ionising microwave radiation), which heats the superficial layers of the bladder wall, and simultaneously flushes the bladder with a chemotherapy drug (thermo-chemotherapy). The drug solution is continuously pumped out of the bladder, cooled, and recirculated to prevent overheating. A miniature antenna in the catheter emits radiofrequency radiation directed at the bladder wall tissue, at a depth which does not generate heat on the external surface of the bladder avoiding injuries to surrounding organs.

Synergo is an intravesical irrigation system combined with an energy-delivering unit. The system has a radiofrequency generator that delivers radiofrequency energy at 915 MHz (the lower limit of microwave electromagnetism). It also includes a drug circulating unit and a microprocessor with application-specific software. The user interface consists of a computer, monitor with touch screen, and barcode reader. The software monitors and records treatment parameters in real time during the treatment session. People receiving Synergo therapy are typically treated as an outpatient. There is no need for general anaesthesia during treatment. Local anaesthesia may be used to insert the treatment catheter. Synergo is most

likely to be administered by healthcare professionals such as bladder cancer nurse specialists in secondary and tertiary care.

1.2 Relevant diseases and conditions

Synergo is intended for use in people with intermediate-risk non-muscle-invasive bladder cancer or people with high-risk cancer whose disease has not responded to intravesical BCG therapy, or in whom intravesical BCG therapy is not available, intolerable or cannot be delivered safely.

Most bladder cancers (75 to 80 percent) are non-muscle-invasive, meaning the cancerous cells are contained within the most superficial layer of the bladder wall (uroepithelium) and do not involve the underlying muscle layer. Non-muscle-invasive bladder cancer is classified as stage Ta when the tumour is confined to the uroepithelium. It is classified as stage T1 when there is spread into the connective tissue layer between the urothelium and the muscle wall. It is also graded on the characteristics of the tumour from G1 (or papillary urothelial neoplasm of low malignant potential [PUNLMP]; least aggressive and slow growing) to G3 (or high grade papillary urothelial carcinoma; most aggressive and fast growing). Carcinoma in situ is a non-papillary (flat) form of tumour consisting of early, high-grade cancer cells confined to the superficial layer of the bladder wall.

It is estimated that around 20,500 people are diagnosed with bladder cancer in the UK each year; around 9,400 of whom have invasive bladder cancer at diagnosis and 11,100 of whom have carcinoma in situ, other bladder cancer, or bladder cancer of uncertain or known behaviour (2016 to 2018; My Diagnosis Counts, Fight Bladder Cancer). According to Cancer Research UK's bladder cancer statistics, in 2017 bladder cancer was the eleventh most common cancer in the UK and the 9th most common cause of cancer death in the UK, accounting for 5,612 deaths (3% of all cancer deaths) in that year (Cancer Research UK bladder cancer statistics are for invasive cancer only [ICD-10 code C67]). For people with stage 1 bladder cancer (cancers that have grown into the connective tissue layer of the bladder wall but have not reached the muscle layer), around 80% of people survived their cancer for 5

years or more (Cancer Research UK, 2018). In some people, non-muscle-invasive bladder cancer may come back after treatment (known as recurrence). According to a recent trial on the use of BCG in people with high-risk non-muscle-invasive bladder cancer (NIMBUS trial; Grimm et al. 2020), approximately 15% of these people experienced tumour recurrence within 2 years following intravesical BCG therapy.

Bladder cancer is three times more common in men than women (My Diagnosis Counts, Fight Bladder Cancer). Although bladder cancer is more common in men, women are more likely to present with advanced stage cancer and typically have a less favourable prognosis and outcomes once diagnosed. The condition is more common in older adults, with most new cases diagnosed in people aged 60 and above. It is also more common in White people than in Asian or Black people. Other factors known to increase the risk of developing bladder cancer include smoking, exposure to certain industrial chemicals, long-term or repeated urinary tract infections (UTIs), having had bladder cancer before and a family history of bladder cancer.

1.3 Current management

People with suspected bladder cancer are usually offered a transurethral resection of bladder tumour (TURBT). This involves the complete removal of all visible papillary tumours, where feasible, and obtaining a sample for biopsy. The outcome of TURBT is used to risk stratify cancers and they are regarded as either low, intermediate, or high risk depending on the size and number of tumours and the histological stage and grade of the cancer. People with high-risk non-muscle-invasive bladder cancer should be offered another TURBT no later than 6 weeks after the first resection. This early re-resection is used to try to ensure complete cancer clearance and improve staging. Treatment for people with a confirmed diagnosis of non-muscle-invasive bladder cancer is guided by this risk classification. In patients with low-risk non-muscle-invasive bladder cancer, TURBT alone may be sufficient. In patients with intermediate or high-risk cancers, additional treatment is usually offered.

Intravesical chemotherapy (usually mitomycin C) is given to people with intermediate-risk non-muscle-invasive bladder cancer. Some centres may offer intravesical device-assisted chemotherapy such as hyperthermic chemotherapy (using heat and chemotherapy) or electromotive drug administration (electrically stimulated chemotherapy). These emerging treatments are aimed at improving the delivery and efficacy of chemotherapy.

A choice of intravesical BCG or radical cystectomy (surgery to remove the whole bladder) is offered to people with high-risk non-muscle-invasive bladder cancer. People in whom symptoms have not responded to intravesical chemotherapy may be considered for intravesical BCG therapy and people for whom symptoms have not responded to intravesical BCG therapy may be considered for cystectomy. The choice of treatment should be based on a discussion with the person being treated, the clinical nurse specialist and a urologist who performs both intravesical BCG and radical cystectomy. The discussion should take into consideration the type, stage and grade of cancer and the risk of disease progression, as well as the benefits and risks of both treatments.

NICE's guideline on bladder cancer: diagnosis and management is relevant to this care pathway.

The guidelines for the management of bladder cancer by West Midlands expert advisory group for urological cancer recommends that when induction BCG has failed, the specialist urology multidisciplinary team should assess the suitability of radical cystectomy (surgery to remove the whole bladder) or further intravesical therapy with hyperthermic mitomycin C, if radical cystectomy is unsuitable, declined by the patient, or if the bladder cancer that recurs is intermediate- or low-risk.

NICE interventional procedures guidance on intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer recommends that RITE therapy should only be used with special arrangements for clinical governance, consent, and audit or research.

1.4 Regulatory status

Synergo received a CE mark in 2001 (last updated in May 2019) as a Class IIb medical device.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Reduced rates of tumour recurrence
- Reduced disease progression
- Reduced need for cystectomy in some people, resulting in reduced morbidity and mortality associated with cystectomy
- No requirement for general anaesthesia
- Additional treatment option for people in whom BCG is indicated but cannot be administered due to contraindications or patient preference

The benefits to the healthcare system claimed by the company are:

- Reduced number of cystectomies performed, potentially leading to fewer post-surgery complications
- Reduced hospital stay
- Treatment moved from an inpatient to outpatient setting
- Reallocation of hospital resources
- Additional treatment option for people in whom BCG is indicated when supply of the drug is limited or delayed

2 Decision problem

Population	People with intermediate or high-risk non-muscle-invasive bladder cancer (as determined by NICE guideline NG2).
Intervention	Radiofrequency-induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 System
Comparator(s)	Intermediate and high-risk: •Other device-assisted chemotherapy options (hyperthermic or electromotive drug administration) Intermediate-risk: •Passive intravesical chemotherapy

	High-risk: •Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy •Cystectomy
Outcomes	The outcome measures to consider include: •Recurrence rates and time to recurrence •Disease progression and changes to treatment indicative of advanced disease •Rates of cystectomy •Complete response rate in papillary non-muscle-invasive bladder cancer •Complete response rate for carcinoma in situ •Disease-specific and overall survival •Health-related quality of life •Treatment tolerability • Length of hospital stay •Treatment delivery rates in inpatient or outpatient settings •Rates of failed treatment delivery due to device-related issues •Adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which can include scenarios in which different numbers and combinations of devices are needed when relevant.
Subgroups to be considered	Where evidence allows the following subgroups may be considered: •People in whom previous intravesical therapy has failed •People with papillary tumours only •People with carcinoma in situ, with or without papillary tumour (ablative therapy) •Subgroups based on risk group (intermediate or high), stage and grade of cancer •Intravesical agent used
Special considerations, including those related to equality	Bladder cancer is more common in men than in women, and most cases happen in people aged 60 and over. Women diagnosed with bladder cancer are more likely to present at an advanced stage and have worse prognosis and outcomes than men. Bladder cancer is more common in white people than in black or Asian people. Age, sex and race are protected characteristics under the Equality Act. People with cancer are considered to have a disability under the Equality Act.

Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	Yes*
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	*Synergo is contraindicated in pregnancy. Pregnancy is a protected characteristic under the Equality Act 2010.	
Any other special considerations	Special consideration is needed when treating people with metallic or magnetic implants (such as pacemakers and prostheses). For people with implantable cardiac devices, it is advised to obtain approval and follow-up from a cardiologist before treatment with Synergo. Awareness to excessive sensitivity is needed in cases of metallic prostheses in the pelvic region.	

3 Related NICE guidance

Published

- Bladder cancer: diagnosis and management (2015) NICE guideline NG2
- Suspected cancer: recognition and referral (2015, last updated 2017) NICE guideline NG12
- Transurethral laser ablation for recurrent non-muscle-invasive bladder cancer (2019) NICE interventional procedures guidance 656
- Electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer (2019) NICE interventional procedures guidance 638
- Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer (2018) NICE interventional procedures guidance 628
- Laparoscopic cystectomy (2009) NICE interventional procedures guidance 287
- Intraoperative red blood cell salvage during radical prostatectomy or radical cystectomy (2008) NICE interventional procedures guidance 258

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association of Cancer Physicians
- Bladder and Bowel Foundation
- British Association of Urological Nurses
- British Association of Urological Surgeons (BAUS)
- British Society of Interventional Radiology
- British Uro-Oncology Group
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Radiologists
- Royal College of Surgeons
- The Association for Cancer Surgery (BASO ~ The Association for Cancer Surgery)
- UK Oncology Nursing Society
- Urology Foundation

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- Action Bladder Cancer UK
- Bladder & Bowel UK
- Fight bladder cancer
- Macmillan cancer support
- Tenovus cancer care

NICE National Institute for Health and Care Excellence

Adoption report: GID-MT553 Synergo for non-muscle-invasive bladder cancer

Summary

Adoption levers identified by contributors

- Provides a treatment option for people in whom intravesical Bacillus Calmette-Guerin (BCG) immunotherapy has failed, is not tolerated or is contraindicated and for those where surgery is contraindicated.
- May provide an option when BCG is not available.
- Treatment could cure bladder cancer or prevent/delay radical cystectomy and the associated financial and quality of life impacts of this.

Adoption barriers identified by contributors

- Initial financial outlay and lack of associated tariff. Lack of NICE guidance on this has made procurement difficult.
- Need for training and time to become proficient at performing the procedure and selecting the correct patients.
- Possible need for patients to travel to receive treatment.
- Physical clinic space needed to host machine.

1 Introduction

The adoption team has collated information from 6 urology consultants working within NHS organisations, 5 of whom have experience of using Synergo. One consultant is looking to purchase Synergo for use within their service and currently refers patients to a service using it.

This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption. It does not represent the opinion of NICE or MTAC.

2 Contributors

The adoption team spoke to six urology consultants all working in secondary and tertiary care NHS trust departments in England. Contributors have been using Synergo for between 0-15 years.

3 Current practice in clinical area

Diagnosis and treatment of non-muscle-invasive bladder cancer usually happens in secondary and tertiary care urology departments. The aim of treatment is to avoid invasion of the tumour into the muscle wall and therefore prevent spread. Following cystoscopy to confirm presence of non-muscle invasive bladder cancer, trans urethral removal of bladder tumour (TURBT) is performed. At the same time as TURBT a single dose of intravesical mitomycin C is given.

Tumour pathology and the person's history indicate if they are low, intermediate, or high risk. People with intermediate risk cancer should have a course of intravesical mitomycin C. If the cancer recurs the person should be referred to a specialist urology multidisciplinary team be considered for further intravesical therapy or cystectomy.

People with high-risk cancer have another TURBT within 6 weeks of the first and are offered intravesical BCG. If BCG fails (this happens in around 30% of patients receiving BCG treatment) and the cancer persists or recurs or if BCG is not tolerated, cystectomy (removal of the bladder) or further intravesical therapy are considered. If BCG is contraindicated or not available, again cystectomy or further intravesical therapy are considered.

Contributors reported that treatment with Synergo is considered as an additional option prior to cystectomy in the relatively small group of people with high-risk non-muscle-invasive bladder cancer where:

- BCG treatment has failed, is not tolerated, or is contraindicated.

- BCG treatment is unavailable. Contributors had not used it for this reason, but all explained it would be useful in this instance as this has happened in recent history.

- Cystectomy is contraindicated or not wanted.

Contributors reported that the procedure takes about an hour to perform but requires one and half hours to be allocated for the appointment. This allows fifteen minutes either side for setting up the machine, the patient undressing and an explanation to be provided.

The company report that there is a defined protocol for treatment. This recommends a total of 12-14 treatments in the first year and an additional 6 in the second year. They report that in practice the average number of treatments per patient is 10 due to recurrences, allergy to mitomycin C, people lost to follow up and patients indicated for only one year of treatment by the caring physician.

Contributors were not aware of this protocol and reported that there is no defined schedule for treatment. They described their use of the technology as weekly sessions for 6-8 weeks (8 weeks if carcinoma is in situ and 6 weeks if not), followed by maintenance sessions. The maintenance session regimen varied from 6 sessions once every 4 to 6 weeks to every two months, for 2 years.

All contributors explained that when introducing the technology into practice the procedure would be carried out by a consultant. Once confidence is established within the department a specialist nurse is trained and carries out the procedure.

4 Reported benefits

The potential benefits of adopting Synergo, as reported to the adoption team by the healthcare professionals using the technology, are:

- Could provide a treatment option for people in whom intravesical BCG has failed, is not tolerated or is contraindicated and for those where surgery is contraindicated or not wanted.

- May provide an option when BCG is not available.
- The radiofrequency (RF) induced system may have an improved 'cancer killing' effect than standard intravesical therapy. This may be due to the combination of simultaneous RF, heat, and chemotherapy. The heating of the bladder walls is thought to allow the treatment to better penetrate cells, improving its efficacy.
- Treatment could cure the cancer.
- Treatment could prevent or delay radical cystectomy and therefore reduce the associated financial and quality of life impacts.

5 Insights from the NHS

Area of application in NHS

As Synergo is considered as a treatment option for people with intermediate (if cancer recurs following course of intravesical mitomycin C) or high-risk bladder cancer, contributors indicated that it should be delivered in specialist centres (on a regional cancer network or supra-network basis). If the machine were in every hospital, it could be used inappropriately in patients who didn't fit the selection criteria.

One contributor suggested that this should not be limited to major pelvic treatment centres as this would impact on delivery of this treatment option to those who could benefit.

Another contributor suggested that regional delivery would limit the need for some patients to travel to a specialist centre.

Patient selection

All contributors highlighted how important patient selection is. Use of Synergo is only appropriate in a small number of patients; Those where intravesical BCG has failed, is not tolerated or is contraindicated and for those where surgery is contraindicated or not wanted.

Two contributors considered that Synergo may be more effective than suggested by the RCT evidence due to poor patient selection in the trials.

One contributor explained that it is important to repeat cystoscopy when a patient is referred for Synergo. This is to check the bladder is clear of disease and if not, to remove any existing tumours prior to treatment. The company indicate that this practice should be adopted in all referring sites to ensure patients do not present to the treatment centre with pre-existing tumours. This same contributor also explained that they biopsy the prostatic urethra to check for cancer cells in the prostate. If cancer cells are in the prostate, they would offer the patient cystectomy rather than Synergo as the disease has spread and Synergo is unlikely to treat extra-vesical sites. If the disease has spread but the patient has contraindications for surgery (e.g., is frail or unfit) they would try treatment with Synergo but would explain to the patient that it may not work.

One contributor's service has had the machine since 2006 and has only treated a maximum of 300 patients. Due to small patient numbers, adoption will require clinician interest.

Procurement

The initial outlay to lease (company provide the device under a fully serviced lease) the machine was highlighted as a barrier, as was the need for an appropriate tariff to cover provision of this treatment.

One contributor explained that it took 2 years for their trust to approve the use of Synergo. They said that this may be because the technology does not have NICE approval. This contributor advised that reimbursement for all procedures has changed to block payments due to COVID-19.

Initial outlay should be offset by the financial and quality of life savings associated with avoiding or delaying cystectomy. Treatment with Synergo may also prevent possible complications of surgery particularly during the pandemic when the preference may be to avoid surgery if possible.

Capacity

Adoption will require consultant capacity at the start of adoption, followed by band 7 specialist nurse time once established. The time allocated to each procedure is 1.5 hours and the patient is continually monitored throughout that time.

Training

Contributors and the company report that all potential operators receive a 4-5 hour training course. Following this, a company representative attends to oversee at least 2 patients being treated for the first time. The company also explain that a 24/7 helpdesk is provided. This training package is provided at no cost. Operators will also need time to become proficient at both carrying out the procedure and selecting the correct patients to offer treatment to.

Contributors explained that the procedure is fairly straight forward, and the machine prompts are helpful.

The Synergo catheter is slightly larger than a standard catheter and is rigid. This can make catheterisation more difficult and requires a skilled operator.

Patient experience

Patients may need to travel to receive treatment. As treatment sessions are weekly at first this could be a barrier for some patients. Contributors reported that in their experience patients were willing to travel to receive the treatment.

Treatment with Synergo may delay or prevent surgery to remove the bladder. This is a significant lever for adoption. Removal of the bladder has significant quality of life implications for patients, as an alternative route and collection of urine outside of the body needs to be created. There is also morbidity and mortality and a 3 to 6 month recovery period associated with surgery to remove the bladder.

Treatment with Synergo is associated with similar side effects to those experienced by the patient receiving intravesical treatment. These Side effects may include infection risk, burning and stinging when passing urine, overactivity of the bladder, feeling tired and urethral strictures. During the procedure, patients may experience

abdominal pain and bladder spasms which can be controlled by reducing the radio frequency energy. These were not considered to be significant barriers to adoption by the contributors.

Clinic space

All contributors reported that clinic space is an issue. The machine ideally needs a dedicated room where it can be covered when not in use rather than needing to be moved. Contributors reported that moving machines can lead to breakages. This barrier may be more significant at present as clinic space has been taken over to respond to the COVID-19 pandemic.

The company reported that the new system is smaller and can easily be moved between rooms. All sites with the old version will have their machine replaced and new sites will be provided with the new model.

6 Comparators

The Combat BRS System was noted by contributors. This technology differs from Synergo as it heats the chemotherapy treatment to high temperature outside of the body and while on its way to the bladder in the tubes and urethra, it cools down and is introduced into the bladder warm and at a constant temperature, pressure and volume flow. It does not measure the temperature of the bladder tissue and has no RF function. One contributor commented that they thought this system was not as effective as Synergo as it doesn't have the RF function and the heating function is different.

Contributors explained that there is a lot of activity and research in this field looking for treatments to prevent the need to remove the bladder. Much of this is pharmacology focussed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT553 Synergo for non-muscle invasive bladder cancer

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Medical Enterprises Europe B.V
Submission date	03 March 2021
Regulatory documents attached	CE certificate, ISO 13485:2016 & EN ISO 13845:2016, Registration status letter from MHRA and User manual 101.3 version 4 December 2020.
Contains confidential information	No

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People with intermediate or high-risk non-muscle-invasive bladder cancer (as determined by NICE guideline NG2)	Not applicable (N/A)	N/A
Intervention	Radiofrequency-induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 System	N/A	N/A
Comparator(s)	Intermediate and high-risk: • Other device-assisted chemotherapy options (hyperthermic or electromotive drug administration). Intermediate-risk: • Passive intravesical chemotherapy High-risk: • Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy • Cystectomy	No robust evidence is offered for Synergo vs other device-assisted chemotherapy options.	The literature search identified one feasibility study comparing Synergo to an electromotive drug procedure (Colombo, 2001). This reported a higher complete response rate with Synergo. This is the only comparative clinical evidence of Synergo vs other device-assisted chemotherapy options. The study is included in Section 4, but the comparator will not be included within the economic model. Also, NICE IPG638 noted that due to limited evidence, electrically stimulated intravesical chemotherapy should only be used in the context of research. This is confirmed by a Cochrane review.

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Outcomes	• The outcome measures to consider include: • Recurrence rates and time to recurrence • Disease progression and changes to treatment indicative of advanced disease • Rates of cystectomy • Complete response rate in papillary non-muscle-invasive bladder cancer • Complete response rate for carcinoma in situ • Disease-specific and overall survival • Health-related quality of life • Treatment tolerability • Length of hospital stay • Treatment delivery rates in inpatient or outpatient settings Rates of failed treatment delivery due to device-related issues Adverse events	N/A	N/A
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the	N/A	N/A

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
	model parameters, which can include scenarios in which different numbers and combinations of devices are needed when relevant.		
Subgroups to be considered	Where evidence allows the following subgroups may be considered: • People in whom previous intravesical therapy has failed • People with papillary tumours only • People with carcinoma in situ, with or without papillary tumour (ablative therapy) • Subgroups based on risk group (intermediate or high), stage and grade of cancer • Intravesical agent used	N/A	We shall seek to identify evidence for these subgroups. Such analysis is important particularly for the high-risk groups who have failed on intravesical therapy and are referred to cystectomy or radiotherapy as standard of care.
Special considerations, including issues related to equality	Bladder cancer is more common in men than in women, and most cases happen in people aged 60 and over. Women diagnosed with bladder cancer are more likely to present at an advanced stage and have worse prognosis and outcomes than men. Bladder cancer is more common in white people than in black or Asian people. Age, sex and race are protected characteristics under the Equality Act. People with cancer are considered to	N/A	N/A

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
	have a disability under the Equality Act.		

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

The Synergo system comprises the following:

1) Radiofrequency Hyperthermia Device (SB-TS 101)

2) Transurethral RF Ablation Applicator and Tubing Line Disposable Set (LI932B and LI932B-S)

3) Synergo System Software

The Synergo system is a Class IIb device under Rule 9 of the COUNCIL DIRECTIVE 93/42/EEC ON MEDICAL DEVICES (ANNEX IX, Section III). The Synergo system will remain a Class IIb device under Rule 9 of the REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL (ANNEX VIII CHAPTER III)

Closed Drainage Set is an accessory Class IIa.

Brand name	Synergo SB-TS 101 & disposable set LI-932B or LI-932B-S and Closed Drainage Set CDS932B (optional)
Approved name	Synergo SB-TS 101; LI932B; LI932B-S; CDS932B
CE mark class and date of authorisation	IIb (IIa for CDS932B); CE issued 23/05/2019 valid 22/5/2024

Version(s)	Launched	Features
SB-TS 101.3	January 2016	Smaller, lighter with Windows OS and new data acquisition circuits and new power supplies which are more efficient.
A newer version will be installed in the UK once Covid 19 restrictions are lifted.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Reduced rates of tumour recurrence Reduced disease progression Reduced need for cystectomy in some people, resulting in reduced morbidity and mortality associated with cystectomy	**Reduced rates of tumour recurrence:** • In a systematic review of evidence, 59% relative reduction in recurrence of intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) patients Lammers (2011). • In intention-to-treat (ITT) analysis of a multinational randomised controlled trial (RCT) comparing Synergo + Mitomycin (MMC) vs. BCG: 78.1% and 64.8% of the participants, respectively, were disease-free (DF) at the 2-year follow-up. Arends (2016a). • In a multinational RCT comparing Synergo+MMC with MMC alone in intermediate- and high-risk NMIBC patients, 82.9% and 42.5% of the participants, respectively, were disease-free at the 2-year follow-up. Colombo (2003). • In an analysis of 90 Synergo + MMC-treated patients, 41 of whom previously failed BCG, 85.7% at 1 year and 75.4% at 2 years were disease-free. van der Heijden (2004).	Adjuvant intravesical instillations with chemotherapy or Bacillus Calmette-Guérin (BCG) are administered to intermediate and high-risk NMIBC patients depending on the risk group. Despite intravesical treatment, these patients have a high five-year recurrence and progression probability (up to 52% and 20% in high risk patients respectively). When intravesical treatment in high-risk patients fails, patients are

Claimed benefit	Supporting evidence	Rationale
	• BCG naive high-risk NMIBC patients, recurrence-free rate of 81.6% over 2 years. Lüdecke (2015b). • 78.3% disease free over 2.9 years. None of those who recurred progressed or needed a cystectomy. Lüdecke (2013). **Long-term follow up:** • Extended follow-up of the RCT participants showed that 53% and 15% of the participants were disease-free at 10-years after treatment administration in the Synergo+MMC and MMC arms, respectively Colombo (2011). • In a single-center (Netherlands) of Synergo + chemotherapy to treat 299 patients, most of whom had failed BCG, (65% – BCG-refractory and 7.7% BCG-intolerant), recurrence free survival rates (RFS) for patients with papillary tumors were 77.9%, 57.5%, and 37.2%, at one, two and five years, respectively. Brummelhuis (2021). • 10-year single-centre experience (UK) in high risk NMIBC patients who failed previous treatment with BCG: 1-, 5- and 10-year recurrence free survival was 63%, 34% and 24% respectively and 1-, 5- and 10-year progression free survival (PFS) was 92%, 71% and 62% respectively following Synergo. 5-year cancer specific survival rate of 79%. Ayres (2018). • 10-year single-centre experience (Italy) RFS at 1, 2 and 5 years was 89.6%, 79.2 and 68.3 respectively and the PFS at 1, 2 and 5 years was 98%, 96.2% and 83.7% following Synergo Canepa (2016). • Single-centre experience 87.5% tumor-free at average of 3.2 years. No cystectomy had to be performed during	referred to a radical cystectomy with urinary diversion or bladder sparing modalities. Microwave-induced hyperthermia (HT) improves MMC effectiveness by enhancing local drug penetration into the urothelium due to increased cellular membrane permeability and modified blood perfusion van Valenberg (2016). Delay in recurrence and bladder preservation have been demonstrated

Claimed benefit	Supporting evidence	Rationale
	that period. Hiebeler (2020) [Paper is in German]. • 10-year single-center experience (Israel): 72% tumour free and 95.3% bladder preservation rate following prophylactic Synergo at mean 32 months; range: 3 months to 7 years. Ablative Synergo initial complete response (CR)rate, durable response rate and bladder preservation rate were 73.1%, 61.5 % and 92.3%, respectively for median: 9 months; range: 2 months to 8 years. Moskovitz (2012). • 10-Year Single Center Experience (Netherlands): 81% of the patients failed previous BCG. 60% and 47% RFS at 1 and 2-year respectively. Arends (2014). **Patients who failed treatment with BCG and candidates for cystectomy:** • 69.6% disease-free at mean period of 26.1 months. Lüdecke (2013). • 72% disease-free at 2-year follow-up. Nativ (2009). • 85% and 48% disease-free at 1 and 2 year respectively. Volpe (2012). • T1G3 patients: 57.1% disease-free at 2-year follow-up. Halachmi (2011). • 41.7% disease-free in patients who were BCG-resistant at 2 years; 66.7% disease-free in early BCG-relapse patients at 2 years. Lüdecke (2015b). • 70% and 33%, 1 and 5-year RFS respectively. 94% and 67%, 1 and 5-year PFS respectively. 80% 5-year cancer specific survival. Ayres (2017). **Bladder preservation rate following Synergo:** • 81.4% at a median of 27 months Sooriakumaran (2016). • 87.6% Lammers (2011).	

Claimed benefit	Supporting evidence	Rationale
	• 80.6% (not stated mean follow up) Kilb (2018). • 75% with a long lasting efficacy Lüdecke (2013) • 95.8% mean follow-up of 35.3 months (prophylactic Synergo) and 78.6% mean follow-up of 20 months (ablative Synergo) in patients who had been heavily pre-treated with over two thirds having failed BCG intravesical therapy. Gofrit (2004). • 65% of patients were disease free and maintained own bladder at median follow up of 18 months Halachmi (2011). • 70.8% at mean follow-up of 55.5 months Brummelhuis (2021). • A prospective single-centre study of patients receiving Synergo and matched against patients undergoing radical cystectomy (RC) for high-risk NMIBC: Significant complication rates classified as a Clavien-Dindo score of greater than 2, was significantly higher in the RC cohort (21% compared to patients receiving MMC-Synergo (0%). There were no deaths associated with MMC-Synergo treatment compared to a ninety-day mortality of 4% in those receiving RC. Nair (2014). **Complete response in neo-adjuvant (ablative) treatment of papillary and Carcinoma in Situ (CIS) patients:** • Synergo in solid tumours: Overall response rate was 90.8%, with 70.4% complete and 20.4% partial response Colombo (1995). • Synergo in papillary vs. chemotherapy alone: complete response 66% vs. 22% respectively. Recurrences: 28% (8/29) after 2 to 22 months vs. 39% (9/23) after 7 to 19 months. Colombo (1996).	

Claimed benefit	Supporting evidence	Rationale
	• CIS complete response: 66.2% at 6 months. 74.5% RFS at 2 years. Overall cystectomy-free rate and overall survival (OS) at mean follow-up 35.8 months were 78.5% and 78.0%, respectively van Valenberg (2018). • 85.5% initial complete response and 69.6% of those remained disease free for a mean period of 26.1 months Lüdecke (2013). • Papillary tumours: 80% complete response at mean follow up of 104.5 days Moskovitz (2005). • Primary or BCG-failing CIS with or without concomitant papillary complete response at 3 months 92%. 50% remained disease free after 2 years Witjes (2009). • Papillary high grade G3 tumours with or without concomitant carcinoma in situ, 75% complete response 80.9% recurrence-free rate after mean follow-up of 20 months Gofrit (2004). • Complete response and follow-up: 83% disease-free at one year and 70% at disease-free 5 years Hiebeler (2020). **Progression to muscle invasive disease during studies median follow ups:** • T1G3 patients treated: 7.9% at mean follow up of 20 months Halachmi (2011). • 11.9 % at median follow-up of 38 months Maffezzini (2014). • 4% at median 75.6-month follow up Arends (2014). • 13.3% after a mean follow-up of about 3 years van Valenberg (2018). • 8.5% during a median follow-up of 55.5 months Brummelhuis (2021)	

Claimed benefit	Supporting evidence	Rationale
	• 10.4% (mean progression time not stated but recurrence free time was 3.5 years) Kilb (2018). • 3% at average time of 16 months Nativ (2009). • 3.1% (systematic review mean progression, time not stated) Lammers (2011). • No stage progression to T2 or disease-related mortality had occurred at median follow-up of 15.2 months (mean 23, range 6 to 90 months) Gofrit (2004). • 4.7% at mean 19 months; range: 2 months to 7 years Moskovitz (2012). • 9% median follow up 47 months (38-58) Ayres (2017).	
No requirement for general anaesthesia	Synergo is usually conducted using local anaesthesia	Non invasive
Additional treatment option for people in whom BCG is indicated but cannot be administered due to contraindications or patient preference	The contraindications to BGC are listed at this link.	In such people the only current standard of care option is cystectomy.
System benefits		
Reduced number of cystectomies performed, potentially leading to fewer post-surgery complications and deaths	Cystectomies are associated with a risk of several adverse effects and high mortality rates	Cystectomies are associated with a risk of several adverse effects including: urinary tract infection; small bowel obstruction or ileus; wound

Claimed benefit	Supporting evidence	Rationale
		infection; sepsis; nerve problems, such as numbness or weakness; stone formation causing stoma blockage and urinary leakage. The procedure also has a mortality risk, with perioperative mortality rate varying between 2.2% to 5.0% Removal of bladder increases such physical risks. It also increases risk of emotional upset.
Reduced hospital stay	The Synergo treatment procedure is delivered in an outpatient setting. A recent study showed that the average length of stay after cystectomy was 15 ± 13 days. In some patients this can be avoided. For instance, Colombo (2011) reported a 10 year disease free survival of 53% with Synergo + MMC vs 15% with MMC. Long-term follow up evidence originating from a single center experience showed a 70.8%. bladder preservation rate for a mean follow-up of 55.5 months was the median time from last TURB to cystectomy was 18 months. In 76.0% of patients, a radical cystectomy could be prevented for 2 years from last TURB, and in 61.1% a radical cystectomy could be prevented for 5 years. Overall survival (OS) rate of patients who underwent radical cystectomy was 71.0%	Evidence reports that Synergo, as adjunctive therapy, extends disease free progression hence delaying, and in some cases avoiding surgery.

Claimed benefit	Supporting evidence	Rationale
	at five years and 42.6% at ten years Brummelhuis (2011). Currently, 49% of patients with bladder cancer require radical cystectomy. Increasing DFS is an important endpoint given that the bladder cancer incidence is strongly related to age, with almost 6 in 10 new cases (56%) being in people aged 75 and over.	
Treatment moved from an inpatient to outpatient setting	See above.	See above.
Reallocation of hospital resources	See above.	See above.
Provides an additional treatment option for people in whom BCG is indicated when supply of the drug is limited or delayed	In 2015, supply of the only UK-licensed BCG vaccine from the contracted supplier, SSI, was interrupted due to manufacturing issues. In turn, this led to ordering restrictions and advice being issued on priority groups for BCG vaccine. The supply issue was not resolved until July 2018 (Public Health England letter, 12 July, 2018). This was not the first incidence of supply interruptions. In 2012 Sanofi ceased production of its Connaught strain of BCG, following an FDA inspection visit to its Toronto manufacturing facility. At the same time, Merck Sharp and Dohme (MSD) ceased production of its TICE® BCG strain. As noted above, in such patients radical cystectomy is indicated and there are no approved bladder-sparring alternatives.	
Cost benefits		
Savings will arise from fewer cystectomies, the	See RCT data on relevant endpoints from Colombo (2003), Colombo (2011) and Arends (2016a). Many more articles exist	The NICE guideline noted: 'the prevalence of

Claimed benefit	Supporting evidence	Rationale
adverse events associated with the procedure and the costs to the NHS to ensure patients have adequate support in managing their stoma.	for bladder sparing (see response to reduced need for cystectomy above.)	the condition and the nature of its management make bladder cancer one of the most expensive cancers for the NHS.' The introduction of an effective alternative to repeat TUR with adjuvant chemotherapies offers the potential for cost saving. The effect will be demonstrated in the economic model.
Other savings are anticipated from a lower recurrence rate, avoiding fewer patients requiring intravesical chemotherapy, intravesical immunotherapy, avoided related adverse events and the related follow-up required, particularly in the first year	See RCT data on relevant endpoints from Colombo (2003), Colombo (2011) and Arends (2016a)	See above
Sustainability benefits		
To avoid repetition, please see below a full response on environmental and sustainability benefits.		

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

Synergo® is a technology also known as Radiofrequency-Induced Thermo-Chemotherapeutic Effect (RITE). It consists of a device and consumable sets (applicator and tubing line) which are connected to the device on one end, and dwell in the patient bladder on the other. It is designed to improve how chemotherapy is given to treat non-muscle-invasive bladder cancer. The treatment is based on controlled radiofrequency emission (non-ionising microwave radiation) of the bladder tissue, along with instillations of the bladder with chemotherapy (thermo-chemotherapy). Synergo® circulates and continuously cools the chemotherapy and flushes the bladder. At the same time, a miniature antenna in centre the applicator emits radiofrequency radiation. The radiofrequency energy is directed at the bladder wall tissue, at a depth which goes past the superficial layer but does not generate heat past the bladder. This avoids injuries to surrounding organs. To ensure this, five thermocouples (miniature thermometers) monitor tissue temperatures during treatment. Three thermocouples are spread out from the applicator and gently deployed against the bladder lining and two others are embedded in the applicator in the urethral segment. Thermocouples monitor temperature to help prevent overheating, and potential degradation of the drug, as well as maintaining patient comfort.

The Synergo® system has a radiofrequency generator that delivers radiofrequency energy at 915 MHz (the lower limit of microwave electromagnetism). It also includes a drug circulating unit (pump and heat exchanger), and a microprocessor with application-specific software. The user interface consists of a computer, monitor with touch screen, and barcode reader. The software monitors and records treatment parameters in real time during the treatment session.

The procedure can be done on an outpatient basis and local analgesic gel (typically lidocaine) is used to desensitise the urethra. Treatment sessions typically last for around 60 minutes and are usually repeated weekly for 6 to 8 weeks (depending on protocol – prophylactic or ablative, respectively), after which a maintenance course of 6 treatments (one every six weeks) ensues for both intents. At the end of each treatment, patients may return to their daily activities.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Sustainability looks to protect the natural environment, human and ecological health, while driving innovation and not compromising way of life. ME considers factors affecting the environment and sustainability during all life stages in its work procedures and its products to meet requirements, whilst satisfying patient and healthcare demand. ME seeks to impose minimal environmental impact at all stages of a device's life cycle: initial concept, design, manufacturing, sales, logistics, installation, use and end-of-life management.

ME provides instructions in accompanying documents to minimise the environmental impact of a product during normal use and for proper disposal at end of life.

Synergo treatment components comprise:

1. Synergo SB-TS 101
2. Applicator Tubing Line Set LI932B and LI932B-S include microwave (RF) antenna and thermometers mounted inside a silicone catheter
3. CDS-bag (optional use) for fluid collection during and at the end of treatment

Chemotherapy is provided locally by the hospital's pharmacy.

Restriction of the use of certain hazardous substances in electrical and electronic equipment:

Based on the information provided by our supply lines, and our certain knowledge of our own processes, products supplied by Medical Enterprise (ME) are compliant with Restriction of Hazardous Substances 3.

Subjects' Privacy – General Data Protection Regulation

ME personnel, it's agents and distributors are instructed not to obtain personal information with identifiable data including photo, either verbal or in writing. Moreover, special software is in- built to hide from ME personnel intervening on the system (e.g. repair) identifiable or traceable information of patients treated by Synergo.

Environmentally conscious system device design and manufacturing

The Synergo SB-TS 101 emits nonionizing RF radiation in order to perform its function. It uses normal sockets and power (220V 50Hz in Europe). It is very efficient in power use. Synergo SB-TS 101 has low level noise, vibration, heat, and does not emit ionizing radiation.

Environmentally sustainable

Synergo SB-TS 101 has no restricted shelf-life. Synergo lifetime is determined by regular wear and tear and is constantly extended if it undergoes periodical maintenance, upgrades, updates, calibrations and provided that the operation of the product fully conforms with operating instructions. Synergo device is not intended for single use. ME manages device collections from medical centres for recycling (to dedicated sites), reuse of parts that can be reused, and seeks to refurbish systems for new placements (under special terms).

Synergo SB-TS 101,when turned-on, but not operated, enters a “safe state” which consumes minimal energy while the RF generator and pump will not operate. At the end of the treatment (or after 75 minutes whichever comes first), the system enters “safe state” with zeroing RF transmission and stopping the pump operation.

Synergo SB-TS 101 has no delayed or long-term use effects and is not subject to any mechanical forces. No paper is used for printing.

Environmental safety of the Synergo device:

Synergo conforms with series of EN ISO standards (see Certificate of Conformity [CoC]).

Applicator Tubing Line Set LI932 B and LI932B-S

Synergo disposable applicator: single use only.

Medical grade silicone; Free of latex; No animal or biological products; Synergo disposables tests have no traces of Phthalates and no detection of chemical leach (HPLC with limit of quantitation of 200 ng/ml).

The materials that constitute the disposables were tested according to the required standards too (See CoC).

Synergo applicator is mounted within a silicone catheter (not harmful as PVC). Studies and regulatory assessments support the safe use of silicone materials in many applications. Within the silicone catheter are the miniaturized antenna and thermometers. Bench performance tests performed during manufacturing ensure RF stray radiation is reduced to the minimum by inspecting 100% of all antennae to ensure antennae emission is exact, accurate and performs efficiently, with no stray radiation that could create a hazard.

Closed Drainage Set

This accessory facilitates the collection and disposal of urine and chemotherapeutic agents, preventing spilling and contact between the agents and operators or patients, thus resulting in a safer and cleaner treatment environment.

Chemotherapy (provided locally by the hospital's pharmacy before each treatment)

Patients suffering from NMIBC receive bladder instillations like BCG and chemotherapy. During these instillations, the patient holds the substance and voids it in the toilet, in most cases without control or in a specific dedicated toilet. This may cause BCG and/or chemotherapy untreated spills or skin irritation during urination.

Chemotherapy used during Synergo treatment is ordered by the medical team before each treatment. Last minute cancellations and/or postponing of treatment does not involve preparation and use of chemotherapy and hence its possible waste. In addition, at the end of each Synergo treatment the operator is requested to empty the patient's bladder so the patients are discharged with no chemotherapy inside their bladder and no chemotherapeutic substances are disposed outside the clinic.

Environmental impact of the clinical results

Reducing disease recurrences and associated surgeries directly reduces various pollutants and contaminators of solid materials and gases, as well as indirect ones (e.g. transport of patients and materials perpetual manufacturing of fuel-based products). In addition, reducing recurrences means fewer chemotherapy instillations, and reducing potential contaminations requiring outpatient attendances.

A study by MacNeil et al (2017) states that operating theatres are a resource-intensive subsector of health care, with high energy demands, consumables throughput, and waste volumes. In 2011, surgical suites were evaluated for greenhouse gas emissions. The UK's John Radcliffe Hospital had an annual carbon footprint of 5,187,936 kg of CO2 equivalents. Theatres were 3 to 6 times more energy-intense than the hospital as a whole, primarily due to heating, ventilation, and air conditioning requirements.

Reducing repeated transurethral bladder operations and cystectomies directly cuts CO2 emissions. Subsequent care post-cystectomy (urostomy pouches, creams, bandages, physician visits etc) also increase pollution and contamination levels (most urostomy pouches need to be changed 1 to 2 times a week for a lifetime). Avoiding cystectomies will undoubtedly reduce use of plastics and reduce contaminated waste.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

The relevant guideline is NICE Guideline Bladder cancer: diagnosis and management (NG2, 2015). Note the guidelines were issued before the NICE IPG638 on Synergo (IPG628, 2018).

NG2 recommends people diagnosed with bladder cancer have papillary tumours removed in a transurethral resection of bladder tumour (TURBT). Following histology, they will be staged for their cancer. Staging, grading, multifocality and frequency of recurrences informs their risk classification, being low, intermediate or high risk.

Intermediate-risk non-muscle-invasive bladder cancer (NMIBC):

- Offer people a course of at least 6 doses of intravesical MMC.
- If intermediate-risk NMIBC recurs after a course of intravesical MMC, refer the person to a specialist urology multidisciplinary team (MDT).

High-risk non-muscle-invasive bladder cancer:

- Offer another TURBT not later than 6 weeks after the first resection.
- Offer the choice of intravesical BCG or radical cystectomy - with the choice informed by a full discussion between the patient and clinical team.

Intravesical BCG:

- Offer induction and maintenance intravesical BCG
- If induction BCG fails (because it is not tolerated, or bladder cancer persists or recurs after treatment with BCG), refer the person to a specialist urology MDT.
- For people in whom induction BCG has failed, the MDT should assess the suitability of radical cystectomy, or further intravesical therapy if radical cystectomy is unsuitable or declined by the person, or if the bladder cancer that recurs is intermediate- or low-risk.

Radical cystectomy

Discuss with candidates to undergo a radical cystectomy the choice of a urinary stoma or a continent urinary diversion (if both are indicated).

Recurrent non-muscle-invasive bladder cancer

Offer transurethral resection (TUR) without biopsy for people with recurrent NMIBC if they meet various conditions: including a disease-free interval of at least 6 months, a solitary papillary recurrence, with a tumour diameter of 3 mm or less.

Follow-up after treatment for NMIBC

Intermediate-risk non-muscle-invasive bladder cancer:

- Offer people with intermediate-risk NMIBC cystoscopy follow-up at 3, 9 and 18 months, and once a year thereafter.

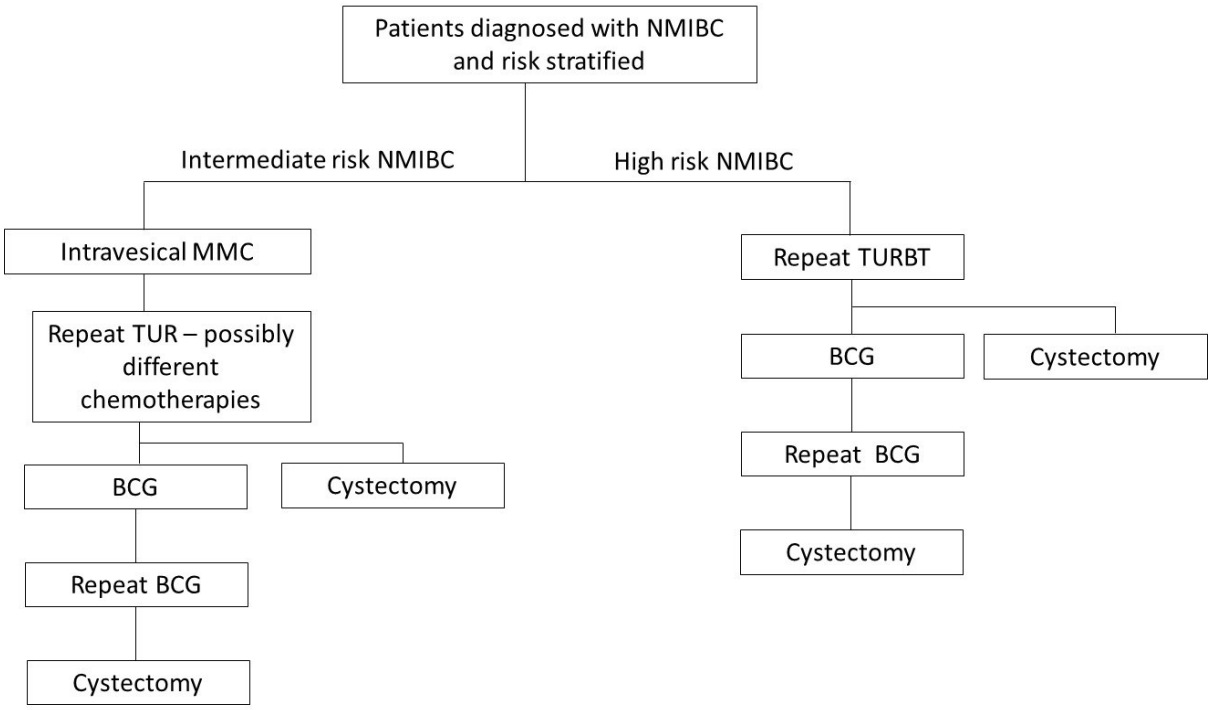
- Consider discharging people who have had intermediate-risk NMIBC to primary care after 5 years of disease-free follow-up.

High-risk non-muscle-invasive bladder cancer:

- Offer people with high-risk NMIBC cystoscopy follow-up every 3 months for the first 2 years, then every 6 months for the next 2 years then once a year thereafter.

The NICE Guideline also identifies the pathway to treat muscle-invasive bladder cancer which will inform the economic model.

NICE current clinical pathway NMIBC



Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

The Synergo® treatment should be performed by certified medical personnel (e.g. physician, nurse or medical technician) who have undergone training in use of the Synergo® device including practical hands-on training with the system.

Company/distributor product specialists provide a formal training which consists of a theoretical course of approximately three hours, and in addition, a hands-on training with at least two patients (approximately three more hours). This is given to clinicians and nursing staff, at which end they receive a certificate. It is also important for the referring urologists, who are not directly providing the treatment, to be involved in the process of these patients so that they provide full patient history and become aware of certain treatment-related side effects.

A thorough patient examination should be performed before starting the Synergo® treatment. The choice of chemotherapeutic agents is the responsibility of the prescribing physician, who should be aware of the licenced indications and doses. Whenever the chemotherapeutic product manufacturer instructs the use of saline solution or buffered distilled water, use sterile distilled water instead. This is to avoid the absorption of energy within the electrolytes in the circulated solution, and by so, the heating and potential degradation of the drug.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		110
Number of studies identified as being relevant to the decision problem.		24
Of the relevant studies identified:		21
	3	3
	0	0

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Arends (2016a)	Arends (2016a) Prior publications: Arends et al (2015) 11 sites in the Netherlands, Israel, Italy, Austria, France and Belgium	RCT	Intermediate- and high-risk NMIBC (EAU criteria). BCG vs Synergo Ta 49% vs 45% T1 51% vs 55% Intermediate: 69% and high-risk 31%; non-CIS: 77.4%; CIS: 22.6% (including CIS only: 13.2% and CIS + papillary: 8.9% plus 1 patient not stated whether CIS was accompanied by papillary or not). With the newly announced 2016 risk classification, the number of high-risk patients is 85 in the intention-to-treat analyses,(Eur Urol 2016;69:1046–52)	Synergo RITE + MMC: 2x20 mg in 50 ml water 50 ml water. Water delivered in 2x30 minutes per treatment 6 times weekly then 6 times every 6 weeks	BCG: full dose 6 times weekly then three weekly treatments at months 3, 6, and 12	RFS at 24 months CR of CIS at 3 months secondary endpoint.

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			Pre-treatment: Prior bladder instillations: Chemo (including MMC): BCG group: 8 (44.4%); Synergo + MMC group: 13 (52.0%) MMC: BCG group: 6 (33.3%); Synergo + MMC group: 6 (24.0%) BCG: BCG group: 4 (22.3%); Synergo + MMC group: 6 (24.0%) Secondary care Follow up: 24 months. There were 6 patients not receiving instillation, 2 were refused Synergo RITE + MMC treatment by the insurance			

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			company, 2 had protocol violations noted (1 Synergo RITE + MMC, 1 BCG) and 2 refused additional therapy (Synergo RITE + MMC). The ITT analysis included all CIS patients and papillary NMIBC patients with at least one treatment given (n = 142; CHT group, 68; BCG group, 74). The PP analysis included 132 papillary NMIBC patients with at least six intravesical instillations as defined in the protocol (CHT group, 60; BCG group, 72). Of the 147 papillary NMIBC patients			

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			recruited, 5 did not start therapy due to insurance issues (n = 2, CHT group), consent withdrawn (n = 2, BCG group), or higher than stage T1 (n = 1, CHT group). In the PP analysis an additional 10 patients had fewer than six treatments due to uncontrolled UTI (n = 1, BCG), consent withdrawn (n = 3; CHT, 2; BCG, 1), lost to follow-up (n = 1, CHT), urethral bleeding (n = 1, CHT), allergic reaction (n = 1, CHT), concomitant squamous cell carcinoma (n = 1, CHT), bladder diverticulae (n = 1, CHT) or >T1 stage at revision of initial			

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			pathology report (n = 1, CHT).			
Tan (2019)	Tan (2019) Prior publications: Tan (2017a, 2017b) 12 sites in the UK	RCT	Recurrence after BCG of intermediate- or high-risk NMIBC according to European Association of Urology guidelines but unfit or unwilling for radical cystectomy. Intermediate: 13.5%; high-risk: 86.5%; non-CIS: 31.7%; CIS: 68.3% (including CIS only: 47.1% and CIS + papillary: 21.2%). Pre-treatment: Previous BCG, n (%) Induction only (≤6 instillations): Synergo + MMC group: 18 (38%);	Synergo RITE + MMC: 2x20 mg in 50 ml water delivered in 2x30 minutes per treatment 6 times weekly then every 6 weeks in the 1st year and every 8 weeks in the 2nd year	BCG: full dose 6 times weekly then three weekly treatments at months 3, 6, 12, 18, and 24 or a second course of BCG or institutional standard of care	CR at 3 months DFS at 24 months

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			control group: 19 (34%) Induction plus maintenance (>6 instillations): Synergo + MMC group: 30 (63%); control group: 37 (66%) Secondary care Follow up: 24 months Two patients in the Synergo RITE+MMC arm did not receive treatment: patient choice (n = 1) and ineligibility post-randomization (n = 1). Three patients in the control arm were not treated: patient choice (n = 2) and significant incontinence (n = 2) after randomization.			

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			Five Synergo RITE+MMC patients did not complete 6 or more instillations due to adverse events, such as skin rash, urinary urgency and nocturia, inability to catheterize (n = 2), hematuria, and patient refusal of treatment, whereas 5 control arm patients were excluded due to adverse events, such as urinary urgency (n = 2), persistent dysuria, hematuria, and patient refusal of treatment. Note there are material issues with the MMC regimen see Witjes (2019) and Section 8.			

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Colombo (2003) Colombo (2011)	Colombo (2003) Extended follow-up publications: Colombo (2011) 3 sites in Italy and Israel.	RCT	Intermediate or high-risk NMIBC, with confirmed complete TURBT. Grade 3: 21.7%; excluded CIS only; 1.2% CIS plus papillary tumors; 98.8% non-CIS. Pre-treatment: Had received previous intravesical treatment with BCG or chemotherapeutic agents (MMC, epirubicin, or other) with a free interval of at least 3 months: Synergo + MMC group: 42.9%; control group: 41.5%. Secondary care Follow up: Original RCT: 24 months of the 83 randomly	Synergo RITE + MMC: 2x20 mg in 50 ml water delivered in 2x30 minutes per treatment 8 times weekly then 4 times monthly	MMC: 2x20 mg in 50 ml water delivered in 2x30 minutes per treatment 8 times weekly then 4 times monthly	Original study: Recurrence Follow up: DFS

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			assigned patients, 75 patients completed the study according to the protocol and had valid cystoscopy results. Three patients in group 1 and 5 patients in group 2 withdrew from the study; reasons were subjective intolerance (two patients), personal decision (2 patients), and protocol violations (4 patients). Extended follow up study: Median follow up 90 (range 6 to 154) months; follow up included all 75 patients who completed trial above			

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Erturhan (2015)	Erturhan (2015) University of Gaziantep, School of Medicine, Gaziantep, Turkey	Prospective case series	High-risk non-muscle invasive bladder cancers based on the EORTC risk tables Pre-treatment: NR Secondary care Follow up: median 16.4 months; no loss to follow up	Synergo RITE + MMC: 2x20 mg in 50 ml water delivered in 2x30 minutes per treatment 6 times weekly then 6 times monthly	NA	Recurrence
Kiss (2015)	Kiss (2015) Single centre: Department of Urology, University of Bern, Bern, Switzerland,	Prospective case series	Intermediate and high risk NMIBC (EAU criteria) Pre-treatment: Number of patients with previous instillation therapies 15 (71%), of which: – BCG 12 (57%) – MMC 10 (48%)	Prophylactic: Synergo RITE + MMC: 20+20 mg in 50 ml water delivered in 2x30 minutes per treatment 6 times weekly Ablative: Synergo RITE + MMC: 40+40 mg in 50 ml water delivered in 2x30	NA	Overall recurrence DSS OS Progression Cystectomy

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			– Farmorubicin 4 (19%) Secondary care Follow up: Median 50 (range 1 to 120) months No loss to follow up	minutes per treatment delivered in 12 weekly sessions. Overall median number of treatments: 6		
Arends (2014)	Arends (2014) Single centre, The Netherlands	Prospective case series	Intermediate and high risk NMIBC (EAU criteria) Pre-treatment: Former intravesical treatment: None: 6 (3.8%) MMC: 8 (5.0%) BCG: 51 (31.9%) MMC + BCG: 74 (46.3%) MMC, BCG + other: 4 (2.5%) Other: 2 (1.4%)	Prophylactic: Synergo RITE + MMC: 20+20 mg or Synergo RITE + epirubicin 25+25 mg Ablative: 40+40 mg MMC or 50+50 mg epirubicin All treatments delivered 6 times weekly then every 6 weeks until end of 1st year in 2x30 minutes per treatment	NA	RFS

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			Instillation unknown: 15 (9.4%) Secondary care Follow up: Median follow-up was 75.6 months. The files of 29 patients were missing.			
Maffezzini (2014)	Maffezzini (2014) Single centre; Italy	Prospective case series	High risk NMIBC (EAU criteria): EORTC recurrence score≥5 or progression score ≥7 Pre-treatment: Chemotherapy: 19 (45.3%) BCG: 8 (19.0%) None: 15 (35.7%) Secondary care	Synergo RITE + MMC: 2x20 mg or 2x40mg in 50 ml water or epirubicin 2x30 mg or 2x50 mg in 50 ml water delivered in 2x30 minutes per treatment 4 weekly sessions, followed by 6 sessions delivered every 2 weeks, and by 4 monthly sessions, for a total of 14 sessions over 8 months		DFS

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			Follow up: Median 38 (range 4 to 73) months. Two patients were lost to follow-up after a negative cystoscopy and biopsy, at 6 and 42 months, respectively, censored as negative.			
Moskovitz (2005)	Moskovitz (2005) Single centre; Israel	Prospective case series	Intermediate and high risk (EAU criteria). Pre-treatment: BCG: Prophylactic group: 13 (59%); Ablative group: 8 (80%) MMC: 7 (32%) and 4 (40%) Other chemotherapy (Immucothel, gemzar, thiotepa and valstar cycles):	Prophylactic: Synergo RITE + MMC: 20+20 mg in 50 ml water delivered in 2x30 minutes per treatment 6-8 times weekly then 4-6 monthly to a total of 12 Ablative: Synergo RITE + MMC: 40+40 mg in 50 ml water delivered in 2x30 minutes per treatment 8 times weekly then 4	NA	Recurrence Progression

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			3 (14%) and 4 (40%) No instillation: 8 (36.5%) and 2 (20%) Secondary care Follow up: Median follow up 10 months. Eight patients were not eligible for analysis (6 prophylactic and 2 ablative). Six of these patients did not meet the inclusion and exclusion criteria The remaining 2 patients did not meet the treatment protocol requirements. Seven other patients that did not reach their first follow-up	monthly		

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			examination were also excluded. Therefore, the efficacy analysis is provided for 32 eligible patients.			
Gofrit (2004)	Gofrit (2004) Italy, Israel, Germany and The Netherlands	Prospective case series	High-grade NMIBC Pre-treatment: BCG: Prophylactic group: 12 (50%); ablative group: 17 (60.1%) Intravesical chemotherapy: 12 (50%) and 11 (39.3%) No prior instillation: 3 (12.5%) and 8 (28.6%) Secondary care Follow up: Median follow-up of 15.2 months (mean 23, range 6 to 90).	Prophylactic: Synergo RITE + MMC: 20+20 mg in 50 ml water delivered in 2x30 minutes per treatment 8 times weekly then 4 monthly to a total of 12 Ablative: Synergo RITE + MMC: 40+40 mg in 50 ml water delivered in 2x30 minutes per treatment 8 times weekly then 4 monthly	NA	Recurrence, progression, cystectomy, complete ablation

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			No loss to follow up			
Colombo (2001)	Colombo (2001) San Raffaele Hospital, Milan, Italy	Prospective case series	Single, recurrent, low-stage, low-grade superficial bladder tumor Pre-treatment: All previously untreated by MMC Secondary care Follow up: To 7–10 days after the last session. No loss to follow up	Synergo RITE + MMC: 40 mg in 50 ml water delivered in 60 minutes per treatment 4 times weekly	EMDA: 20 mA of electric intensity with 40 mg in 150 ml delivered in 20 minutes per treatment 4 times weekly MMC: 4 times weekly 40 mg in 50 ml water delivered in 60 minutes per treatment with postural position change every 10 min	Feasibility and toxicity
Brummelhuis (2021)	Brummelhuis (2021) Single centre; Radboud University Medical Center, The Netherlands	Retrospective case series	Intermediate and high risk NMIBC with the majority refractory or intolerant to BCG; papillary lesions without concomitant CIS resected in all but 22 cases Pre-treatment:	Synergo RITE + MMC: 2x20 mg or 2x40mg in 50 ml water or epirubicin 2x30 mg or 2x50 mg in 50 ml water delivered in 2x30 minutes per treatment then every 6 weeks in the 1st year every 8 weeks in the 2nd	NA	CR and durable response rate or RFS.

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			Previous BCG treatment: 255 (85.3%), including: Refractory 194 (64.9%) and intolerant 23 (7.7%) No previous BCG treatment: 39 (13.0%) Secondary care Follow up: Median follow-up was 55.5 months. No loss to follow up	year every 12 weeks in the 3rd year		
Van Valenberg (2018)	van Valenberg (2018) Six international centres (Radboud University Medical Center, Nijmegen, The Netherlands; Ente Ospedaliero Ospedali Galliera, Genova,	Retrospective case series	150 patients with results at 6 months of follow-up were reported comprising CIS, including BCG-unresponsive (50), other BCG-treated (50), treatment-naïve (50) Pre-treatment:	Synergo RITE + MMC: 2x40 mg in 50 ml water delivered in 2x30 minutes per treatment 4-8 times weekly then every 4-8 weeks unknown number of treatments	NA	CR

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
	Italy; Justus-Liebig University Giessen, Germany; Bnai-Zion Hospital, Haifa, Israel; Darent Valley Hospital, Dartford, UK; St. George's Hospital, London, UK		50 treatment-naïve; 100 had prior BCG treatment Secondary care Follow up: Mean 35.8 months 270 CIS patients treated with RF-CHT were identified. Of these, 236 patients had received≥6 RF-CHT instillations, whereas pathology or cystoscopy and cytology results at 6 months of follow-up were available in 150 patients			
Moskovitz (2012)	Moskovitz (2012) Single centre; Bnai-Zion Medical Center (Haifa, Israel).	Retrospective case series	Intermediate and high risk NMIBC (EAU criteria) Pre-treatment: BCG: Adjuvant: 39 (59.1%);	Prophylactic: Synergo RITE + MMC: 20+20 mg in 50 ml water delivered in 2x30 minutes per treatment 6 times weekly then 6	NA	Recurrence, DFS, bladder preservation rate, CR, durable response

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			neoadjuvant: 20 (76.9%) MMC: 15 (22.7%) and 7 (26.9%) Others (including gemcitabine, keyhole limpet hemocyanin, interferon, valrubicin, Immucothel®, Thiotepa and Taxol®): 15 (22.7%) and 6 (23.1%) None (TURBT-naive): 17 (25.8%) and 5 (19.2%) Secondary care Follow up: Median 23 months (range 3 months up to 7 years). 2 patients withdrew from follow up	treatments every 6 weeks Ablative: Synergo RITE + MMC: 40+40 mg in 50 ml water delivered in 2x30 minutes per treatment 8 times weekly then 6 treatments every 6 weeks of Synergo RITE + MMC: 20+20 mg in 50 ml water delivered in 2x30 minutes per treatment * Seven patients, who had more than five prior episodes of tumor recurrence received additional unknown number of treatments every 3 months		

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Witjes (2009)	Witjes (2009) 15 centres in Israel, Italy, Germany, Switzerland, Austria and the Netherlands	Retrospective case series	CIS with or without papillary with 2/3 previously failing BCG Pre-treatment: Previous intravesical treatments included BCG (n = 34/51 [66.7%]), MMC (n = 11 [21.6%]), epirubicin (n = 4 [7.8%]), gemcitabine (n = 3 [5.9%]), Keyhole–Limpet hemocyanin (KLH) (n = 1 [2.0%]), valrubicin (n = 1 [2.0%]) and radiation therapy (n = 1 [2.0%]). Of the 34 patients previously treated with BCG, 17 (50.0%) were BCG refractory, 2 (5.9%) BCG intolerant and	Patients with unresected papillary tumors or wide areas of CIS: Synergo RITE + MMC: 40+40 mg in 50 ml water delivered in 2x30 minutes per treatment 8 times weekly then 6 times every 6 weeks of Synergo RITE + MMC: 20+20 mg in 50 ml water delivered in 2x30 minutes per treatment Others: Synergo RITE + MMC: 20+20 mg in 50 ml water delivered in 2x30 minutes per treatment 6 times weekly then 6 treatments every 6 weeks	NA	Eradication of CIS

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			15 (44.1%) patients relapsed. Secondary care Follow up: Median 22 (range 3 to 77) months No loss to follow up			
Van der Heijden (2004)	van der Heijden (2004) Multicentre; 9 European hospitals	Retrospective case series	Intermediate or high-risk with confirmed complete TURBT (22 had failed previous BCG therapy) Pre-treatment: BCG: 22 (24.4%) MMC: 7 (7.8%) Epirubicin: 5 (5.6%) BCG + Epirubicin: 6 (6.7%) BCG + MMC: 10 (11.1%) Epirubicin + MMC: 3 (3.3%)	Synergo RITE + MMC: 20+20 mg in 50 ml water delivered in 2x30 minutes per treatment 6-8 times weekly then 4-6 monthly	NA	Recurrence

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			BCG + Epirubicin + MMC: 3 (3.3%) None: 34 (37.8%) Secondary care Follow up: Median 18 (range 2 to 24) months. No loss to follow up			
Nativ (2009)	Nativ (2009) Israel.	Retrospective case series	Recurrent papillary non-muscle invasive urothelial cell carcinoma of the bladder after previous bacillus Calmette-Guerin treatment; 77% high-risk and 23% intermediate-risk; CIS excluded. Pre-treatment: All 111 patients had had prior BCG. Patients were divided into 4 major groups: BCG	After complete tumor(s) resection thermo-chemotherapy treatment was given with prophylactic (adjuvant) intent with the Synergo® device on an outpatient basis weekly for 6 weeks, followed by 6 maintenance sessions at 4 to 6-week intervals. Each treatment included 2	NA	Time to disease recurrence and progression

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			refractory—failure to achieve a disease-free state by 6 months after initial BCG therapy: 42 (38%), BCG resistant—improved disease grade or stage by 3 months and resolution with further BCG treatment 6 (5%), BCG relapse—recurrence after achieving a disease-free state at 6 months (early— within 12 months: 19 [17%], intermediate—12 to 24 months: 22 [20%] and late—greater than 24 months: 16 [14%]), and BCG intolerant—early termination of treatment due to	consecutive 30-minute cycles with 20 mg/50 ml MMC solution and bladder wall hyperthermia to 42C +/- 2C.		

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			drug toxicity: 6 (5%), plus Unknown: 1 (1%). Secondary care Median follow-up was 16 months No loss to follow up			

In addition, 5 reviews were identified Bahouth (2016), Colombo (2016), van Valenberg (2016), Soria (2015) and Lammers (2011) which included overlapping groups of the above studies. None of these was comprehensive and up to date, so the data are reported for each of the primary studies separately.

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Ayres (2018)	Ayres (2018) (conference abstract) Prior publications: Ayres (2017) (conference abstract)	Prospective case series	Only high risk with failure after BCG Pre-treatment: All 130 had failed BCG, of whom 45 (35%) were BCG unresponsive.	Synergo RITE + MMC: 2x40 mg in 50 ml water delivered in 2x30 minutes per treatment 6 times weekly then unknown number of treatments with	NA	RFS

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
	Ayres (2012) (conference abstract) Ayres (2010) (conference abstract) St George's University Hospitals, NHS Foundation Trust, London, United Kingdom		Secondary care Follow up: 10 years Unable to complete induction treatment due to significant side effects: 5/135 (4%): significant side effects of pain, incontinence or severe rash.	Synergo RITE + MMC: 2x20 mg in 50 ml water delivered in 2x30 minutes per treatment every 6 weeks		
Kilb (2018)	Kilb (2018) (conference abstract) University Clinics of Gießen, Justus-Liebig University, Gießen, Germany	Prospective case series	High risk NMIBC by EORTC calculation Pre-treatment: 57 (85%) of the patients were treated alternatively to BCG with primary Synergo + MMC (i.e. no pre-treatment) whereas 10 (15%) were BCG failure patients treated alternatively to indicated cystectomy.	Synergo RITE + MMC: 2x40 mg delivered in 2x30 minutes per treatment 8 times weekly then 6 treatments of Synergo RITE + MMC 2x20 mg delivered in 2x30 minutes per treatment every 6 weeks	NA	Bladder preservation rate

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			Secondary care Follow up: 10 years No loss to follow up			
Luedecke (2015)	Luedecke (2015) (conference abstract) 7 centres; Germany, Israel, UK and The Netherlands	Prospective case series	High risk (EAU criteria) with failure after BCG Pre-treatment: Less than half were BCG-naive Secondary care Follow up: Average follow-up time 2.2 years (range 28 days - 12.9 years) No loss to follow up	Synergo RITE + MMC: 2x40 mg delivered in 2x30 minutes per treatment 8 times weekly then 6 treatments of Synergo RITE + MMC 2x20 mg delivered in 2x30 minutes per treatment every 6 weeks	NA	Response Tumor-free Recurrence

Table 3 Summary of all relevant ongoing or unpublished studies

None identified. There is a study registered in ClinicaTrials.gov of Synergo but this is not sponsored by the company (NCT01955408).

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
NA	NA	NA	NA	NA	NA	NA

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results			Company comments
Arends (2016a) **Prior publications:** **Arends et al (2015)**	**Size of study groups**	**Treatment**	Papillary: Synergo + MMC (n=68) CIS: Synergo + MMC (n=21)	RCT
		Control	Papillary: BCG (n=74) CIS: BCG (n=22)	
	Study duration	**Time unit**	24 months follow-up	
	Type of analysis	**Intention-to-treat/per protocol**	ITT and PP	
	Outcome	**Name**	ITT Recurrence-free survival (RFS) (n=142)	
		Unit	%	
	Effect size	**Value**	Synergo RITE+MMC: 78.1% BCG: 64.8% Please note the authors updated the results in light of a change in the definition of risk (Babjuk [2011]). Under the new risk classification, the number of high-risk patients was 85 in the intention-to-treat analyses, resulting in	

Study	Results				Company comments
				significantly higher recurrence-free survival for this subgroup of patients (p = 0.043) Arends (2016b).	
			95% CI	Synergo RITE+MMC: 65.2% to 86.7% BCG: 52.2% to 74.9%	
		Statistical test	**Type**	Primary endpoint: Kaplan-Meier survival analysis with log-rank test.	
			p value	P=0.08	
		Other outcome	**Name**	Per protocol (at least 6 treatments) RFS (n=132):	
			Unit	%	
		Effect size	**Value**	Synergo RITE+MMC 81.8% BCG 64.8%	
			95% CI	Synergo RITE+MMC 68.7% to 89.8% BCG: 52.2% to 74.9%	
		Statistical test	**Type**	Primary endpoint: Kaplan-Meier survival analysis with log-rank test.	
			p value	P=0.02	
		Other outcome	**Name**	CIS patients only: CR	
			Unit	%	
		Effect size	**Value**	Synergo RITE+MMC: 89% BCG: 86%	
			95% CI	NR	
		Statistical test	**Type**	**Secondary end points**: count and percentage compared between the groups with the Fisher exact test.	
			p value	*P*=1	

<table>
<tr><th>Study</th><th>Results</th><th>Company comments</th></tr>
<tr><td></td><td>
<table>
<tr><td>Other outcome</td><td>Name</td><td>Progression to MIBC:</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>Synergo RITE+MMC: 0/68
BCG: 1/74 (1.4%)</td></tr>
<tr><td></td><td>95% CI</td><td>NR</td></tr>
<tr><td>Statistical test</td><td>Type</td><td>Secondary end points: count and percentage compared between the groups with the Fisher exact test.</td></tr>
<tr><td></td><td>p value</td><td>P=1</td></tr>
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<tr><td>Tan (2019)

Prior publications:
Tan (2017a, 2017b)</td><td>
<table>
<tr><td>Size of study groups</td><td>Treatment</td><td>Total
Synergo + MMC (n=48)
CIS:
Synergo + MMC (n=21)</td></tr>
<tr><td></td><td>Control</td><td>Total:
Control (BCG or institutional standard) (n=56)
CIS:
Control (BCG or institutional standard) (n=28)</td></tr>
<tr><td>Study duration</td><td>Time unit</td><td>24 months</td></tr>
<tr><td>Type of analysis</td><td>Intention-to-treat/per protocol</td><td>ITT</td></tr>
<tr><td>Outcome</td><td>Name</td><td>CR rate of patients with CIS at baseline (pre-planned subgroup)*</td></tr>
</table>
</td><td>RCT

** inter-publication conflicting reports: in both Tan et al (2017a, 2017b) abstracts report the CR rate of patients with CIS at baseline as:
Synergo + MMC: 75%
Control: 80%
P=0.62

Neither these percentages nor the ones reported above fit with whole numbers of</td></tr>
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Study	Results			Company comments
			Unit	% at 3 months	participants, given the denominators. The study also reported relevant analysis of the effect of RITE on patients with CIS at baseline. This showed that the detrimental effect on DFS was marked in those with concurrent papillary and CIS disease (n = 22) compared to those with CIS only (n = 49; Fig. 3). There was no evidence of a differential treatment effect in CIS only patients (HR 1.53, 95% CI 0.77–3.05, p = 0.22).
		Effect size	**Value**	Synergo + MMC: 30% Control: 47%	
			95% CI	OR 0.43, 95% CI, 0.18–1.28	
		Statistical test	**Type**	Kaplan-Meier method was used to assess time-to-event outcomes; treatment arms were compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HRs)	
			p value	*P*=0.15	
		Other outcome	**Name**	Overall DFS	
			Unit	% at 24 months	
		Effect size	**Value**	Synergo + MMC: 35% Control: 41%	
			95% CI	HR 1.33, 95% CI, 0.84–2.10	
		Statistical test	**Type**	Kaplan-Meier method was used to assess time-to-event outcomes; multivariable Cox regression model with stratification factors (CIS status and therapy history) included as covariates to give adjusted HRs and *P* values as a sensitivity analysis.	
			p value	*P*=0.23; adjusted *P*=0.49	
		Other outcome	**Name**	DFS in patients with CIS at baseline	
			Unit	% at 24 months	
		Effect size	**Value**	HR 2.06 (i.e. Synergo + MMC had lower DFS than control)	

Study	Results			Company comments
			95% CI	95% CI 1.17–3.62
		Statistical test	Type	Kaplan-Meier method was used to assess time-to-event outcomes; treatment arms were compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HRs)
			p value	*P*=0.01
		Other outcome	Name	DFS in non-CIS patients
			Unit	% at 24 months
		Effect size	Value	Synergo + MMC: 53% Control: 24%
			95% CI	HR 0.50, 95% CI 0.22–1.17
		Statistical test	Type	Kaplan-Meier method was used to assess time-to-event outcomes; treatment arms were compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HRs)
			p value	*P*=0.11
		Other outcome	Name	PFS
			Unit	% at 24 months
		Effect size	Value	Synergo + MMC: 83% Control: 87%
			95% CI	NR
		Statistical test	Type	Kaplan-Meier method was used to assess time-to-event outcomes; treatment arms were compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HRs)

Study	Results				Company comments
			p value	*P*=0.16	
		Other outcome	**Name**	OS	
			Unit	% at 24 months	
		Effect size	**Value**	Synergo + MMC: 85% Control: 90%	
			95% CI	NR	
		Statistical test	**Type**	Kaplan-Meier method was used to assess time-to-event outcomes; treatment arms were compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HRs)	
			p value	*P*=0.18	
		Other outcome	**Name**	RFS	
			Unit	% at 24 months	
		Effect size	**Value**	Synergo + MMC: 23% Control: 40%	
			95% CI	NR	
		Statistical test	**Type**	Kaplan-Meier method was used to assess time-to-event outcomes; treatment arms were compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HRs)	
			p value	*P*=.98	
		Other outcome	**Name**	DSS	
			Unit	% at 24 months	
		Effect size	**Value**	Synergo + MMC: 89% Control: 96%	
			95% CI	NR	
		Statistical	**Type**	Kaplan-Meier method was used to assess time-to-event outcomes; treatment arms were	

Study	Results			Company comments
	test		compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HRs)	
		p value	*P*=0.04	
Colombo (2003) **Extended follow-up publications:** **Colombo (2011)**	**Size of study groups**	**Treatment**	Total: Synergo + MMC (n=42) Evaluated for efficacy (per-protocol): Synergo + MMC (n=35)	RCT Extended follow-up publications: Colombo (2011)
		Control	Total: MMC (n=41) Evaluated for efficacy (per-protocol): MMC (n=40)	
	Study duration	**Time unit**	24 months follow-up	
	Type of analysis	**Intention-to-treat/per protocol**	PP	
	Outcome	**Name**	**Recurrence**	
		Unit	%	
	Effect size	**Value**	Synergo RITE+MMC: 6/35 (17%) MMC: 23/40 (58%)	
		95% CI	Hazard ratio for chemotherapy alone v chemotherapy with Synergo, 4.821; 95% CI, 1.953 to 11.899	
	Statistical test	**Type**	Kaplan-Meier survival analysis with log-rank test.	
		p value	*P*=0.0002	

Study	Results			Company comments
	Other outcome	**Name**	Progression to MIBC	
		Unit	%	
	Effect size	**Value**	Synergo RITE+MMC: 0/41 MMC: 1/40 (3%)	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	*P*=1	
	Study duration	**Time unit**	10-year follow-up	
	Other outcome	**Name**	**DFS rates**	
		Unit	%	
	Effect size	**Value**	Crude rate: Synergo RITE + MMC: 60.0%; MMC: 20.0% 5-year KM estimated: 61.7% vs. 21.3% 10-year KM estimated: 52.8% vs. 14.6%	
		95% CI	NR	
	Statistical test	**Type**	Kaplan-Meier survival analysis with log-rank test.	
		p value	*P*<0.001	
	Other outcome	**Name**	At end of follow up: **Recurrence**	
		Unit	%	
	Effect size	**Value**	Synergo RITE + MMC: 14/35 (40%); MMC: 32/40 (80%)	
		95% CI	NR	
	Statistical	**Type**	Kaplan-Meier survival analysis with log-rank test.	

Study	Results				Company comments
		test	**p value**	*P*<0.001	
		Other outcome	**Name**	**Disease progression**	
			Unit	%	
		Effect size	**Value**	Tumour progression (T > T1): Synergo RITE + MMC: 2/35 (6%); MMC: 3/40 (8%)	
			95% CI	NR	
		Statistical test	**Type**	NR	
			p value	NR	
		Other outcome	**Name**	**Rates of radical cystectomy (RC)**	
			Unit	%	
		Effect size	**Value**	RC for superficial disease: Synergo RITE + MMC: 1/35 (2.9%); MMC: 3/40 (7.5%)	
			95% CI	NR	
		Statistical test	**Type**	Kaplan-Meier survival analysis with log-rank test.	
			p value	*P*=0.129	
		Other outcome	**Name**	Bladder preservation at 10 years	
			Unit	%	
		Effect size	**Value**	Synergo RITE+MMC: 86.1% MMC: 78.9%	
			95% CI	NR	
		Statistical test	**Type**	Kaplan-Meier survival analysis with log-rank test.	
			p value	*P*=0.129	

Study	Results			Company comments
	Other outcome	**Name**	**Mortality**	
		Unit	Patients	
	Effect size	**Value**	**Total death:** Synergo RITE + MMC: 6 patients; MMC: 9 patients **Rate of cancer-related deaths.** Could not be established, as the cause of death was missing in five patients.	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	NR	
Ayres (2018) (conference abstract) **Prior publications:** **Ayres (2017) (conference abstract)** **Ayres (2012) (conference abstract)** **Ayres (2010) (conference abstract)**	**Size of study groups**	**Treatment**	Synergo + MMC (n=135)	Case series; abstracts only
		Control	NA	
	Study duration	**Time unit**	10 years	
	Type of analysis	**Intention-to-treat/per protocol**	PP	
	Outcome	**Name**	RFS	
		Unit	%	
	Effect size	**Value**	1 year: 63% 5 years: 34% 10 years: 24%	
		95% CI	NR	
	Statistical	**Type**	NA	

Study	Results			Company comments
	test	p value	NA	
	Other outcome	Name	PFS	
		Unit	%	
	Effect size	Value	1 year: 92% 5 years: 71% 10 years: 62%	
		95% CI	NR	
	Statistical test	Type	NR	
		p value	NR	
	Other outcome	Name	**OS**	
		Unit	%	
	Effect size	Value	1 year: 98% 5 years: 63% 10 years: 54%	
		95% CI	NR	
	Statistical test	Type	NR	
		p value	NR	
	Other outcome	Name	**DSS**	
		Unit	%	
	Effect size	Value	1 year: 100% 5 years: 79% 10 years: 75%	
		95% CI	NR	
	Statistica	Type	NR	

Study	Results				Company comments
		l test	**p value**	NR	
		Other outcome	**Name**	**Progression**	
			Unit	%	
		Effect size	**Value**	To MIBC: 11 (8%) Prostatic urethral stromal disease: 6 (5%)	
			95% CI	NR	
		Statistical test	**Type**	NR	
			p value	NR	
		Other outcome	**Name**	**Metastatic** disease	
			Unit	%	
		Effect size	**Value**	Metastatic disease: 6 (5%), including 2 patients with inguinal node involvement Subsequent upper urinary tract recurrences: 8 (6%)	
			95% CI	NR	
		Statistical test	**Type**	NR	
			p value	NR	
		Other outcome	**Name**	**Cystectomy rate**	
			Unit	%	
		Effect size	**Value**	10 years: 30 (23%) including 20 patients with persistent CIS	
			95% CI	NR	
		Statistica	**Type**	NR	

<table>
<tr><th>Study</th><th>Results</th><th>Company comments</th></tr>
<tr><td></td><td><table>
<tr><td>I test</td><td>p value</td><td>NR</td></tr>
</table></td><td></td></tr>
<tr><td>Kilb (2018) (conference abstract)</td><td><table>
<tr><td rowspan="2">Size of study groups</td><td>Treatment</td><td>Synergo RITE + MMC (67)</td></tr>
<tr><td>Control</td><td>NA</td></tr>
<tr><td>Study duration</td><td>Time unit</td><td>5 years</td></tr>
<tr><td>Type of analysis</td><td>Intention-to-treat/per protocol</td><td>ITT</td></tr>
<tr><td rowspan="2">Outcome</td><td>Name</td><td>Tumor persistence at week 11 after induction therapy</td></tr>
<tr><td>Unit</td><td>%</td></tr>
<tr><td rowspan="2">Effect size</td><td>Value</td><td>10/67 (14.9%)</td></tr>
<tr><td>95% CI</td><td>NR</td></tr>
<tr><td rowspan="2">Statistical test</td><td>Type</td><td>NR</td></tr>
<tr><td>p value</td><td>NR</td></tr>
<tr><td rowspan="2">Other outcome</td><td>Name</td><td>Recurrence-free time</td></tr>
<tr><td>Unit</td><td>Years</td></tr>
<tr><td rowspan="2">Effect size</td><td>Value</td><td>Mean 3.5 years</td></tr>
<tr><td>95% CI</td><td>NR</td></tr>
<tr><td rowspan="2">Statistical test</td><td>Type</td><td>NR</td></tr>
<tr><td>p value</td><td>NR</td></tr>
</table></td><td>Case series; abstract only</td></tr>
</table>

Study	Results			Company comments
	Other outcome	**Name**	Progression	
		Unit	%	
	Effect size	**Value**	10.4% progressed to MIBC including 6% metastatic tumors, high risk NMIBC was observed in 6% resulting in cystectomy and low risk NMIBC recurrence was 1.5% with organ preservation.	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
	Other outcome	**Name**	**Bladder preservation rate**	
		Unit	%	
	Effect size	**Value**	3 months: 94.0% 5 years: 53.8%	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	NR	
	Other outcome	**Name**	**Bladder cancer death rate**	
		Unit	%	
	Effect size	**Value**	1/67 (1.5%)	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	NR	
Erturhan (2015)				Case series

<table>
<tr><th>Study</th><th>Results</th><th>Company comments</th></tr>
<tr><td></td><td>
<table>
<tr><td>Size of study groups</td><td>Treatment</td><td>Synergo RITE + MMC (26)</td></tr>
<tr><td></td><td>Control</td><td>NR</td></tr>
<tr><td>Study duration</td><td>Time unit</td><td>Median follow-up time of 16.4 months</td></tr>
<tr><td>Type of analysis</td><td>Intention-to-treat/per protocol</td><td>ITT</td></tr>
<tr><td>Outcome</td><td>Name</td><td>Recurrence</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>3/26 (11.5%)</td></tr>
<tr><td></td><td>95% CI</td><td>NR</td></tr>
<tr><td>Statistical test</td><td>Type</td><td>NR</td></tr>
<tr><td></td><td>p value</td><td>NR</td></tr>
<tr><td>Other outcome</td><td>Name</td><td>Recurrence-free survival</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>88.4%</td></tr>
<tr><td></td><td>95% CI</td><td>NR</td></tr>
<tr><td>Statistical test</td><td>Type</td><td>NR</td></tr>
<tr><td></td><td>p value</td><td>NR</td></tr>
</table>
</td><td></td></tr>
<tr><td>Kiss (2015)</td><td>
<table>
<tr><td>Size of study groups</td><td>Treatment</td><td>21</td></tr>
<tr><td></td><td>Control</td><td>NA</td></tr>
</table>
</td><td>Case series</td></tr>
</table>

Study	Results			Company comments
	Study duration	**Time unit**	Median 50 (range 1 to 120) months	
	Type of analysis	**Intention-to-treat/per protocol**	ITT	
	Outcome	**Name**	**Overall recurrence**	
		Unit	%	
	Effect size	**Value**	71% (15/21)	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	NR	
	Outcome	**Name**	**Cystectomy**	
		Unit	%	
	Effect size	**Value**	29% (6/21) due to multifocal recurrence or progression	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	NR	
	Outcome	**Name**	**OS**	
		Unit	%	
	Effect size	**Value**	67% (14/21)	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	NR	

Study	Results			Company comments
	Outcome	**Name**	**Progression requiring cystectomy**	
		Unit	%	
	Effect size	**Value**	19% (4/21)	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	NR	
	Outcome	**Name**	**Disease-specific mortality**	
		Unit	%	
	Effect size	**Value**	2/21 (9.5%)	
		95% CI	NR	
	Statistical test	**Type**	NR	
		p value	NR	
Luedecke (2015) (conference abstract)	**Size of study groups**	**Treatment**	271	Case series; abstract only
		Control	NA	
	Study duration	**Time unit**	Average follow-up time 2.2 years (range 28 days - 12.9 years)	
	Type of analysis	**Intention-to-treat/per protocol**	ITT	
	Outcome	**Name**	**Response**	
		Unit	%	
	Effect size	**Value**	Complete response: 76.1% Partial response: 7.6% No change in tumor status: 16.3%	

Study	Results			Company comments
			95% CI	NR
		Statistical test	Type	NA
			p value	NA
		Other outcome	Name	**Tumor-free**
			Unit	%
		Effect size	Value	**Tumor-free for 28 months:** 76.8% out of the group of patients with completed induction and maintenance therapy **Tumour-free rate at 2-year follow-up:** 80.6%
			95% CI	NR
		Statistical test	Type	NA
			p value	NA
		Other outcome	Name	**Recurrence rate at 2-year follow-up:**
			Unit	%
		Effect size	Value	19.4%
			95% CI	NR
		Statistical test	Type	NA
			p value	NA
Arends (2014)		**Size of study**	**Treatment**	**Synergo + MMC (140)** Due to MMC allergy, additional 20 patients (12.5%) were treated with Synergo + EPI.	Case series

Study	Results				Company comments
		groups	**Control**		
		Study duration	**Time unit**	Median follow-up was 75.6 months	
		Type of analysis	**Intention-to-treat/per protocol**	ITT	
		Outcome	**Name**	**RFS overall**	
			Unit	%	
		Effect size	**Value**	1 year: 59.5% 2 years: 47.0%	
			95% CI	NR	
		Statistical test	**Type**	Kaplan-Meier plots were used to calculate RFS. The log rank test was used to compare subgroups. The Cox proportional hazard model was used to adjust for potential confounding variables.	
			p value	NR	
		Other outcome	**Name**	**RFS by treatment group**	
			Unit	%	
		Effect size	**Value**	**Synergo + MMC:** 1 year RFS: 58.9% 2 years RFS: 45.9% **Synergo + Epirubicin:** 1 year RFS: 63.6% 2 years RFS: 54.5%	
			95% CI	NR	
		Statistical test	**Type**	Kaplan-Meier plots were used to calculate RFS. The log rank test was used to compare subgroups. The Cox proportional hazard model was used to adjust for potential confounding	

<table>
<tr><th>Study</th><th>Results</th><th>Company comments</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>variables.</td></tr>
<tr><td></td><td>p value</td><td>P=0.30</td></tr>
</table>
<table>
<tr><td>Other outcome</td><td>Name</td><td>Progression in total group</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>7/160 (4.3%)</td></tr>
<tr><td></td><td>95% CI</td><td>NR</td></tr>
<tr><td>Statistical test</td><td>Type</td><td>NA</td></tr>
<tr><td></td><td>p value</td><td>NA</td></tr>
<tr><td>Other outcome</td><td>Name</td><td>Initial CR rate 6 weeks after the induction phase and negative cytology in the ablative group</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>41/53 (77.5%)</td></tr>
<tr><td></td><td>95% CI</td><td>NR</td></tr>
<tr><td>Statistical test</td><td>Type</td><td>NA</td></tr>
<tr><td></td><td>p value</td><td>NA</td></tr>
</table>
</td><td></td></tr>
<tr><td>Maffezzini (2014)</td><td>
<table>
<tr><td>Size of study groups</td><td>Treatment</td><td>CHT + MMC (32)
CHT + epirubicin in cases of persistent intolerance to MMC (10)</td></tr>
<tr><td></td><td>Control</td><td>NR</td></tr>
<tr><td>Study duration</td><td>Time unit</td><td>Median 38 (range 4 to 73) months</td></tr>
</table>
</td><td>Case series</td></tr>
</table>

Study	Results			Company comments
	Type of analysis	**Intention-to-treat/per protocol**	ITT	
	Outcome	**Name**	**DFS**	
		Unit	%	
	Effect size	**Value**	Before study: no evidence of disease 14.9% (95% CI 5.5 to 28.8) vs 88.8% (95% CI 73.7 to 94.8) after CHT	
		95% CI	NR	
	Statistical test	**Type**	Kaplan–Meier estimates and log-rank test	
		p value	*P*<0.0001.	
	Other outcome	**Name**	**Recurrence**	
		Unit	%	
	Effect size	**Value**	13/42 (30.9%)	
		95% CI	NR	
	Statistical test	**Type**	Kaplan–Meier estimates of the cumulative probability of recurrence	
		p value	NA	
	Other outcome	**Name**	**Progression to pT2**	
		Unit	%	
	Effect size	**Value**	5/42 (12%)	
		95% CI	NR	
	Statistical	**Type**	NA	

Study	Results	Company comments
	test: p value: NA Other outcome: Name: Radical cystectomy; Unit: % Effect size: Value: 7/42 (16.6%); 95% CI: NR Statistical test: Type: NA; p value: NA	
Moskovitz (2005)	Size of study groups: Treatment: 32 analysed: Prophylactic group (22) Ablative group (10); Control: NA Study duration: Time unit: Median follow up 10 months Type of analysis: Intention-to-treat/per protocol: PP Other outcome: Name: Complete response in ablative group; Unit: % Effect size: Value: 8/10 (80%); 95% CI: NR Statistical test: Type: NA; p value: NA	Case series

<table>
<tr><th>Study</th><th>Results</th><th>Company comments</th></tr>
<tr><td></td><td>
<table>
<tr><td>Outcome</td><td>Name</td><td>Recurrence</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>Prophylactic group at 10 months: 2/22 (9%)
Ablative group at 9 months: 2/10 (20%)</td></tr>
<tr><td></td><td>95% CI</td><td>NR</td></tr>
<tr><td>Statistical test</td><td>Type</td><td>NA</td></tr>
<tr><td></td><td>p value</td><td>NA</td></tr>
<tr><td>Other outcome</td><td>Name</td><td>Progression</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>None</td></tr>
<tr><td></td><td>95% CI</td><td>NR</td></tr>
<tr><td>Statistical test</td><td>Type</td><td>NA</td></tr>
<tr><td></td><td>p value</td><td>NA</td></tr>
</table>
</td><td></td></tr>
<tr><td>Gofrit (2004)</td><td>
<table>
<tr><td>Size of study groups</td><td>Treatment</td><td>The prophylactic protocol was administered to 24 patients.
The ablative protocol was given to 28 patients.</td></tr>
<tr><td></td><td>Control</td><td>NA</td></tr>
<tr><td>Study duration</td><td>Time unit</td><td>Median follow-up of 15.2 months (mean 23, range 6 to 90)</td></tr>
<tr><td>Type of analysis</td><td>Intention-to-treat/per protocol</td><td>ITT</td></tr>
</table>
<table>
<tr><td>Outcome</td><td>Name</td><td>Response (ablative group)</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
</table>
</td><td>Case series</td></tr>
</table>

Study	Results	Company comments

Effect size	Value	Ablative group: Complete response (i.e. complete ablation of tumor): 21/28 (75%) 7/28 (25%) non-responders discontinued treatment; 4 of the non-responders were treated with radical cystectomy and 3 with transurethral resection only.
	95% CI	NR
Statistical test	Type	NA
	p value	NA

Outcome	Name	Recurrence
	Unit	%
Effect size	Value	**Prophylactic group**: 15/24 (62.5%) recurrence-free at mean follow up 35.3 months; 9/2 (37.5%) had recurrence after mean 10 months. **Ablative group**: 21 original responders entered the follow-up program; 4/21 (19%) of them developed tumor recurrence after an average period of 13.7 months from the tumor eradication date. After a mean follow-up of 20 months from the complete eradication date, 17/21 initial responders (80.9%) were recurrence free.
	95% CI	NR
Statistical test	Type	NA
	p value	NA

Study	Results			Company comments
	Other outcome	**Name**	**Radical cystectomy**	
		Unit	%	
	Effect size	**Value**	Prophylactic group: 1/24 (4.2%) Ablative group: 4/28 (14.3%) early non-responders plus 2/21 (9.5%) in the follow up program who had recurrence	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
	Other outcome	**Name**	**Bladder preservation**	
		Unit	%	
	Effect size	**Value**	Prophylactic group: 23/24 (95.8%) Ablative group: 22/28 (78.6%)	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
Colombo (2001)	**Size of study groups**	**Treatment**	MMC intravesically administered in combination with local hyperthermia (Synergo) (29)	Case series
		Control	Standard intravesical chemotherapy (ICT) using MMC solution (36) MMC administered according to the electromotive drug administration (EMDA) technique (15)	
	Study duration	**Time unit**	7–10 days after treatment completion	
	Type of analysis	**Intention-to-treat/per**	ITT	

Study	Results			Company comments
		protocol		
	Outcome	Name	Complete response	
		Unit	%	
	Effect size	Value	Standard intravesical chemotherapy (ICT) using MMC solution 10/36 (27.7%) MMC intravesically administered in combination with local hyperthermia (Synergo) 19/29 (66.0%) MMC administered according to the electromotive drug administration (EMDA) technique 6/15 (40%)	
		95% CI	NR	
	Statistical test	Type	NA	
		p value	NA	
Brummelhuis (2021)				Case series
	Size of study groups	Treatment	≥6 treatment sessions of RF-CHT (274, of whom 146 had papillary disease and 128 (concomitant) CIS)	
		Control	NA	
	Study duration	Time unit	Median follow-up was 55.5 months.	
	Type of analysis	Intention-to-treat/per protocol	PP	
	Outcome	Name	**CR** (excluding the 124 patients with papillary tumor treated with complete TURB and 13 patients with missing follow up data at 6 months, i.e. 137 patients, of whom 116 had CIS and 21	

Study	Results				Company comments
				papillary)	
			Unit	%	
		Effect size	**Value**	CIS and papillary patients with tumor at baseline 76/137 (55.5%): of whom: (Concomitant) CIS 65/116 (56.0%) Papillary 11/ 21 (52.4%) The CR rate at six months in the BCG refractory subgroup was 54.5% for CIS patients (48/88 with available follow-up data at six months) and 43.8% (7/16) for patients with residual papillary tumor at baseline.	
			95% CI	NR	
		Statistical test	**Type**	NA	
			p value	NA	
		Other outcome	**Name**	**Durable response rate** of patients with (concomitant) CIS or RFS for patients with papillary disease.	
			Unit	%	
		Effect size	**Value**	Durable response rates of patients with (concomitant) CIS at one-, two-, and five-years were 79.7%, 66.5%, and 40.3%, respectively (n=70). The RFS rates for patients with papillary disease at one-, two-, and five-years were 77.9%, 57.5%, and 37.2%, respectively (n=134). In the subgroup of BCG refractory patients, durable response rates (for CIS patients, n = 52) were 79.2%, 65.5%, 38.7%, and RFS rates (for	

Study	Results				Company comments
				papillary patients, n = 68) were 72.5%, 54.0%, 31.7%, at one-, two- and five years, respectively.	
			95% CI	% 1-Year RFS (95% CI); % 2-Year RFS (95% CI); % 5-Year RFS (95% CI) Overall (n = 204): 78.6 (72.9–84.3); 60.3 (53.2–67.4); 38.1 (30.5–45.7) Baseline histology: (concomitant) CIS (n = 70): 79.7 (69.7–89.7); 66.5 (54.3–78.7); 40.3 (25.2–55.4) Papillary (n = 134): 77.9 (70.8–85.0); 57.5 (48.9–66.1); 37.2 (28.4–46.0)	
		Statistical test	**Type**	NA	
			p value	NA	
		Other outcome	**Name**	**Progression to MIBC**	
			Unit	%	
		Effect size	**Value**	In total, 22 (8.5%) of all patients progressed to MIBC, of whom 20 had a high-grade tumor prior to RF-CHT and all 22 patients previously have been treated with BCG (21 BCG refractory, 1 unknown reason for BCG discontinuation). Eleven (4.3%) patients had distant metastases up to one year after treatment.	
			95% CI	NR	
		Statistical test	**Type**	NA	
			p value	NA	
		Other	**Name**	**Overall Survival (OS), Relative Survival (RS) and Cancer Specific Survival)**	

Study	Results				Company comments
		outcome	**Unit**	%	
		Effect size	**Value**	Follow-up data of 249 (91%), 212 (77%), 129 (47%) and 59 (22%) patients was available for at least one, two, five and ten years, respectively. 105/274 (38.3%) patients died in the period from start of RF-CHT to the moment of retrieving data from the registry of the Statistics Netherlands (CBS; December 2019), a median time 91.5 months. Within the BCG refractory subgroup, the OS rates were 70.5% and 43.9%, Relative survival (RS) rates 78.6% and 57.5% and cancer-specific survival (CSS) rates 85.7% and 73.1%, at 5 and 10 years, respectively.	
			95% CI	Survival (n = 274): 5-Year, % (95% CI); 10-Year, % (95% CI) OS: 72.3 (66.4–87.2); 51.0 (43.4–58.6) RS: 80.6 (74.0–87.1); 65.1 (55.2–75.1) CSS: 86.6 (81.7–91.5); 77.6 (70.3–84.9)	
		Statistical test	**Type**	NA	
			p value	NA	
		Other outcome	**Name**	**Radical cystectomy**	
			Unit	%	
		Effect size	**Value**	80/274 patients (29.2%) received a radical cystectomy with or without neoadjuvant chemotherapy.	
			95% CI	NR	
		Statistical	**Type**	NA	

Study	Results			Company comments
	test	**p value**	NA	
	Other outcome	**Name**	**Bladder preservation**	
		Unit	%	
	Effect size	**Value**	194/274 (70.8%). The median time from last TURB to cystectomy was 18 months. In 76.0% of patients, a radical cystectomy could be prevented for two years from last TURB, and in 61.1% a radical cystectomy could be prevented for five years.	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
van Valenberg (2018)	**Size of study groups**	**Treatment**	Synergo + MMC (150)	Case series
		Control	NA	
	Study duration	**Time unit**	The mean time of follow-up for the overall group (n=150), BCG-unresponsive patients (n=50), other BCG-treated patients (n=46, missing n=4), and treatment naive patients (n=47, missing n=3) was 35.8 months, 27.5 months, 38.5 months, and 40.6 months, respectively.	
	Type of analysis	**Intention-to-treat/per protocol**	PP	
	Outcome	**Name**	**CR at 6 months**	

Study	Results			Company comments
		Unit	%	
	Effect size	**Value**	Overall CIS: 96/143 (66.2%); 7 missing BCG- unresponsive CIS: 23/50 (46.0%) Other BCG-treated CIS: 33/46 (71.7%); 4 missing Treatment-naïve: 39/47 (83.0%); 3 missing	
		95% CI	NR	
	Statistical test	**Type**	Complete response was assessed and compared between BCG-unresponsive, other BCG-treated, and treatment naïve patients using the chi-square test.	
		p value	Significant difference between BCG-unresponsive, other BCG-treated, and treatment naïve CIS patients, $p < 0.001$.	
	Other outcome	**Name**	**Recurrence**	
		Unit	2-year recurrence rate n (% of patients with CR)	
	Effect size	**Value**	Overall CIS: 18/96 (18.8%) BCG- unresponsive CIS: 4/23 (17.4%) Other BCG-treated CIS: 9/33 (27.3%) Treatment-naïve: 5/39 (12.8%)	
		95% CI	NR	
	Statistical test	**Type**	Kaplan-Meier analysis with Mantel-Cox log rank tests	
		p value	In patients with a CR, the subsequent recurrence rate after 2 years of follow-up did not differ significantly between any of the groups	
	Other outcome	**Name**	**Recurrence-free survival**	
		Unit	2-year RFS cumulative surviving proportion (%)	

Study	Results				Company comments
		Effect size	**Value**	Overall CIS: 74.5% BCG- unresponsive CIS: 68.9% Other BCG-treated CIS: 68.6% Treatment-naïve: 83.6%	
			95% CI	NR	
		Statistical test	**Type**	Kaplan-Meier analysis with Mantel-Cox log rank tests	
			p value	No significant difference between BCG-unresponsive, other BCG-treated, and treatment naive CIS patients was observed, p = 0.08.	
		Other outcome	**Name**	**Progression** to MIBC with or without lymph node or distant metastasis at final follow-up	
			Unit	%	
		Effect size	**Value**	Overall CIS: 13.3% BCG- unresponsive CIS: 16.0% Other BCG-treated CIS: 13.0% Treatment-naïve: 10.6%	
			95% CI	NR	
		Statistical test	**Type**	Chi-square test	
			p value	P=0.74	
		Other outcome	**Name**	**Bladder preservation rate at final follow-up**	
			Unit	%	
		Effect size	**Value**	Overall CIS: 113/144 (78.5%); 6 missing BCG- unresponsive CIS: 35/49 (71.4%); 1 missing Other BCG-treated CIS: 37/44 (84.1%); 6 missing Treatment-naïve: 39/45 (86.7%); 5 missing	

Study	Results				Company comments
			95% CI	NR	
		Statistical test	**Type**	Chi-squared test	
			p value	Significant difference between BCG-unresponsive and both other BCG-treated and treatment naive CIS patients (p = 0.006).	
		Other outcome	**Name**	**Cystectomy-free time**	
			Unit	Months	
		Effect size	**Value**	Overall CIS: 99.9 months BCG- unresponsive CIS: 45.2 months	
			95% CI	Overall CIS: 86.7 to 113.1 months BCG- unresponsive CIS: 35.7 to 54.7 months	
		Statistical test	**Type**	Kaplan-Meier analysis with Mantel-Cox log rank tests	
			p value	Differed significantly between BCG-unresponsive and both other BCG-treated and treatment naive patients (p = 0.006)	
		Other outcome	**Name**	**Survival at final follow up**	
			Unit	%	
		Effect size	**Value**	Overall CIS: 117/150 (78.0%) BCG- unresponsive CIS: 38/50 (76.0%) Other BCG-treated CIS: 32/46 (69.6%); 4 missing Treatment-naïve: 41/47 (87.2%); 3 missing	
			95% CI	NR	
		Statistical test	**Type**	Chi squared test	
			p value	Trend towards a significant difference between other BCG-treated and treatment naive CIS patients, P=0.06.	
		Other outcome	**Name**	**Mean survival time**	
			Unit	Months	

Study	Results				Company comments
		Effect size	**Value**	Overall CIS: 89.5 months BCG- unresponsive CIS: 79.7 months	
			95% CI	Overall CIS: 74.7 to 104.8 months BCG- unresponsive CIS: 65.2 to 94.3 months	
		Statistical test	**Type**	Kaplan-Meier analysis with Mantel-Cox log rank tests	
			p value	A trend towards a significant difference between other BCG-treated and treatment naive CIS patients was observed, p = 0.06	
		Other outcome	**Name**	**Relative survival** was determined, defined as the ratio of overall survival of the patients by the survival of a similar general Dutch population matched on age, sex and calendar year and was used as an approximation of cancer-specific survival.	
			Unit	%	
		Effect size	**Value**	Overall: 89% after 3 years and 84% after 5 years of follow-up	
			95% CI	95% confidence intervals overlapped substantially between the actually observed overall survival and the relative survival.	
		Statistical test	**Type**	NA	
			p value	NA	
Moskovitz (2012)		**Size of study groups**	**Treatment**	Synergo + MMC (92, of which 66 adjuvant and 26 neoadjuvant)	Case series
			Control	NA	
		Study duration	**Time unit**	Median follow up 23 months (range 3 months up to 7 years)	

Study	Results			Company comments
	Type of analysis	**Intention-to-treat/per protocol**	PP and ITT	
	Outcome	**Name**	**Neoadjuvant protocol: initial response**	
		Unit	%	
	Effect size	**Value**	Neoadjuvant protocol (PP analysis): CR: 19/24 patients (79.2%), Partial response: 2/24 (8.3%), No change: 3/24 (12.5%). Neoadjuvant protocol (ITT analysis): CR: 19/26 patients (73.1%).	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
	Outcome	**Name**	**Neoadjuvant protocol: durable response**	
		Unit	%	
	Effect size	**Value**	Neoadjuvant protocol (PP analysis): The 19 complete responders continued follow-up for a mean time of 18 months (median: 9 months; range: 2 months to 8 years). During this time, 16 patients (84%) remained tumor free and three patients (16%) were diagnosed with a tumor recurrence; so a durable response was observed in 16/24 patients (67%). Neoadjuvant protocol (ITT analysis): Durable response: 16/26 (61.5%)	
		95% CI	NR	
	Statistical	**Type**	NA	

Study	Results			Company comments
	test	p value	NA	

Outcome	Name	**Adjuvant protocol: Tumor recurrence**
	Unit	%
Effect size	Value	Adjuvant protocol (PP analysis): 18/64 patients (28%) Recurrence rate at 2 years was 32.8%
	95% CI	NR
Statistical test	Type	NA
	p value	NA
Other outcome	Name	**Adjuvant protocol: time to recurrence**
	Unit	Months
Effect size	Value	Adjuvant protocol (PP analysis): Median time to recurrence was 13 months (mean: 19 months; range: 2 months to 7 years).
	95% CI	NR
Statistical test	Type	Kaplan–Meier (KM) method
	p value	NA

Other outcome	Name	**Disease-free survival**
	Unit	Years
Effect size	Value	Adjuvant protocol (PP analysis): Median 6.9 years
	95% CI	NR
Statistical	Type	NA

Study	Results			Company comments
	test	**p value**	NA	
	Other outcome	**Name**	Progression rate to invasive bladder cancer	
		Unit	%	
	Effect size	**Value**	Adjuvant protocol (PP analysis): 3/64 (4.7%).	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
	Other outcome	**Name**	**Radical cystectomy**	
		Unit	%	
	Effect size	**Value**	Adjuvant protocol (PP analysis): 3/64 (4.7%) Neoadjuvant protocol (PP analysis): 2/24 (8.3%)	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
	Other outcome	**Name**	**Bladder preservation rate**	
		Unit	%	
	Effect size	**Value**	Adjuvant protocol (PP analysis): 61/64 (95.3%) Neoadjuvant protocol (PP analysis): 22/24 (91.7%) Neoadjuvant protocol (ITT analysis): 24/26 (92.3%)	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
Witjes (2009)				Case series

Study	Results			Company comments
	Size of study groups	**Treatment**	Synergo + MMC (51)	
		Control	NA	
	Study duration	**Time unit**	Median follow up 22 (range 3 to 77) months	
	Type of analysis	**Intention-to-treat/per protocol**	PP	
	Outcome	**Name**	**Complete biopsy and cytology proven disappearance of CIS at 3 months.**	
		Unit	%	
	Effect size	**Value**	45/49 evaluable (92%). In two additional patients CIS disappeared but the concomitant papillary tumor persisted	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
	Other outcome	**Name**	**Recurrence**	
		Unit	%	
	Effect size	**Value**	Of all 45 complete responders, additional follow-up is available with a mean follow-up of 27 (3–77, median 22) months. Of these 45 patients, 22 (49%) had a recurrence.	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	

<table>
<tr><th>Study</th><th>Results</th><th>Company comments</th></tr>
<tr><td></td><td>
<table>
<tr><td>Other outcome</td><td>Name</td><td>Cystectomy</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>5 had cystectomy due to recurrence and 1 due to a contracted bladder, but he was tumor free (6/49 [12.2%])</td></tr>
<tr><td></td><td>95% CI</td><td>NR</td></tr>
<tr><td>Statistical test</td><td>Type</td><td>NA</td></tr>
<tr><td></td><td>p value</td><td>NA</td></tr>
</table>
</td><td></td></tr>
<tr><td>van der Heijden (2004)</td><td>
<table>
<tr><td>Size of study groups</td><td>Treatment</td><td>Local microwave hyperthermia and chemotherapy (MMC) (90)</td></tr>
<tr><td></td><td>Control</td><td>NA</td></tr>
<tr><td>Study duration</td><td>Time unit</td><td>Median 18 (range 4 to 24) months</td></tr>
<tr><td>Type of analysis</td><td>Intention-to-treat/per protocol</td><td>PP</td></tr>
<tr><td>Outcome</td><td>Name</td><td>Recurrence</td></tr>
<tr><td></td><td>Unit</td><td>%</td></tr>
<tr><td>Effect size</td><td>Value</td><td>Pathology proven tumour recurrence was seen in 14/90 (15.6%) patients, of whom 5 had multiple lesions.

The risk of recurrence after 1 year follow-up was 14.3% (SE 4.5%), while the risk of recurrence was 24.6% (SE 5.9%) after 2 years of follow-up.

For the patients with prior BCG treatment, the</td></tr>
</table>
</td><td>Case series</td></tr>
</table>

Study	Results				Company comments
				risk of recurrence after one year of follow-up was 23.1% (SE 7.7%) and 41.2% (SE 9.9%) after 2 years of follow-up.	
			95% CI	NR	
		Statistical test	**Type**	Kaplan–Meier plots were drawn to assess the risk of recurrence.	
			p value	NA	
		Other outcome	**Name**	**Disease-free**	
			Unit	%	
		Effect size	**Value**	At 24 months, 64% and 92% of patients with high risk TCC and intermediate risk TCC, respectively, were disease free.	
			95% CI	NR	
		Statistical test	**Type**	Kaplan–Meier plots were drawn to assess the risk of recurrence. Statistical significance of differences in risk of recurrence between subgroups was evaluated with the log rank test.	
			p value	P=0:03 between high-risk and intermediate-risk subgroups.	
Nativ (2009)					
		Size of study groups	**Treatment**	Synergo + MMC (n=111)	
			Control	NA	
		Study duration	**Time unit**	Median follow-up was 16 months	
		Type of analysis	**Intention-to-treat/per protocol**	PP (Six patients (5.4%) withdrew from treatment due to adverse events before the first evaluation cystoscopy, including 2 due to MMC allergy and 1 each due to pain, hematuria, difficult catheter insertion and incontinence. Thus, they could not be evaluated, leaving 105	

Study	Results			Company comments
			patients available for efficacy analysis.)	
	Outcome	**Name**	**Recurrence-free probability**	
		Unit	%	
	Effect size	**Value**	85% at 1 year 56% at 2 years	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
	Other outcome	**Name**	**Cystectomy**	
		Unit	%	
	Effect size	**Value**	1/105 (1%)	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	
	Other outcome	**Name**	**2-year recurrence rate**	
		Unit	%	
	Effect size	**Value**	Intermediate-risk patients: 18% High-risk patients: 49% BCG refractory patients: 56%	
		95% CI	NR	
	Statistical test	**Type**	NA	
		p value	NA	

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Arends (2016a) Prior publications: Arends et al (2015)	
How are the findings relevant to the decision problem?	The study included the patient population, intervention, comparator and outcomes relevant to the decision problem as laid out in the scope. It included intermediate- (69%) and high-risk patients (31%); non-CIS: 77.4%; CIS: 22.6% (including CIS only: 13.2% and CIS + papillary: 8.9% plus 1 patient not stated whether CIS was accompanied by papillary or not). It excluded patients who had had intravesical MMC treatments during the previous 12 months or any previous BCG therapy <48 months (i.e. first-line treatment),
Does this evidence support any of the claimed benefits for the technology? If so, which?	This study supports a statistically significant benefit in terms of recurrence among patients receiving at least 6 treatments (P=0.02). It also supported Synergo + MMC as an additional treatment option for people in whom BCG is indicated when supply of the drug is limited or delayed, as the population studied were eligible to receive BCG.
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	The study was underpowered
How was the study funded?	Medical Enterprises (the manufacturer of the Synergo system) provided support and was involved in the design and conduct of the study and the collection and management of the data.

Tan (2019) Prior publications: Tan (2017a, 2017b)	
How are the findings relevant to the decision problem?	The study included the patient population, intervention, comparator and outcomes relevant to the decision problem as laid out in the scope. This study included intermediate- (13.5%) and high-risk patients (86.5%); non-CIS: 31.7%; CIS: 68.3% (including CIS only: 47.1% and CIS + papillary: 21.2%). It included patients with recurrence following induction/maintenance BCG (i.e. second-line treatment). However, the dose of MMC given with the Synergo was inadequate (40mg rather than the 80mg which is standard). Other issues with the RCT include: The treatment arms were unbalanced. A post hoc analysis showed a higher number of concurrent papillary and CIS tumours in the RITE arm than in the control arm (25% vs 16%; p = 0.38). As noted by the authors this group is at increased risk of disease recurrence and progression. There is also no information on whether groups were balanced in respect of BCG failures. The trial was closed early which made it underpowered in respect of the primary endpoint but particularly for the subgroups (see Witjes (2019)).
Does this evidence support any of the claimed benefits for the technology? If so, which?	This study supported Synergo + MMC as an additional treatment option for people in whom BCG is indicated when supply of the drug is limited or delayed, as the population studied were eligible to receive BCG.
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	The study was underpowered
How was the study funded?	This trial was clinician-initiated and led, sponsored by the University College London. Cancer Research UK funded the trial administration (trial number CRUK/09/012). Kyowa Kirin Pharmaceutical Development Ltd. provided funds which helped to fund the

	procurement and maintenance costs of the Synergo system. Medical Enterprises Europe B.V. supplied the Synergo system at a discounted rate and its associated disposables to the participating sites. None of the funders had a role in the study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit the paper for publication.

Colombo (2003) Extended follow-up publications: Colombo (2011)	
How are the findings relevant to the decision problem?	The study included the patient population, intervention, comparator and outcomes relevant to the decision problem as laid out in the scope. This study included Grade 3 patients (21.7%); excluded CIS only; and included 1.2% CIS plus papillary tumors; 98.8% of patients had non-CIS disease. it included patients with either primary (first-line) or recurrent disease (second-line).
Does this evidence support any of the claimed benefits for the technology? If so, which?	This study supports a benefit in terms of recurrence. The combined treatment of Synergo + MMC was noted by the authors to be more expensive and cumbersome than the routine instillation of chemotherapeutic agents or bacilli Calmette-Guerin. A larger catheter must be used and its insertion becomes more invasive.
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	The study was underpowered
How was the study funded?	Funding not stated

Ayres (2018) (conference abstract) Prior publications:

Ayres (2017) (conference abstract) Ayres (2012) (conference abstract) Ayres (2010) (conference abstract)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits. Supports the reduced need for cystectomy in some people who had previously failed BCG, resulting in reduced morbidity and mortality associated with cystectomy.
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence. This study was only reported as abstracts.
How was the study funded?	None

Kilb (2018) (conference abstract)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence. This study was only reported as abstracts.
How was the study funded?	NR

Erturhan (2015)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Kiss (2015)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Luedecke (2015) (conference abstract)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits

Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence. This study was only reported as abstracts.
How was the study funded?	NR

Arends (2014)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Maffezzini (2014)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Moskovitz (2005)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Gofrit (2004)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Colombo (2001)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but the comparators were not randomised
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits

Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Brummelhuis (2021)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes this provides evidence supporting the reduced need for cystectomy. As noted earlier, 65% of the patients were BCG-refractory and additional 8% were BCG intolerant. Surgery is the only option for these patients. The CR rate at six months in the BCG refractory subgroup was 54.5% for CIS patients (48/88 with available follow-up data at six months) and 43.8% (7/16) for patients with residual papillary tumor at baseline. Specifically, with regard to this result, Food and Drug Administration and American Urological Association considered 40% CR at 6 months a clinically meaningful effect (Jarow (2014)).
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	None

van Valenberg (2018)

How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits. Supports the reduced need for cystectomy in some people who had previously failed BCG, resulting in reduced morbidity and mortality associated with cystectomy
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Moskovitz (2012)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Witjes (2009)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits

Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

van der Heijden (2004)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	No comparative data to support claimed benefits
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

Nativ (2009)	
How are the findings relevant to the decision problem?	Patient population, intervention and outcomes are relevant but no comparator
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes, supports delay to cystectomy as recurrence free probability was 56% at 2 years in this group who had recurrence after BCG.
Will any information from this study be used in the economic model?	Potentially
What are the limitations of this evidence?	Case series provide only a low quality of evidence.
How was the study funded?	NR

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

None found in MAUDE or MHRA website

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

Key adverse events that occurred more frequently with Synergo + MMC than comparators in the RCTs included bladder pain, urethral strictures, bladder tissue reaction, bladder spasms and catheterisation difficulties.

In the first (underpowered, n=184 patients) RCT Arends (2016a) Prior publications: Arends et al (2015)), compared with BCG, the overall side effect rate was higher for the Synergo + MMC group, mainly due to the relatively high frequency of mild symptoms of pain during or after CHT and catheterization difficulties. It should be noted that Synergo + MMC side effects were registered during treatment, whereas BCG side effects were registered before the next instillation, at least 1 week later. The authors subsequently noted that the higher side effects with Synergo were mainly due to the relatively high frequency of mild symptoms of pain during or after treatment and catheterization difficulties. If these side effects were excluded, the authors stated there no difference was observed in the overall rate of adverse events. Moreover, Synergo side effects were registered during treatment, whereas BCG side effects were registered before the next instillation, at least 1 week later Arends (2016b).

The side effects were:

Adverse event (number of events)	Synergo + MMC (1540 treatments among 90 patients)	BCG (1923 treatments among 94 patients)	OR (95% CI) Synergo + MMC vs. BCG	Significant difference in favour of:
Fever	NR	NR	0.09 (0.04 to 0.10)	Synergo + MMC
Arthralgia	NR	NR	0.09 (0.03 to 0.31)	Synergo + MMC
Fatigue	NR	129 (8.5%)	0.17 (0.11 to 0.28)	Synergo + MMC
Incontinence	NR	NR	0.22 (0.12 to 0.37)	Synergo + MMC

Haematuria	NR	170 (11.2%)	0.56 (0.42 to 0.74)	Synergo + MMC
Urinary frequency	141 (9.9%)	274 (18.0%)	0.61 (0.49 to 0.75)	Synergo + MMC
Nocturia	147 (10.3%)	227 (14.9%)	0.79 (0.63 to 0.98)	Synergo + MMC
Bladder pain between sessions	NR	NR	1.6 (1.2 to 2.3)	BCG
Urethral strictures	NR	NR	2.3 (1.3 to 4.1)	BCG
Allergy	NR	NR	2.7 (1.6 to 4.6)	BCG
Bladder tissue reaction	NR	NR	5.8 (4.0 to 8.3)	BCG
Bladder spasms during treatment	206 (14.4%)	NR	15.5 (9.7 to 25.0)	BCG
Catheterisation difficulties	NR	NR	16.7 (5.1 to 54.0)	BCG
Bladder pain during treatment	202 (14.1%)	NR	26.3 (14.3 to 48.5)	BCG
Dysuria	167 (11.7%)	229 (15.0%)	NR	NR
Probably related serious AEs	5 (one contracted bladder, one urethral bleeding, and three fever)	4 (retention, haematuria, UTI, and fever).	NR	NR

In the second (underpowered, n=104 patients) RCT (Tan (2019) Prior publications: Tan (2017a, 2017b)), no difference in adverse events between Synergo + MMC and the comparator group of BCG or institutional standard therapy (BCG in 33 [59%], MMC in 10 [18%] and EMDA MMC in 13 [23%]) was reported. It should be noted that the dose of MMC used was 40 mg rather than 80 mg which is the standard. Adverse events reported were:

Adverse event	**Synergo + MMC (n=48)**	**BCG or institutional standard therapy (n=56)**	**Synergo + MMC (n=48)**	**BCG or institutional standard therapy (n=56)**	**Synergo + MMC (n=48)**	**BCG or institutional standard therapy (n=56)**
	Overall		Grade 3/4		**Grade ≥4 toxicities**	
One or more adverse events	42/48 (87.5%)	42/56 (75.0%)	-	-	NR	There were two grade≥4 toxicities in the control arm, one which was due to arthritis, and the other BCG-related sepsis resulting in

						death.
Pain	22/48 (46%)	31/56 (56%)	2/48 (4%)	0		
Dysuria	26/48 (54%)	33/56 (59%)	0	0		
Increased frequency	25/48 (52%)	30/56 (54%)	0	1/56 (2%)		
Increased urgency	20/48 (42%)	27/56 (48%)	0	2/56 (4%)		
Incontinence	11/48 (23%)	10/56 (18%)	0	0		
Nocturia	16/48 (33%)	21/56 (38%)	0	2/56 (4%)		
Haematuria	23/48 (48%)	20/56 (36%)	1/48 (2%)	0		
Fatigue	16/48 (33%)	21/56 (38%)	2/48 (4%)	1/56 (2%)		
Fever	6/48 (13%)	14/56 (25%)	0	0		
UTI	13/48 (27%)	10/56 (18%)	0	1/56 (2%)		
Rash	7/48 (15%)	14/56 (25%)	1/48 (2%)	2/56 (4%)		
Stricture	3/48 (6%)	2/56 (4%)	0	0		

In the third (underpowered, n=83 patients) RCT (Colombo (2003); Extended follow-up publications: Colombo (2011)), the Synergo + MMC group had more pain and thermal reactions of the posterior bladder wall than the MMC group (both p<0.001). It should be notes that the authors suggest that the dose they used, of 20 mg of MMC for 1 hour, may be suboptimal.

	Synergo + MMC (n=42)				**MMC (n=41)**				**p value**
Side effect	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	
No side effect	5	-	-	-	15	-	-	-	
Pain	-	7	7	3	-	-	-	-	<0.001*
Posterior-wall thermal reaction	-	1	5	4	-	1	-	-	<0.001*
Tissue reaction	-	16	4	1	-	15	5	-	0.999
Dysuria	-	7	2	1	-	2	1	1	0.141
Hematuria	-	1	2	-	-	1	1	-	0.999
Urethral stenosis	-	1	2	-	-	1	-	-	0.999
Skin allergy	-	1	1	3	-	-	2	-	0.433

* The only significant differences were pelvic pain and thermal reaction of the posterior wall, which were greater in the Synergo + MMC group. No patients terminated the protocol treatment because of pain. In all occurrences, these events were localized and transient during delivery of therapeutic heat during treatment and resolved with no residual effects. Thermal reaction of the posterior bladder wall appeared as a small, superficial, black discoloration patch surrounded by hyperemia. In most cases, the posterior wall hyperemia resolved spontaneously within a few days. There was only one case of severe and prolonged

thermal reaction. It was greater than 2 cm in diameter and underwent spontaneous healing after 3 months. It was not associated with urinary symptoms. In the remaining cases, the lesions had disappeared at the control cystoscopy performed at 3-month follow-up. The exact time of recovery between cystoscopic controls in the other cases cannot be assessed because of the interval of 3 months between cystoscopies.			
Clinical complications			
Complication	1: reduced bladder capacity with urge incontinence (maximum bladder volume 150 mL)	-	-

Bladder pain, urethral strictures, bladder tissue reaction, bladder spasms and catheterisation difficulties were also reported in the case series (further details are shown in Appendix B).

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

NA

Report all relevant results, including diagrams if appropriate.

NA

Explain the main findings and conclusions drawn from the evidence synthesis.

NA

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

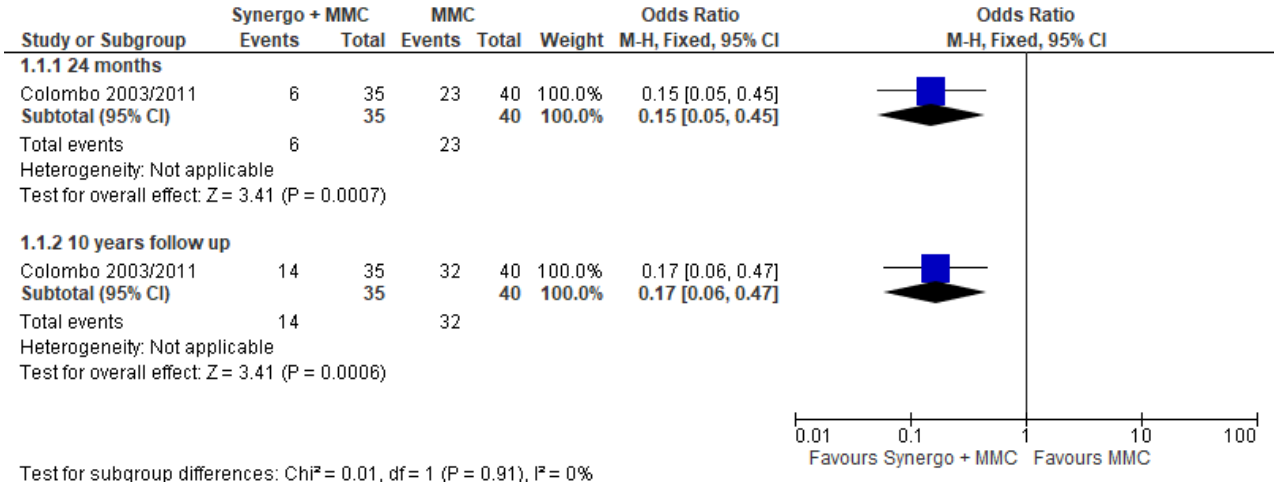
Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

The three RCTs were considered for meta-analysis but were found to be unsuitable due to three different control arms.

The key outcomes reported by the three RCTs are summarised below. Forest plots are used to aid visualisation and interpretation of each study individually but there is no attempt to use them for meta-analysis due to heterogeneity between the studies.

One study compared Synergo + MMC vs. MMC (Colombo (2003) with long-term follow up Colombo (2011)). This study found a significant benefit of Synergo + MMC vs. MMC alone on the outcomes of recurrence at 24 months and at the 10-year follow up (see Forest plot below).

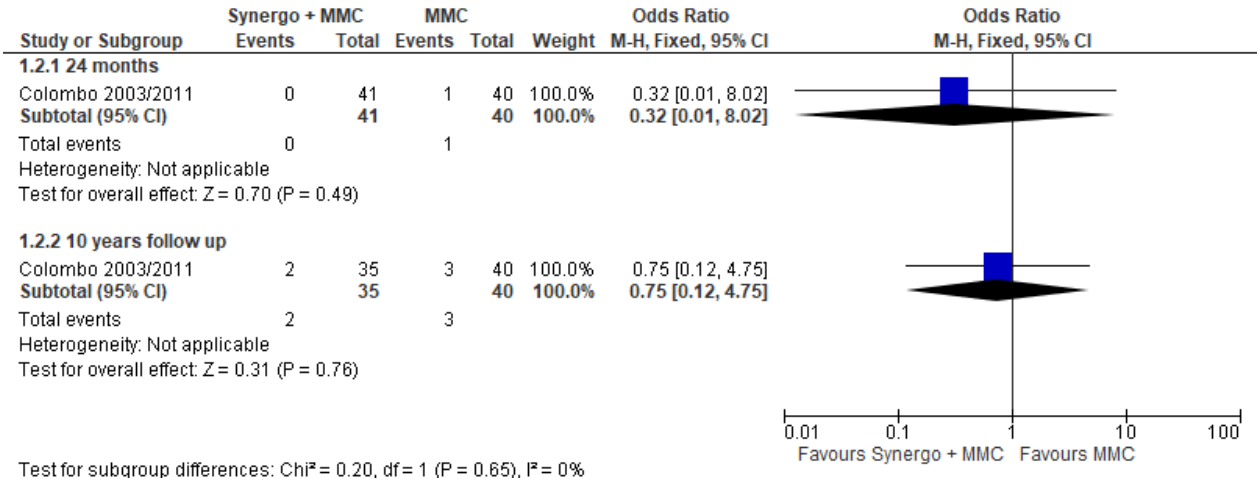
Forest plot of comparison: 1 Synergo + MMC vs. MMC, outcome: 1.1 Recurrence.



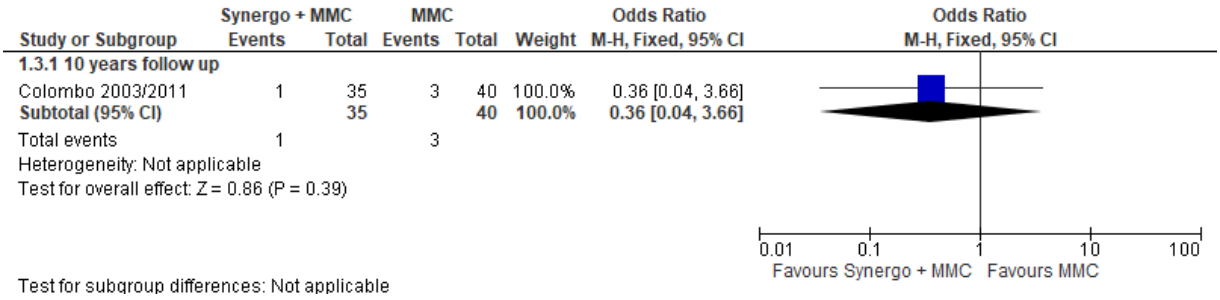
However, the other outcomes reported (progression to MIBC, radical cystectomy, mortality) were not significantly different between the groups at the reported time points (see Forest plots below).

Lack of statistical significance may be due, in part, to the heterogeneity of patients in this study. Intermediate-risk subjects have inherently lower risks for all three parameters. As the analysis does not separate between the intermediate- and high-risk groups (definitions have also changed since the publications), it is possible that this analysis is influenced by the low sample size and the generally lower chance for detection of these events, compared to recurrence. In addition, the study was never powered to provide answers to any of these 3 questions (beside the fact that its premature closure left it underpowered for the primary outcome).

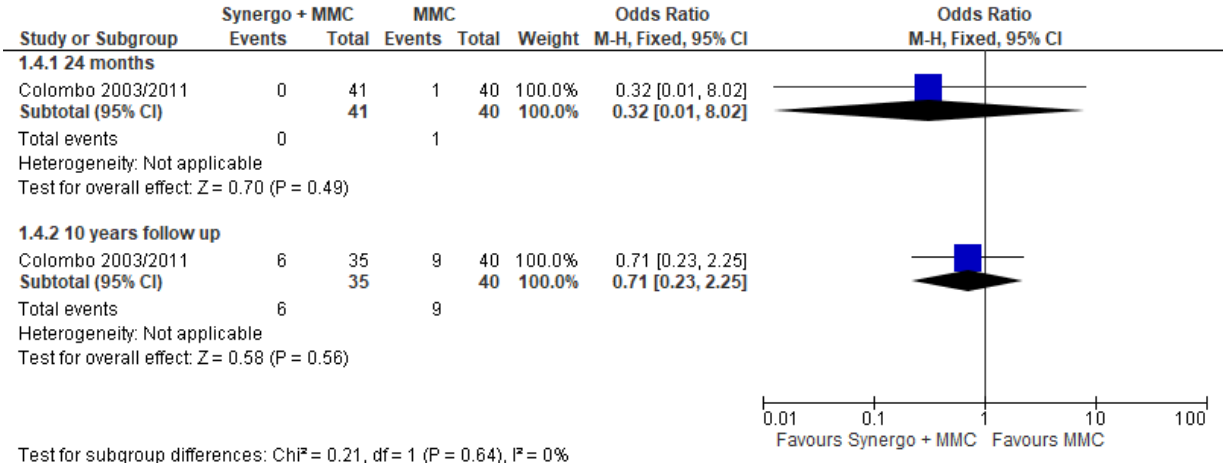
Forest plot of comparison: 1 Synergo + MMC vs. MMC, outcome: 1.2 Progression to MIBC.



Forest plot of comparison: 1 Synergo + MMC vs. MMC, outcome: 1.3 Radical cystectomy.



Forest plot of comparison: 1 Synergo + MMC vs. MMC, outcome: 1.4 Mortality.



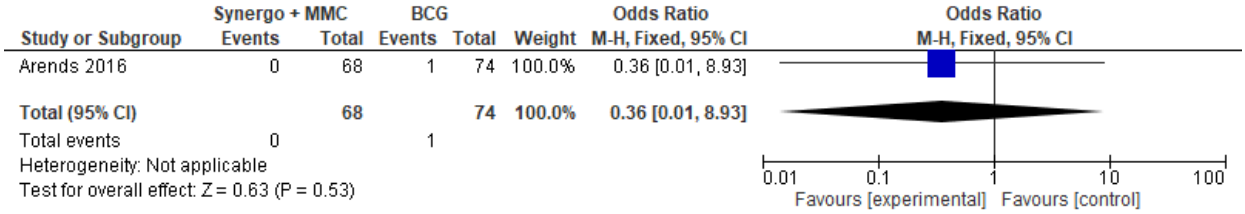
The outcomes derived from Kaplan-Meier plots in this study are summarised in the Table below:

Publication	Outcome	Comparison	HR, 95% CI	P value
Colombo (2003)	Recurrence	MMC vs. Synergo + MMC	4.821; 95% CI, 1.953 to 11.899	*P*=0.0002
Colombo (2011)	DFS	MMC vs. Synergo + MMC	NR	*P*<0.0001
Colombo (2011)	Radical cystectomy	MMC vs. Synergo + MMC	NR	*P*=0.129
Colombo (2011)	Overall survival	MMC vs. Synergo + MMC	NR	*P*=0.558

This study had adequate randomisation and allocation concealment and the groups were similar at baseline. There were small numbers of drop-outs in both arms. Analysis was for the per protocol population only. A major concern is that this study closed prematurely and thus is underpowered.

Arends (2016a) compared Synergo + MMC vs. BCG and found no difference between the groups on progression to MIBC (see Forest plot below). Again, the lack of significance may be partly due to the fact that the study was not powered to detect a difference in this outcome, as well as being underpowered for the primary outcome due to low enrolment. In addition, most patients were intermediate- rather than high-risk.

Forest plot of comparison: 2 Synergo + MMC vs. BCG, outcome: 2.1 Progression to MIBC.



The outcome measure data derived from Kaplan-Meier plots (i.e. the 24-month RFS percentage estimate and 95% CIs) are shown in the Table below:

	Synergo + MMC	BCG	p value between groups
ITT analysis	78.1% (65.2–86.7)	64.8% (52.2–74.9)	*P*=0.08
PP analysis	81.8% (68.7–89.8)	64.8% (52.2–74.9)	P=0.02

This study had adequate randomisation and allocation concealment and the groups were similar at baseline. As with all the RCTs, blinding of treatment for patients and physicians was impossible, which may have resulted in unavoidable bias. There were low numbers of drop-outs in both groups. Both ITT and PP results were reported using Kaplan-Meier curves. However, a major concern is that this study closed prematurely and thus is underpowered.

Tan (2019) used a control arm of either BCG or the institution's standard of care but reported no dichotomous outcomes suitable for Forest plots. It reported DFS at 24 months derived from Kaplan-Meier analysis as shown in the Table below:

HR (95% CI)	p value	Adjusted p value
1.33 (0.84 to 2.10)	0.23	0.49

This study had adequate randomisation and allocation concealment and the groups were similar at baseline. Blinding was not possible in part due to different treatment schedules. There were small numbers of drop-outs in both arms. Both ITT and PP results were reported using Kaplan-Meier curves. However, a major concern is that this study closed prematurely and thus is underpowered.

The case series reported various outcomes including tumor persistence, CR, RFS, PFS, OS, DSS, progression, metastatic disease, cystectomy and bladder preservation rates among patients receiving Synergo + MMC. The case series all represent a lower quality of evidence; some were only reported as abstracts; and some of the reported populations may overlap. For example, data from the retrospective case series Brummelhuis (2021), van Valenberg (2018), Moskovitz (2012), Witjes (2009) and van der Heijden (2004) appear to overlap in part in terms of dates and locations.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

The evidence base comprises three RCTs (each with a different comparator arm and all open-label) plus 21 case series.

One RCT compared Synergo + MMC vs. MMC (total n=83; Colombo (2003) with long-term follow up Colombo (2011)). This study found a significant benefit of Synergo + MMC vs. MMC alone on the outcomes of recurrence at 24 months and at the 10-year follow up (HR for recurrence: 4.821; 95% CI, 1.953 to 11.899; P=0.0002; DFS P<0.0001). The other outcomes reported (progression to MIBC, radical cystectomy, mortality) were not significantly different between the groups. Notably, the study was not powered to detect differences in these outcomes. Also, the population included both intermediate-risk and high-risk patients. By definition, intermediate-risk disease is less likely than high-risk to progress, require cystectomy or be fatal, especially at 2 years. Considering the low absolute risk of the secondary events, detecting significant differences in these endpoints was highly unlikely, Adverse events which were reported to be more frequent in the Synergo + MMC arm were pelvic pain and thermal reaction of the posterior wall (both p<0.001).

One RCT, Arends (2016a), compared Synergo + MMC vs. BCG. The 24-month RFS percentage estimate and 95% CIs derived from Kaplan-Meier plots favoured Synergo + MMC on the PP analysis (81.8% [68.7–89.8] vs. 64.8% [52.2–74.9], P=0.02) but not in the ITT analysis (78.1% [65.2–86.7] vs. 64.8% [52.2–74.9], p=0.08). The PP analysis sets in this study included the data of subjects with at least 6 intravesical instillations. In this regard, it may be worth noting that the disease recurrence rate was found to be inversely correlated to the total number of treatment sessions of Synergo + MMC by Colombo (2003), and in the case series of 111 patients treated with Synergo + MMC after failing BCG reported by Nativ (2009). In Arends (2016a), 77% had non-CIS disease; 31% had high-risk and 69% intermediate-risk disease. No difference was detected between the groups on progression to MIBC (total n=190), probably due also to the low absolute event rates. Adverse events which were reported to be significantly more frequent in the Synergo + MMC arm were bladder pain and spasms during treatment, bladder pain between sessions, bladder tissue reaction, allergy, urethral strictures and catheterisation difficulties. Adverse events occurring significantly less frequently with Synergo + MMC than BCG were fever, arthralgia, fatigue, incontinence, hematuria, urinary frequency and nocturia. Note BCG events were recorded at least 1 week later, whilst those for Synergo were recorded during the procedure. Arends (2016b) notes that if the within procedure side effects are excluded, no difference was observed in the overall rate of adverse events.

One RCT, Tan (2019), compared Synergo + MMC with a control arm of either BCG or the institution's standard of care (total n=104; 86.5% high-risk and 13.5% intermediate-risk) and found no difference between the groups on DFS at 24 months (adjusted p value 0.49). Pre-planned subgroup analysis showed no significant difference in DFS between treatment arms in non-CIS patients. DFS of Synergo-treated patients was significantly lower than that of control in patients with baseline CIS (HR 2.06, 95% CI 1.17–3.62, p = 0.01). The difference in the response of patients with only CIS was not statistically different; the pivotal effect was due to the small group of patients with CIS+papillary tumours. Witjes (2019), in a letter to the editor in response to Tan (2019), amplified concerns expressed by Tan (2019) concerning the sub-

optimal concentration of MMC administered via Synergo, particularly for these mostly CIS patients (68.3%; including 47.1% CIS only and 21.2% CIS + papillary);. It reported no significant differences between groups regarding adverse events.

Case series evidence support the claim for bladder preservation in some patients treated with Synergo + MMC who would otherwise undergo radical cystectomy as the standard of care. Examples include: In one case series including only patients who had failed BCG treatment Ayres (2018), the cystectomy rate at 10 years was only 23% of 135 participants. In another case series reporting the subgroup of 50 BCG-unresponsive patients separately van Valenberg (2018), this subgroup had a bladder preservation rate of 78.5% at 27.5 months follow up. Brummelhuis (2021) reported a bladder preservation rate of 71% at 55.5 months (n = 274, of whom 146 had papillary disease and 128 concomitant CIS).

The case series also reported adverse events of bladder pain, urethral strictures, bladder tissue reaction, bladder spasms and catheterisation difficulties.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The three RCTs matched the patient population, intervention, comparator and outcomes in the Scope. There was one RCT for each comparator assessed.

One RCT supported a benefit of Synergo + MMC vs. MMC alone in terms of recurrence. One RCT which compared Synergo + MMC vs. BCG supported a benefit in terms of recurrence among patients receiving at least 6 treatments (the PP population) and for high risk patients (including T1 as high risk) but this effect was non-significant for the ITT complete set of papillary patients population. It also supported Synergo + MMC as an additional treatment option for people in whom BCG is indicated when supply of the drug is limited or delayed or when BCG is contra-indicated or not tolerated. The third RCT also supported Synergo + MMC as an additional treatment option for people in whom BCG is indicated when supply of the drug is limited or delayed or when BCG is not tolerated, as the population studied were eligible to receive BCG.

The overall quality of the RCTs is limited as they were underpowered due to premature closure and blinding was not possible due to different treatment schedules between intervention and comparators and bladder particular view after Synergo+MMC treatments. Results of one RCT may have been significantly biased against Synergo as the treatment was administered with MMC at one-half of the consensus concentration for the population under study known at the time the study was initiated Witjes (2019).

The cases series included the relevant patient population, intervention and outcomes. Most had no comparator; where comparators were included these were not allocated through randomisation.

It is important to take cognisance of the U.S. FDA guidance, FDA (2019), on study design. The U.S. FDA notes that patients with BCG-unresponsive NMIBC are extremely unlikely to benefit from further therapy with BCG and represent a unique population for the study of new therapies, as the standard of care for these patients is radical cystectomy. Further, in CIS patients who are unresponsive to BCG, the U.S. FDA, in unison with the American Urological Association, Jarow (2014), advises the clinical trial sponsors to conduct single-arm trials, requesting complete response rate and duration of response as primary endpoints to provide evidence of effectiveness to support a marketing application. It adds the goal of therapy should be to avoid cystectomy, with delay, also providing evidence of effectiveness. This advice recognises that many patients prefer to avoid cystectomy.

Hence there is a large body of evidence, from 24 studies, with relevant study designs and reported in 31 documents. The studies included patients typical of the range of patients with NMIBC treated in the NHS (including patients with CIS or papillary disease; those with intermediate- or high-risk disease; and whether patients were pre-treated or treatment naïve) and were conducted in similar clinical settings. Hence, they are judged to have high external validity. The studies show an overall consistency in the direction of results in favour of Synergo + MMC in delaying progression of NMIBC in studies with MMC as the comparator and similar outcomes with the high-risk population managed on BCG. Adverse events associated with the therapy were mainly experienced during the procedure and were not serious. The results are directly relevant to the Scope.

The results for the subgroup who have failed on BCG or are contraindicated to it or cannot tolerate it offer the greatest potential benefit to patients. Use of Synergo in this group will delay or avoid cystectomy and its accompanying physical and emotional difficulties, loss in quality of life and high NHS and environmental cost.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The first RCT, Arends (2016a), was conducted in 11 sites in the Netherlands, Israel, Italy, Austria, France and Belgium. Inclusion criteria were:

1. Superficial TCC: Any G3 or any T1 and/or CIS
2. Multifocal (>1) Ta lesions
3. Multiple recurrences (>2) of Ta lesions in the last 24 months
4. Complete tumor eradication must be confirmed
5. WHO performance status 0-2 (Appendix V)
6. Life expectancy of more than 24 months

Exclusion criteria included:

1. Intravesical MMC treatments during the last 12 months
2. Previous intravesical BCG therapy (any intravesical BCG therapy in the last 24 months, or more than 6 BCG intravesical instillations in the last 48 months)
3. Urinary incontinence
4. Urethral stricture
5. Allergy to MMC or BCG

This trial population would have excluded patients who had a poor performance status, life expectancy under 2 years, prior MMC or BCG treatment, BCG allergy or urinary symptoms, which might be expected to be represented among patients having routine care in the UK NHS. This study included mainly intermediate-risk patients (69%) and high-risk 31%; non-CIS: 77.4%; CIS: 22.6% (including CIS only: 13.2% and CIS + papillary: 8.9% plus 1 patient not stated whether CIS was accompanied by papillary or not).

The second RCT, Tan (2019), was conducted in 12 sites in the UK. Inclusion criteria were:

1. Both males and females, age ≥18 years
2. Previous BCG induction or maintenance therapy for non-muscle-invasive bladder cancer (NMIBC)
3. Recurrence of disease following induction or maintenance BCG defined as:

a. Grade 3 or Grade 2, stage Ta or T1 disease
b. Carcinoma in situ (CIS) with Grade 3, Grade 2 or Grade 1 stage Ta or T1 disease
c. CIS alone

4. Have undergone a re-resection of all T1 disease to exclude muscle invasive disease
5. World Health Organization (WHO) performance status 0, 1, 2, 3 or 4
6. Normal kidneys and ureters on imaging study within the past 12 months
7. Pre-treatment hematology and biochemistry values within acceptable limits:

a. Hemoglobin ≥10 g/dl
b. Platelets ≥100 x 10^9/l
c. White blood cells (WBC) >=3.0 x 10^9/l or absolute neutrophil count (ANC) ≥1.5 x 10^9/l
d. Serum creatinine <1.5 x Upper Normal Limit (UNL)

8. Negative pregnancy test for women of child-bearing potential
9. Available for long-term follow-up
10. Unfit or unwilling to have a cystectomy

Exclusion criteria included:

1. Previous intravesical chemotherapy in the past 6 months, other than single instillation post-TUR

2. Known or suspected reduced bladder capacity (<250 ml)
3. Urethral stricture
4. Significant urinary incontinence

While this study was set in the UK and included a wider range of performance status, it would still have excluded some patients in routine practice, such as those suitable for full or partial cystectomy. It included mainly high-risk and CIS patients: intermediate: 13.5%; high-risk: 86.5%; non-CIS: 31.7%; CIS: 68.3% (including CIS only: 47.1% and CIS + papillary: 21.2%).

The third study, Colombo (2003), was conducted in 3 sites in Italy and Israel. Inclusion criteria were:

1. Intermediate and high-risk superficial TCC of the bladder (i.e., Ta-T1, G1-G2, multifocal, either primary or recurrent) and superficial high-risk bladder cancer (i.e., T1, G3, and CIS in association with papillary tumours).
2. Complete tumor eradication possible.

Exclusion criteria included:

1. Primary (de novo) CIS
2. Urethral stricture
3. Large benign prostatic hyperplasia or big middle lobe
4. Performance status WHO > 2

This trial population would have excluded patients who had a poor performance status, CIS only or benign prostatic hyperplasia (a condition that might be expected commonly in this patient age group). It included Grade 3: 21.7%; 1.2% CIS plus papillary tumors; 98.8% non-CIS and excluded CIS-only patients.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

Patients would need to have proven intermediate or high-risk non-muscle-invasive bladder cancer. The treatment is likely to be most suitable for patients for whom treatment with BCG vaccine is contraindicated or unsuitable, has been unsuccessful, or when the vaccine is not available and those who prefer to avoid cystectomy or are unfit for it. It showed benefit on recurrence-free survival in the sole RCT comparing it with MMC alone. Thus patients who respond poorly to MMC alone may be offered this as an alternative to BCG.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The three RCTs all had limitations: all three closed before recruiting the number of patients specified in the power calculations and were open-label.

The other identified studies were at a lower level of evidence as they were all case series, mostly uncontrolled. This study type is nonetheless relevant to patients with CIS who are unresponsive to BCG (FDA, 2019).

There was an unspecified amount of overlap between the patient samples included in the retrospective case series as they covered overlapping date ranges and included varying combinations of the same study centres.

9 References

Please include all references below using NICE's standard referencing style.

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	01 Feb 2021
Date span of search:	Search dates: 01-Jan-2000 to 01-Feb-2021
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Search strategy: 1 - cancer 2 - neoplasm 3 - tumor 4 - tumour 5 - #1 OR #2 OR #3 OR #4 6 - transitional 7 - urothelial 8 - urinary 9 - bladder 10 - #5 OR #6 OR #7 OR #8 11 - #9 AND #10 12 - thermochemo*[tw] 13 - thermo-chemo*[tw] 14 - chemotherm*[tw] 15 - chemo-therm*[tw] 16 - chemohypertherm*[tw] 17 - hypertherm* 18 - #12 OR #13 OR #14 OR #15 OR #16 OR #17 19 - #11 AND #18 20 - non-muscle-invasive 21 - non-muscle invasive 22 - non-invasive 23 - superficial 24 - nmibc 25 - stcc 26 - papillar* 27 - CIS 28 - in-situ 29 - #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 30 - #19 AND #29 31 - synergo[tw] 32 - microwave[tw] 33 - radiofrequency[tw]	

34 - radio-frequency[tw]
35 - #31 OR #32 OR #33 OR #34
36 - #30 AND #35
Databases:

1. PubMed – US National Library of Medicine (NLM)
2. Embase – Elsevier
3. Cochrane Library – Cochrane Collaboration

PubMed

Original query:

(((((cancer) OR neoplasm) OR tumor) OR tumour)) AND (((((transitional) OR urothelial) OR urinary OR bladder)) AND (((((((thermochemo*[tw]) OR thermo-chemo*[tw]) OR chemotherm*[tw]) OR chemo-therm*[tw] OR chemohypertherm*[tw] OR hypertherm*) AND (((((non-muscle-invasive) OR non-muscle invasive) OR non-invasive) OR superficial) OR nmibc) OR stcc OR papillar* OR CIS OR in-situ)) AND ((((synergo[tw] OR microwave[tw]) OR radiofrequency[tw]) OR radio-frequency[tw])))) AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]) AND English[lang]

Translations:

cancer	"cancer's"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]
neoplasm	"neoplasm's"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]
tumor	"cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor's"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]
tumour	"cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor's"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]
transitional	"transit"[All Fields] OR "transited"[All Fields] OR "transiting"[All Fields] OR "transition"[All Fields] OR "transitional"[All Fields] OR "transitionals"[All Fields] OR "transitioned"[All Fields] OR "transitioning"[All Fields] OR "transitions"[All Fields] OR "transits"[All Fields]
urinary	"urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]
bladder	"bladder's"[All Fields] OR "urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields] OR "bladders"[All Fields]

invasive	"invasibility"[All Fields] OR "invasible"[All Fields] OR "invasion"[All Fields] OR "invasions"[All Fields] OR "invasive"[All Fields] OR "invasively"[All Fields] OR "invasiveness"[All Fields] OR "invasives"[All Fields] OR "invasivity"[All Fields]
superficial	"superficial"[All Fields] OR "superficially"[All Fields] OR "superficials"[All Fields]
nmibc	"nmibc"[All Fields] OR "nmibcs"[All Fields]

Translated query:

("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] OR ("neoplasm s"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields])) AND (("transit"[All Fields] OR "transited"[All Fields] OR "transiting"[All Fields] OR "transition"[All Fields] OR "transitional"[All Fields] OR "transitionals"[All Fields] OR "transitioned"[All Fields] OR "transitioning"[All Fields] OR "transitions"[All Fields] OR "transits"[All Fields] OR "urothelial"[All Fields] OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("bladder s"[All Fields] OR "urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields] OR "bladders"[All Fields])) AND ((((("thermochemo*"[Text Word] OR "thermo chemo*"[Text Word] OR "chemotherm*"[Text Word] OR "chemo therm*"[Text Word] OR "chemohypertherm*"[Text Word] OR "hypertherm*"[All Fields]) AND ("non-muscle-invasive"[All Fields] OR ("non-muscle"[All Fields] AND ("invasibility"[All Fields] OR "invasible"[All Fields] OR "invasion"[All Fields] OR "invasions"[All Fields] OR "invasive"[All Fields] OR "invasively"[All Fields] OR "invasiveness"[All Fields] OR "invasives"[All Fields] OR "invasivity"[All Fields])) OR "non-invasive"[All Fields] OR ("superficial"[All Fields] OR "superficially"[All Fields] OR "superficials"[All Fields]) OR ("nmibc"[All Fields] OR "nmibcs"[All Fields]))) OR "stcc"[All Fields] OR "papillar*"[All Fields] OR "CIS"[All Fields] OR "in-situ"[All Fields]) AND ("synergo"[Text Word] OR "microwave"[Text Word] OR "radiofrequency"[Text Word] OR "radio-frequency"[Text Word]))) AND 2000/01/01:3000/12/31[Date - Publication] AND "English"[Language]

Embase–Elsevier

No.	Query	Results	Date
#1	cancer OR neoplasm OR 'malignant neoplasm'	4703463	01-Feb-21
#2	'transitional cell carcinoma'/exp OR 'urothelial bladder cancer' OR 'urothelial cancer' OR 'urothelial carcinoma of the bladder'/exp OR 'urothelial carcinoma of the bladder' OR 'bladder carcinoma'/exp OR 'bladder cancer'/exp OR 'bladder tumor'/exp OR 'non muscle invasive bladder cancer'/exp	111067	01-Feb-21
#3	#1 AND #2	94213	01-Feb-21

#4	thermochemotherapy OR 'thermo chemo*' OR thermochemo* OR chemotherm* OR 'chemo therm*' OR chemohyperthermia OR thermotherapy	22537	01-Feb-21
#5	#3 AND #4	370	01-Feb-21
#6	synergo OR 'microwave thermotherapy' OR 'radiofrequency therapy' OR 'radiofrequency-induced'	5833	01-Feb-21
#7	#5 AND #6 AND [humans]/lim AND [english]/lim AND [2000-2021]/py	71	01-Feb-21

Cochrane Library – Cochrane Collaboration

Column1	Column2	Column3
Search Name:	MEL	
Date Run:	01/02/2021 11:48:48	
Comment:		
ID	Search	Hits
#1	cancer	185558
#2	neoplasm	26196
#3	tumor	66018
#4	#1 OR #2 OR #3	210553
#5	transitional	2606
#6	urothelial	1168
#7	urinary OR bladder	52832
#8	#5 OR #6 OR #7	54431
#9	#4 AND #8	9711
#10	thermochemo*	35
#11	thermo NEXT chemo*	11
#12	chemotherm*	10
#13	chemo NEXT therm*	4
#14	chemohypertherm*	37
#15	hypertherm*	2209
#16	#10 OR #11 OR #12 OR #13 OR #14 OR #15	2250
#17	#9 AND #16	107
#18	non NEXT muscle NEXT invasive	652
#19	non NEXT "muscle invasive"	652
#20	non NEXT invasive	11852
#21	superficial	7703
#22	nmibc	382
#23	stcc	15
#24	papillar*	1645
#25	CIS	10035
#26	in NEXT situ	6655
#27	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	36494
#28	#17 AND #27	67
#29	synergo	11
#30	microwave	828
#31	radiofrequency	4602

#32	radio NEXT frequency	441
#33	#29 OR #30 OR #31 OR #32	5409
#34	#28 AND #33 with Cochrane Library publication date Between Jan 2000 and Jan 2021, in Cochrane Reviews	6

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Medical Enterprises continuously monitors the published literature for the presence of studies related to Synergo, as part of its clinical evaluation efforts. Medical Enterprises is not aware of any ongoing studies of Synergo other than those previously published or sponsored by Medical Enterprises. Nonetheless, a search was performed to identify all relevant published works using the general specifications.

Inclusion and exclusion criteria:

Inclusion criteria

Population: People with intermediate or high-risk non-muscle-invasive bladder cancer (NMIBC) who are a) BCG-unresponsive/resistant or b) indicated for BCG after failing previous instillations other than BCG but either cannot tolerate it, do not wish to be treated with it, contra-indicated to it, or cannot be administered it due to shortage in supply.

Interventions: Radiofrequency-induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 System

Outcomes:

- Recurrence rates and time to recurrence
- Disease progression and changes to treatment indicative of advanced disease
- Rates of cystectomy
- Complete response rate for carcinoma in situ
- Disease-specific and overall survival
- Health-related quality of life
- Treatment tolerability
- Length of hospital stay
- Treatment delivery rates in inpatient or outpatient settings
- Device-related adverse events

Study design: Original clinical research.

Prospective and retrospective studies with one or more arms that report outcome data by target population.

Language restrictions: Publications in English only

Exclusion criteria:

Population: NA

Interventions: NA

Outcomes: NA

Study design: Insufficient detail of methods and results to enable data extraction, such as:

- dosage of the drug administered with the device not reported clearly or at all

□ number of administered treatments not reported Language restrictions: NA Search dates: NA
Data abstraction strategy:
Single abstraction. Juxtaposition of study article PDFs to electronic data abstraction forms

Excluded studies

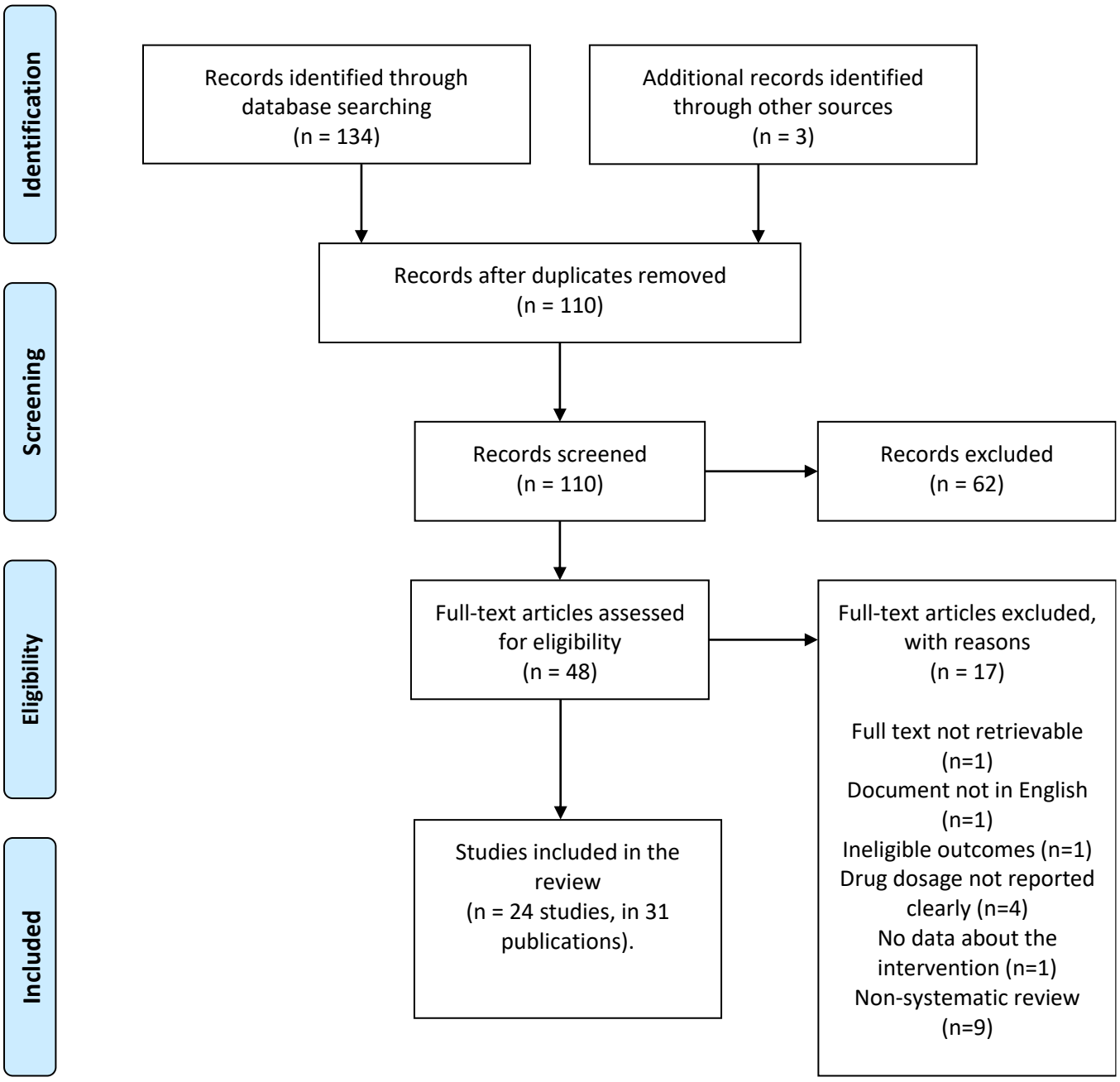
List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

NA

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

PRISMA 2009 Flow Diagram



Structured abstracts for unpublished studies:

NA

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Included in the search above, plus MHRA website and MAUDE

Date search conducted:	Enter text.
Date span of search:	Enter text.
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Enter text.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

<table>
<tr><th>Study</th><th>Design and intervention(s)</th><th>Details of adverse events</th><th>Company comments</th></tr>
<tr>
<td>Arends (2016a)

Prior publications:
Arends et al (2015)</td>
<td>RCT
<table>
<tr><th>Synergo + MMC (1540 treatments among 90 patients)</th><th>BCG (1923 treatments among 94 patients)</th></tr>
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<table>
<tr><th>Adverse event (number of events)</th><th>Synergo + MMC (1540 treatments among 90 patients)</th><th>BCG (1923 treatments among 94 patients)</th><th>OR (95% CI) Synergo + MMC vs. BCG</th><th>Significant difference in favour of:</th></tr>
<tr><td>Fever</td><td>NR</td><td>NR</td><td>0.09 (0.04 to 0.10)</td><td>Synergo + MMC</td></tr>
<tr><td>Arthralgia</td><td>NR</td><td>NR</td><td>0.09 (0.03 to 0.31)</td><td>Synergo + MMC</td></tr>
<tr><td>Fatigue</td><td>NR</td><td>129 (8.5%)</td><td>0.17 (0.11 to 0.28)</td><td>Synergo + MMC</td></tr>
<tr><td>Incontinence</td><td>NR</td><td>NR</td><td>0.22 (0.12 to 0.37)</td><td>Synergo + MMC</td></tr>
<tr><td>Haematuria</td><td>NR</td><td>170 (11.2%)</td><td>0.56 (0.42 to 0.74)</td><td>Synergo + MMC</td></tr>
<tr><td>Urinary frequency</td><td>141 (9.9%)</td><td>274 (18.0%)</td><td>0.61 (0.49 to 0.75)</td><td>Synergo + MMC</td></tr>
<tr><td>Nocturia</td><td>147 (10.3%)</td><td>227 (14.9%)</td><td>0.79 (0.63 to 0.98)</td><td>Synergo + MMC</td></tr>
<tr><td>Bladder pain between sessions</td><td>NR</td><td>NR</td><td>1.6 (1.2 to 2.3)</td><td>BCG</td></tr>
<tr><td>Urethral strictures</td><td>NR</td><td>NR</td><td>2.3 (1.3 to 4.1)</td><td>BCG</td></tr>
<tr><td>Allergy</td><td>NR</td><td>NR</td><td>2.7 (1.6 to 4.6)</td><td>BCG</td></tr>
</table>
</td>
<td>This study was underpowered. It should be noted that Synergo + MMC side effects were registered during treatment, whereas BCG side effects were registered before the next instillation, at least 1 week later.</td>
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<tr><td>Bladder tissue reaction</td><td>NR</td><td>NR</td><td>5.8 (4.0 to 8.3)</td><td>BCG</td></tr>
<tr><td>Bladder spasms during treatment</td><td>206 (14.4%)</td><td>NR</td><td>15.5 (9.7 to 25.0)</td><td>BCG</td></tr>
<tr><td>Catheterisation difficulties</td><td>NR</td><td>NR</td><td>16.7 (5.1 to 54.0)</td><td>BCG</td></tr>
<tr><td>Bladder pain during treatment</td><td>202 (14.1%)</td><td>NR</td><td>26.3 (14.3 to 48.5)</td><td>BCG</td></tr>
<tr><td>Dysuria</td><td>167 (11.7%)</td><td>229 (15.0%)</td><td>NR</td><td>NR</td></tr>
<tr><td>Probably related serious AEs</td><td>5 (one contracted bladder, one urethral bleeding, and three fever)</td><td>4 (retention, haematuria, UTI, and fever).</td><td>NR</td><td>NR</td></tr>
</table>
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<tr>
<td>Tan (2019)

Prior publications:
Tan (2017a, 2017b)</td>
<td>RCT

<table>
<tr><th>Synergo + MMC (n=48)</th><th>BCG or institutional standard therapy (n=56)</th></tr>
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<table>
<tr><th>Adverse event</th><th>Synergo + MMC (n=48)</th><th>BCG or institutional standard therapy (n=56)</th></tr>
<tr><td>Did not complete six or more than six instillations</td><td>5: skin rash, urinary urgency and nocturia, inability to catheterise (n=2), haematuria, and patient refusal of treatment.

2 others not treated: patient choice and ineligibility post-randomisation.</td><td>5: urinary urgency (n=2), persistent dysuria, haematuria, and patient refusal of treatment.

3 others not treated: patient choice and significant incontinence after randomisation.</td></tr>
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</td>
<td>This study was underpowered and the dose of MMC used was 40 mg rather than 80 mg which is the standard.</td>
</tr>
</table>

	Overall	
One or more adverse events	42/48 (87.5%)	42/56 (75.0%)
Pain	22/48 (46%)	31/56 (56%)
Dysuria	26/48 (54%)	33/56 (59%)
Increased frequency	25/48 (52%)	30/56 (54%)
Increased urgency	20/48 (42%)	27/56 (48%)
Incontinence	11/48 (23%)	10/56 (18%)
Nocturia	16/48 (33%)	21/56 (38%)
Haematuria	23/48 (48%)	20/56 (36%)
Fatigue	16/48 (33%)	21/56 (38%)
Fever	6/48 (13%)	14/56 (25%)
UTI	13/48 (27%)	10/56 (18%)
Rash	7/48 (15%)	14/56 (25%)
Stricture	3/48 (6%)	2/56 (4%)

	Grade 3/4 adverse event	
	Synergo + MMC (n=48)	**BCG or institutional standard therapy (n=56)**
One or more adverse events	NA	NA
Pain	2/48 (4%)	0
Dysuria	0	0
Increased frequency	0	1/56 (2%)
Increased urgency	0	2/56 (4%)

		Incontinence	0	0
		Nocturia	0	2/56 (4%)
		Haematuria	1/48 (2%)	0
		Fatigue	2/48 (4%)	1/56 (2%)
		Fever	0	0
		UTI	0	1/56 (2%)
		Rash	1/48 (2%)	2/56 (4%)
		Stricture	0	0
			No difference in adverse events between each treatment modality was observed.	
			There were two grade ≥4 toxicities in the control arm, one which was due to arthritis, and the other BCG-related sepsis resulting in death.	

Colombo (2003)

Extended follow-up publications:
Colombo (2011)

RCT

Synergo + MMC (n=42)	MMC (n=41)

	Synergo + MMC (n=42)				MMC (n=41)				p value
Side effect	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	
No side effect	5	-	-	-	15	-	-	-	
Pain	-	7	7	3	-	-	-	-	<0.001*
Posterior-wall thermal	-	1	5	4	-	1	-	-	<0.001*

This study was underpowered and only used a dose of 20 mg of MMC.

		reaction								
		Tissue reaction	-	16	4	1	-	15	5	-	0.999
		Dysuria	-	7	2	1	-	2	1	1	0.141
		Hematuria	-	1	2	-	-	1	1	-	0.999
		Urethral stenosis	-	1	2	-	-	1	-	-	0.999
		Skin allergy	-	1	1	3	-	-	2	-	0.433

* The only significant differences were pelvic pain and thermal reaction of the posterior wall, which were greater in the Synergo + MMC group. No patients terminated the protocol treatment because of pain. In all occurrences, these events were localized and transient during delivery of therapeutic heat during treatment and resolved with no residual effects. Thermal reaction of the posterior bladder wall appeared as a small, superficial, black discoloration patch surrounded by hyperemia. In most cases, the posterior wall hyperemia resolved spontaneously within a few days. There was only one case of severe and prolonged thermal reaction. It was greater than 2 cm in diameter and underwent spontaneous healing after 3 months. It was not associated with urinary symptoms. In the remaining cases, the lesions had disappeared at the control cystoscopy performed at 3-month follow-up. The exact time of recovery between cystoscopic controls in the other cases cannot be assessed because of the interval of 3 months between cystoscopies.

Clinical complications: 1 in Synergo + MMC group: reduced bladder capacity with urge incontinence (maximum bladder
volume 150 mL)

Ayres (2018) (conference abstract)	Case series	Unable to complete induction treatment due to significant side effects	5/135 (4%): significant side effects of pain, incontinence or severe rash.	Abstract only; low quality evidence

<table>
<tr><td>Kilb (2018) (conference abstract)</td><td>Case series</td><td><table><tr><td>Incomplete treatments induced by SAE</td><td>6/67 (9%)</td></tr></table></td><td>Abstract only; low quality evidence</td></tr>
<tr><td>Erturhan (2015)</td><td>Case series</td><td><table><tr><td>Side effects</td><td></td></tr><tr><td>Dysuria</td><td>11/26 (42.3%)</td></tr><tr><td>Storage functions</td><td>5/26 (19.2%)</td></tr><tr><td>Hematuria</td><td>4/26 (15.3%)</td></tr><tr><td>Pain of procedure</td><td>10/26 (38.4%)</td></tr><tr><td>Allergic reactions</td><td>2/26 (7.6%)</td></tr><tr><td>Thermal reaction in the posterior wall</td><td>7/26 (26.9%)</td></tr><tr><td>Discontinued treatment due to side effects</td><td>0</td></tr></table></td><td>Low quality evidence</td></tr>
<tr><td>Kiss (2015)</td><td>Case series</td><td><table><tr><td>Any adverse effects</td><td colspan="5">18/21 (86%)</td></tr><tr><td>Urgency-frequency</td><td colspan="5">11/21 (52.4%)</td></tr><tr><td>Pain</td><td colspan="5">8/21 (38.1%)</td></tr><tr><td>Gross hematuria</td><td colspan="5">5/21 (23.8%)</td></tr><tr><td>Bladder spasm</td><td colspan="5">5/21 (23.8%)</td></tr><tr><td>Urethral stricture/via falsa</td><td colspan="5">2/21 (9.5%)</td></tr><tr><td>Allergic reaction</td><td colspan="5">2/21 (9.5%)</td></tr><tr><td>Others</td><td colspan="5">1/21 (4.8%)</td></tr><tr><td>Adverse effects by highest grade</td><td>Grade 0 (none)</td><td>Grade 1 (mild)</td><td>Grade 2 (moderate)</td><td>Grade 3 (severe)</td><td>Grade 4 (life-threatening)</td></tr><tr><td>Any adverse effects</td><td>3/21 (14.3%)</td><td>1/21 (4.8%)</td><td>6/21 (28.6%)</td><td>9/21 (42.9%)</td><td>2/21 (9.5%)</td></tr><tr><td colspan="6">Treatment discontinuation</td></tr><tr><td>Therapy abandoned because of severe</td><td colspan="5">8/21 (38%): (drug-resistant pain in 3/8 patients, severe bladder spasms in 2/8, allergic reaction in 2/8, iatrogenic urethral perforation in 1/8).</td></tr></table></td><td>Low quality evidence</td></tr>
</table>

<table>
<tr><td></td><td></td><td><table><tr><td>adverse effects</td><td></td></tr></table></td><td></td></tr>
<tr><td>Luedecke (2015) (conference abstract)</td><td>Case series</td><td>Adverse events not reported</td><td>Abstract only; low quality evidence</td></tr>
<tr><td>Arends (2014)</td><td>Case series</td><td><table>
<tr><th>Reported AEs by CTCAE 4.0 grade at 1,671 treatment sessions</th><th>% Grade 1</th><th>% Grade 2</th><th>% Grade 3</th><th>% Grade 4</th></tr>
<tr><td>During induction:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pain</td><td>9.6</td><td>1.1</td><td>0.2</td><td>10.9</td></tr>
<tr><td>Spasms</td><td>8.2</td><td>4.5</td><td>0.6</td><td>13.3</td></tr>
<tr><td>Catheter problems</td><td>3.3</td><td>2.2</td><td>1.0</td><td>6.5</td></tr>
<tr><td>After induction:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Dysuria</td><td>12.0</td><td>3.0</td><td>0.0</td><td>15.0</td></tr>
<tr><td>Hematuria</td><td>3.7</td><td>0.9</td><td>0.0</td><td>4.5</td></tr>
<tr><td>Allergy</td><td>0.5</td><td>0.2</td><td>0.1</td><td>0.8</td></tr>
<tr><td>Urinary tract infection</td><td>0.3</td><td>0.1</td><td>0.1</td><td>0.5</td></tr>
<tr><td>Nocturia</td><td>2.6</td><td>1.3</td><td>0.5</td><td>4.5</td></tr>
<tr><td>Incontinence</td><td>0.8</td><td>0.1</td><td>0.0</td><td>1.0</td></tr>
<tr><td>Frequency/urgency</td><td>15.4</td><td>2.0</td><td>0.2</td><td>17.7</td></tr>
<tr><td>Other</td><td>1.0</td><td>0.0</td><td>0.0</td><td>1.0</td></tr>
<tr><td>During maintenance:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pain</td><td>5.5</td><td>0.3</td><td>0.1</td><td>5.9</td></tr>
<tr><td>Spasms</td><td>5.9</td><td>3.5</td><td>0.5</td><td>10.0</td></tr>
<tr><td>Catheter problems</td><td>2.2</td><td>0.7</td><td>0.4</td><td>3.3</td></tr>
<tr><td>After maintenance:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Dysuria</td><td>6.2</td><td>1.3</td><td>0.1</td><td>7.6</td></tr>
<tr><td>Hematuria</td><td>2.1</td><td>0.1</td><td>0.0</td><td>2.2</td></tr>
<tr><td>Allergy</td><td>0.1</td><td>0.1</td><td>0.0</td><td>0.2</td></tr>
<tr><td>Urinary tract infection</td><td>0.1</td><td>0.1</td><td>0.0</td><td>0.1</td></tr>
<tr><td>Nocturia</td><td>1.7</td><td>1.0</td><td>0.0</td><td>2.8</td></tr>
<tr><td>Incontinence</td><td>0.6</td><td>0.3</td><td>0.0</td><td>0.9</td></tr>
</table></td><td>Low quality evidence</td></tr>
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<tr><td></td><td></td><td>
<table>
<tr><td>Frequency/urgency</td><td>7.9</td><td>1.6</td><td>0.1</td><td>9.6</td></tr>
<tr><td>Other</td><td>0.3</td><td>0.0</td><td>0.0</td><td>0.3</td></tr>
<tr><td colspan="5">Overall adverse events</td></tr>
<tr><td>Total adverse events</td><td colspan="4">1,979 AEs of which 1,912 (96.6%) were grade 1 or 2.</td></tr>
<tr><td>During treatment</td><td colspan="4"></td></tr>
<tr><td>Bladder spasms</td><td colspan="4">23.3% of all treatment sessions</td></tr>
<tr><td>Bladder pain</td><td colspan="4">16.8% of all treatment session</td></tr>
<tr><td>After treatment</td><td colspan="4"></td></tr>
<tr><td>Dysuria</td><td colspan="4">22.6%</td></tr>
<tr><td>Frequency/urgency</td><td colspan="4">27.3%</td></tr>
</table>
</td><td></td></tr>
<tr><td>Maffezzini (2014)</td><td>Case series</td><td>
<table>
<tr><th>Toxicity</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td>Frequency</td><td>20</td><td>18</td><td>-</td><td>-</td></tr>
<tr><td>Cystitis (non-infectious)</td><td>16</td><td>14</td><td>-</td><td>-</td></tr>
<tr><td>Hematuria</td><td>25</td><td>1</td><td>-</td><td>-</td></tr>
<tr><td>Incontinence</td><td>8</td><td>4</td><td>-</td><td>-</td></tr>
<tr><td>Bladder/pelvic pain (treatment interruption in 5 patients, after 4 sessions in 1 patient, 6 in two patients, and 10 in two patients)</td><td>10</td><td>2</td><td>-</td><td>-</td></tr>
<tr><td>Urinary retention</td><td>1</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td colspan="5">All symptoms resolved spontaneously. A thermal reaction was visible on the posterior bladder wall in all patients after treatment; however, it was not associated with symptoms and self-healing. Bladder spasms were associated with reduction in bladder capacity and caused the interruption of treatment in five patients. Recovery was attained by three patients in 1–3 months following treatment withdrawal, whereas long-term reduction in bladder capacity <100 mL was persistent in two patients.</td></tr>
</table>
</td><td>Low quality evidence</td></tr>
<tr><td>Moskovitz (2005)</td><td>Case series</td><td>
<table>
<tr><td>Adverse events reported per patient</td></tr>
</table>
</td><td>Low quality evidence</td></tr>
</table>

		Cystitis	2/47 (4.3%)
		Posterior wall thermal reaction (cystoscopy)	9/47 (19.2%)
		Skin allergy	2/47 (4.3%)
		Urethral stenosis	3/47 (6.4%): Two of them are highly recurrent patients that underwent multiple procedures and previous instillations and had a known and documented urethral stenosis prior to Synergo treatment. One patient underwent internal urethrotomy and the other required dilatations. This patient was treated with Synergo as a last treatment resort. The third patient (following two mapping TURs and 12 Synergo treatments) required internal urethrotomy. No data of pre-inclusion status is available. All the patients completed their treatments.
		Adverse events reported per treatment (so a patient could have the same event more than once)	
		Dysuria	1/398 (0.3%)
		Hematuria	8/398 (2.0%)
		Pain during treatment	31/398 (7.8%)
		Difficult catheter insertion	4/398 (1.0%)
		Urge and/or incontinence during session (spasms)	8/398 (2.0%)
Gofrit (2004)	Case series		Low quality evidence

Side effect	**Prophylactic group***	**Ablative group***
Posterior wall thermal reaction (not associated with specific symptoms and had disappeared on subsequent cystoscopies)	15 (65.2%)	18 (62%)
Dysuria for <48 hours	14 (60.1%)	16 (55%)
Pain during treatment	6 (26%)	6 (20.7%)

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<tr><td>Bladder spasms</td><td>4 (17.4%)</td><td>4 (13.8%)</td></tr>
<tr><td>Urinary tract infection</td><td>3 (13.0%)</td><td>2 (6.9%)</td></tr>
<tr><td>Reduced bladder capacity</td><td>2 (8.7%)</td><td>3 (10.3%)</td></tr>
<tr><td>Palmar or plantar rash</td><td>2 (8.7%)</td><td>2 (6.9%)</td></tr>
<tr><td>Other</td><td>NR</td><td>Macrohematuria, hypotonic bladder and urethral stricture, each in 1 patient. Three patients reported general weakness and malaise.</td></tr>
<tr><td colspan="3">*Text states n=24 in prophylactic group and 28 in ablative group, but Table has percentages calculated as if the denominators were 23 and 29, respectively</td></tr>
</table>
</td><td></td></tr>
<tr><td>Colombo (2001)</td><td>Case series</td><td>
<table>
<tr><td></td><td>MMC (n=36)</td><td>Synergo + MMC (n=29)</td><td>Electromotive drug administration (EMDA) (n=15)</td></tr>
<tr><td>Local side effects (symptoms were assessed using a non-validated questionnaire)</td><td>Fewer cystitis symptoms than with the other two regimens</td><td>Local side effects were mainly described as urgency and nocturia</td><td>Mild suprapubic pain and urethral burning were prevalent</td></tr>
<tr><td>Major complications</td><td>None</td><td>None</td><td>None</td></tr>
</table>
</td><td>Low quality evidence</td></tr>
<tr><td>Brummelhuis (2021)</td><td>Case series</td><td>
<table>
<tr><td>At least one adverse event</td><td colspan="4">277/294 (94.2%)</td></tr>
<tr><td>Adverse event</td><td>Any grade</td><td>Grade 1</td><td>Grade 2</td><td>Grade 3</td></tr>
<tr><td>Spasms</td><td>183 (62.2%)</td><td>85 (28.9%)</td><td>93 (31.6%)</td><td>5 (1.7%)</td></tr>
<tr><td>Pain</td><td>82 (27.8%)</td><td>60 (20.1%)</td><td>17 (5.7%)</td><td>5 (1.7%)</td></tr>
</table>
</td><td>Low quality evidence</td></tr>
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<table>
<tr><td>Catheter problems</td><td>52 (17.7%)</td><td>30 (10.2%)</td><td>18 (6.1%)</td><td>4 (1.4%)</td></tr>
<tr><td>Dysuria</td><td>156 (53.1%)</td><td>126 (42.9%)</td><td>26 (8.8%)</td><td>4 (1.4%)</td></tr>
<tr><td>Hematuria</td><td>88 (29.9%)</td><td>83 (28.2%)</td><td>5 (1.7%)</td><td>0 (0%)</td></tr>
<tr><td>Urinary tract infection</td><td>46 (15.6%)</td><td>0 (0%)</td><td>39 (13.3%)</td><td>7 (2.4%)</td></tr>
<tr><td>Nocturia</td><td>43 (14.6%)</td><td>22 (7.5%)</td><td>16 (5.4%)</td><td>5 (1.7%)</td></tr>
<tr><td>Incontinence</td><td>18 (6.1%)</td><td>12 (4.1%)</td><td>6 (2.0%)</td><td>0 (0%)</td></tr>
<tr><td>Discontinued treatment due to side effects</td><td colspan="4">34 (11.4%)</td></tr>
</table>
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<td></td>
</tr>
<tr>
<td>van Valenberg (2018)</td>
<td>Case series</td>
<td>
<table>
<tr><td>Had to stop induction instillations due to adverse events</td><td>20/150 (13.4%)</td></tr>
<tr><td>Had to stop maintenance instillations due to adverse events</td><td>23/130 (17.8%)</td></tr>
<tr><td colspan="2">Pooled for both induction and maintenance, adverse events that led to patients having to stop treatment</td></tr>
<tr><td>Pain or spasms during an installation</td><td>11/150 (7.8%)</td></tr>
<tr><td>Allergy</td><td>12/150 (8.2%)</td></tr>
<tr><td>Frequency or urge between installations</td><td>10/150 (7.5%)</td></tr>
</table>
</td>
<td>Low quality evidence</td>
</tr>
<tr>
<td>Moskovitz (2012)</td>
<td>Case series</td>
<td>
<table>
<tr><th>Adverse event</th><th>Any grade</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th></tr>
<tr><td>Pain</td><td>27/92 (29.3%)</td><td>12/92 (13.0%)</td><td>15/92 (16.3%)</td><td>0/92 (0.0%)</td></tr>
<tr><td>Spasm</td><td>20/92 (21.7%)</td><td>4/92 (4.3%)</td><td>15/92 (16.3%)</td><td>1/92 (1.1%)</td></tr>
<tr><td>Posterior wall tissue reaction</td><td>12/92 (13.0%)</td><td>11/92 (12.0%)</td><td>1/92 (1.1%)</td><td>0/92 (0.0%)</td></tr>
<tr><td>Nocturia</td><td>8/92 (8.7%)</td><td>4/92 (4.3%)</td><td>4/92 (4.3%)</td><td>0/92 (0.0%)</td></tr>
<tr><td>Hematuria</td><td>6/92 (6.5%)</td><td>5/92 (5.4%)</td><td>0/92 (0.0%)</td><td>1/92 (1.1%)</td></tr>
<tr><td>Urethral stenosis</td><td>5/92 (5.4%)</td><td>1/92 (1.1%)</td><td>4/92 (4.3%)</td><td>0/92 (0.0%)</td></tr>
<tr><td>Urinary incontinence</td><td>4/92 (4.3%)</td><td>4/92 (4.3%)</td><td>0/92 (0.0%)</td><td>0/92 (0.0%)</td></tr>
<tr><td>Urethral stricture</td><td>3/92 (3.3%)</td><td>0/92 (0.0%)</td><td>1/92 (1.1%)</td><td>2/92 (2.2%)</td></tr>
</table>
</td>
<td>Low quality evidence</td>
</tr>
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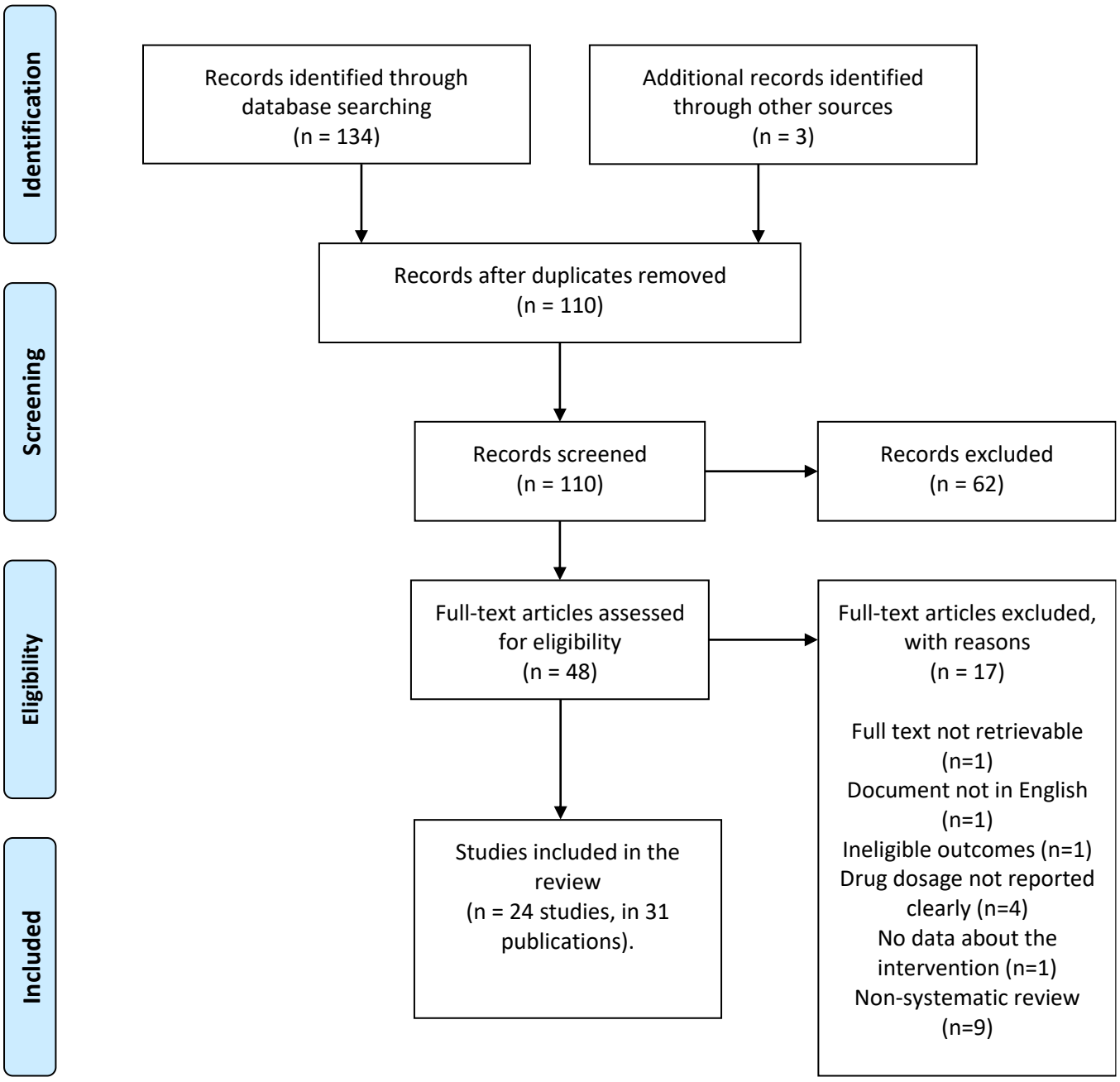
<tr><td></td><td></td><td>
<table>
<tr><td>Dysuria</td><td>3/92 (3.3%)</td><td>3/92 (3.3%)</td><td>0/92 (0.0%)</td><td>0/92 (0.0%)</td></tr>
<tr><td>Allergy</td><td>1/92 (1.1%)</td><td>1/92 (1.1%)</td><td>0/92 (0.0%)</td><td>0/92 (0.0%)</td></tr>
<tr><td>Urinary tract infection</td><td>1/92 (1.1%)</td><td>0/92 (0.0%)</td><td>1/92 (1.1%)</td><td>0/92 (0.0%)</td></tr>
<tr><td>Any adverse event</td><td>40/92 (43.5%)</td><td>9/92 (9.8%)</td><td>27/92 (29.3%)</td><td>4/92 (4.3%)</td></tr>
<tr><td>Withdrew from treatment before completing induction cycle</td><td colspan="4">4/92 (4.4%)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Witjes (2009)</td><td>Case series</td><td>
<table>
<tr><th colspan="2">Session-related adverse events, measured per session (total number of treatments given to the study group is 503 among 51 patients)</th></tr>
<tr><td>Pain</td><td>64/503 sessions (12.7%)</td></tr>
<tr><td>Bladder spasms</td><td>66/503 sessions (13.1%)</td></tr>
<tr><td>Dysuria</td><td>31/503 sessions (6.2%)</td></tr>
<tr><td>Hematuria</td><td>15/503 sessions (3.0%)</td></tr>
<tr><td>Difficult catheter insertion</td><td>1/503 sessions (0.2%)</td></tr>
<tr><td>Urge/incontinence during treatment</td><td>2/503 sessions (0.4%)</td></tr>
<tr><td>Frequency/urgency</td><td>8/503 sessions (1.6%)</td></tr>
<tr><td>Nocturia</td><td>11/503 sessions (2.2%)</td></tr>
<tr><td>Dropped out during initial treatment</td><td>2: one patient with hematuria after the second treatment and one patient with a false route after the fourth treatment</td></tr>
</table>
</td><td>Low quality evidence</td></tr>
<tr><td>van der Heijden (2004)</td><td>Case series</td><td>
<table>
<tr><td>One or more side effects</td><td>65/90 (72.2%)</td></tr>
<tr><td>Dysuria</td><td>22/90 (24.4%)</td></tr>
<tr><td>Hematuria</td><td>8/90 (8.9%)</td></tr>
<tr><td>Pain</td><td>33/90 (36.7%)</td></tr>
<tr><td>Posterior wall thermal reaction (in general, these lesions were asymptomatic and healed spontaneously. However, there was one case of severe and prolonged thermal reaction (though</td><td>23/90 (25.6%)</td></tr>
</table>
</td><td>Low quality evidence</td></tr>
</table>

<table>
<tr><td></td><td></td><td><table>
<tr><td>asymptomatic), consisting of a lesion greater than 2 cm in diameter of which healing took more than 3 months)</td><td></td></tr>
<tr><td>Skin allergy</td><td>8/90 (8.9%)</td></tr>
<tr><td>Urethral stenosis</td><td>4/90 (4.4%)</td></tr>
<tr><td>Tissue reaction</td><td>22/90 (24.4%)</td></tr>
<tr><td>No side effects</td><td>25/90 (27.8%)</td></tr>
</table></td><td></td></tr>
<tr><td>Nativ (2009)</td><td>Case series</td><td><table>
<tr><td>Adverse event</td><td>% Grade 1</td><td>% Grade 2</td><td>% Grade 3</td><td>Total %</td></tr>
<tr><td>Spasm</td><td>17.1</td><td>10.8</td><td>2.7</td><td>30.6</td></tr>
<tr><td>Pain</td><td>18.9</td><td>5.4</td><td>2.7</td><td>27.0</td></tr>
<tr><td>Hematuria</td><td>9.9</td><td>5.4</td><td>3.6</td><td>18.9</td></tr>
<tr><td>Dysuria</td><td>9.9</td><td>3.6</td><td>2.7</td><td>16.2</td></tr>
<tr><td>Transient incontinence</td><td>9.0</td><td>0.9</td><td>0.0</td><td>9.9</td></tr>
<tr><td>Allergy</td><td>3.6</td><td>0.9</td><td>3.6</td><td>8.1</td></tr>
<tr><td>Nocturia</td><td>1.8</td><td>3.6</td><td>2.7</td><td>8.1</td></tr>
<tr><td>Urethral stenosis</td><td>1.8</td><td>0.9</td><td>0.0</td><td>2.7</td></tr>
<tr><td>Urethral stricture</td><td>1.8</td><td>0.9</td><td>0.0</td><td>2.7</td></tr>
<tr><td>Urinary tract infection</td><td>0.9</td><td>0.9</td><td>0.0</td><td>1.8</td></tr>
<tr><td>Any</td><td>25.2</td><td>11.7</td><td>8.1</td><td>45.0</td></tr>
</table></td><td></td></tr>
</table>

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

PRISMA 2009 Flow Diagram



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

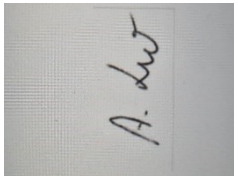
Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	03/03/2021
Print:	Dr. Avigdor Lev	**Role / organisation:**	Director
Contact email:	[redacted]		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT553 Synergo for non-muscle invasive bladder cancer

Company evidence submission

Part 2: Economic evidence

Company name	Medical Enterprises Europe B.V.
Submission date	29 March 2021
Contains confidential information	No

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		110
Number of studies identified as being relevant to the decision problem.		0
Of the relevant studies identified:	Number of published studies.	0
	Number of abstracts.	0
	Number of ongoing studies.	0

(Note these values exclude the quality of life search as this was not systematic.)

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

The literature search described in appendix A was conducted to identify clinical papers. It was not re-run to identify any economic or cost studies because the company knows that there are no published economic or cost papers.

Table 1 Summary of all relevant studies (published and unpublished)

Not relevant

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
Text	Text	Text	Text	Text	Text	Text

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Not relevant.

Insert study name	
What are main differences in resource use and clinical outcomes between the technologies?	
How are the findings relevant to the decision problem?	Text
Does this evidence support any of the claimed benefits for the technology? If so, which?	Text
Will any information from this study be used in the economic model?	Text
What cost analysis was done in the study? Please explain the results.	Text
What are the limitations of this evidence?	Text
How was the study funded?	Text

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

The patient group included in the model has intermediate or high-risk non-muscle-invasive bladder cancer (NMIBC). All patients are assumed to have failed to respond to previous intravesical chemotherapy (usually mitomycin C [MMC]), or in whom a tumour(s) recurs and who have not been able to tolerate intravesical Bacillus Calmette-Guérin (BCG) immunotherapy, or are contraindicated to BCG or BCG is not available.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

The NICE clinical guideline on bladder cancer (NICE, 2015) advises the treatment options for these patients include radical cystectomy (RC) or some form of bladder sparing treatment.

In the model the comparator is further intravesical chemotherapy. This avoids the removal of the bladder but, as the guideline notes, carries the risk that the tumour may not respond and will progress to invasion or spread beyond the bladder. Hence, once such recurrence is detected, the model assumes RC will be performed.

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

This model is designed to capture the clinical and economic outcomes of patients with intermediate or high risk NMIBC who have failed on first-line chemotherapy and are contraindicated or intolerant to BCG, or BCG is unavailable.

Synergo + intravesical MMC is compared to intravesical MMC. This is the only relevant treatment option (apart from RC) for intermediate and high-risk NMIBC patients when BCG is not a relevant comparator. Following recurrence, patients were assumed to require RC. The alternative of allowing progression to muscle invasive bladder cancer was not modelled, being inconsistent with the NICE guideline (NICE, 2015). However, for those who decline RC or are unsuitable for it, the cancer may spread into the muscle or elsewhere in the body.

The hypothesis is that Synergo + MMC, compared with MMC only, may delay recurrence, thereby delaying RC, and indeed for some patients may enable them to avoid a RC. Such delay provides cost savings through delaying or eliminating the need for surgery, thereby reducing the requirement for stoma products and improves quality of life.

The model has 4 health states: remission, recurrence /RC, post-RC and death. Costs and quality of life (QoL) are associated with each state. The main clinical events modelled are tumour recurrence, RC and mortality.

Patients are assumed to have no carcinoma on entry to the model and are treated with 2 x 20 mg of MMC in 50 mL of water of MMC per treatment for 12 cycles. This is administered either using intravesical MMC in combination with Synergo or intravesical MMC only. Patients can remain tumour-free i.e. remain in remission, experience a recurrent tumour, or die. Those experiencing a recurrent tumour are assumed to require RC. They may die preoperatively or shortly after this procedure (within 30 days), or they recover and move to the post-RC health state. In the post-RC state, they are assumed to have the same overall survival as that reported by Afshar (2018). This study used Hospital Episode Statistics (HES) data and the Office for National Statistics mortality data to calculate overall survival post-RC. (Note this study was conducted on all RCs conducted on patients with bladder cancer, not just those patients with NMIBC and hence generalisability may be an issue). The stoma impacts on their quality of life and imposes costs for the NHS.

The health state membership (remission; recurrence/cystectomy; post-cystectomy; dead) of a cohort of patients are modelled over a lifetime horizon, using a Markov model. Health state transitions are populated using data from Colombo (2011), which provides 10-year follow-up data from a RCT comparing the efficacy of intravesical MMC delivered via Synergo against intravesical MMC alone. Kaplan Meier curves were reported, enabling data on recurrence free survival (RFS) to be estimated for each of the 10 years.
rkov models have yearly cycles and are half-year corrected.

The assumption that patients are tumour-free when entering the model arises because the best source of data to populate the model is Colombo (2003 and 2011), which only enrolled patients who were pre-treated with a transurethral resection of bladder tumour (TURBT).

Colombo (2011) reported there was no disease specific mortality recorded at 10 years, so both arms are assumed to have the same mortality as the general population until they move into the post-cystectomy health state. Mortality rates were assumed equivalent across patients in remission and those with recurrences (see Kauffman 2009 and Zietman 2001).

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
Patients with recurrence move to RC	Consistent with NICE guideline	NICE (2015)
Age on model entry of 64 years	Mean age of RC is 66.8 years and median	NHS Digital
Males are 75% of population	Consistent with national RC analysis	NHS Digital

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
RFS at 10 years Synergo + MMC	Colombo 2011	52.8%	Not reported (NR)	Patients remain in RFS in accordance with these %. As rate falls they move to recurrence/RC.
RFS at 10 years MMC	Colombo 2011	14.6%	NR	Patients remain in RFS in accordance with these %. As rate falls they move to recurrence/RC
RFS years 1 to 9	Colombo 2011 Fig 2. Web plot digitizer used to extract data	Synergo + MMC Year 1 83.1% reducing to 52.8% MMC Year 1 51.6% reducing to 14.6%	NR	Patients remain in RFS in accordance with these %. As rate falls they move to recurrence/RC. Annual risk of recurrence was calculated for each year in the first 5 years and separately for each year in the second 5 years. This approach was adopted because the KM showed a levelling off in changes in RFS at around year 5.
OS	Office for National Statistics. National life tables UK (2017-19). (2020)	Survival data for general population by year	NR	Colombo (2011) reported there was no disease specific mortality recorded at 10 years, so both arms are assumed to have the same mortality as the general population until they move into remission/RC.

Procedure-related risk of death at 30 days with RC	Afshar (2018)	2.1%	NR	Applied to all patients who undergo a RC in decision tree and Markov model
Annual mortality risk after RC	Afshar (2018)	5.0%	NR	Afshar (2018) reported a median time of 5.4 years post RC and provided a KM survival curve. KM data were used to calculate the annual mortality risk post-RC

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

RFS

The KM curves from Colombo 2011 indicted a distinct reduction in the rate of change of annual RFS over time at year 5, with the curves flattening out. Hence the years 6 to 10 data were used to inform the extrapolation. Remission to recurrence rates were estimated using the reported recurrence rates from year 6 to year 10 and expressing that probability as an annual risk of recurrence giving:

Annual risk of recurrence: Synergo + MMC: 2.7%
MMC: 1.4%

OS

The general mortality data from the ONS data continued to be applied whilst patients were in remission or recurrence, together with the procedure related mortality at 30 days for people who enter recurrence (and require cystectomy).

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	Lifetime	Benefit of the device is material over lifetime and this is consistent with NICE reference case	NICE (2013)
Discount rate	3.5% for costs and benefits	Consistent with NICE reference case	NICE (2013)
Perspective (NHS/PSS)	NHS/PSS	Consistent with NICE reference case	NICE (2013)
Cycle length	1 year	Consistent with data	Colombo (2011)
Transition probabilities	Described above	Mainly from published studies	Described above
Health states	Remission, recurrence/RC, Post RC and dead	Reflect major changes in health states that change treatments and outcomes, thereby driving costs and benefits	NICE (2015)
Sources of unit costs	Procedures and diagnostics	National dataset	NHS Reference costs
	Drug costs	National dataset	BNF
	Staff costs and GP attendances	National dataset	Unit Costs of Health and Social Care 2020
	Device costs	Only source	Company
	Drug costs	National dataset	BNF
	Palliative care	No national dataset values are available for NMIBC; the data used are NMIBC specific	Cox (2020)
Inflation index to 2021	NHS cost inflation index	NHS specific index	Unit Costs of Health and Social Care 2020, with the last reported annual rate (2.21%) assumed to apply to index prices to 2021
Utilities RFS Recurrence and post RC	 0.85 0.65	See next section on health state utilities	Cox (2020) and Mason (2018)

Health state utilities (This box has been added by the authors to describe approach to valuing QoL)

An ad hoc search identified a recent literature review that summarised empirical evidence relating to psychosocial health following ostomy surgery. Twenty-seven articles were included. Most of the studies were conducted to determine psychosocial problems and emotions of the individuals, their adaptation to the stoma, and their quality of life. Most of the psychosocial problems identified in these studies were poor body image perception and self-respect, depression, sexual problems, and lower psychosocial adaptation (Ayaz-Alkaya, 2018).

None of these studies used a standardised and validated generic quality of life measure such as EQ-5D, as recommended by NICE for use in its reference case (NICE, 2013).

Hence a literature search was undertaken in google scholar to identify studies reporting quality of life, using a validated generic measure, in people with a stoma, ideally after bladder cancer. None were found. One study did report a score of 0.85 for patients in remission in the UK (Cox, 2020). The data were measured in a RCT including patients with NMIBC, at intermediate and high risk. The value was measured using the NICE preferred measure of EQ-5D-3L. This was judged to generalise to the patients in the model.

In the absence of any appropriate published utility values of QoL post stoma, data were extracted from a second study by Mason (2018). The study was designed by the Department of Health to identify changes in QoL after bladder cancer. In total 673 patients responded to the survey, although not all replied to the stoma-related questions. The paper reported the number of patients with and without a stoma, experiencing problems for each of the 5 EQ-5D domains. The values are problems with:

- pain 49.5% vs 35.4% (with and without stoma respectively)
- anxiety 37.4% vs 36.1%
- usual activities 52.3% vs 39.3%
- mobility 34.0% vs 36.5%
- self-care 18.9% vs15.5%.

The p values for pain and usual activities are statistically significantly lower for patients with a stoma ($p < 0.01$ and $p = 0.014$ for pain and usual activities respectively). The other 3 domains had much higher p values. Assuming that the without stoma group had a perfect quality of life, recording an EQ-5D score of 1,1,1,1,1 but those with a stoma had a one point lower value for pain and usual activities (1,1,2,2,1), then the associated utility is 1.000 and 0.7845. This difference is -0.2155.

Hence these data from a well-conducted large survey of relevant patients in the UK suggest QoL is lower for those with a stoma. Particularly, they have more pain and are less able to manage usual activities. The difference between their QoL and those without a stoma has been estimated at -0.2155. In the model the decrement was rounded to 0.20 in order to be conservative.

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

All patients are assumed to enter the model in remission (RFS). Patients in RFS can move to recurrence or remain in RFS (in line with an annual risk of recurrence calculated from Colombo 2011 study data), or die based on the general population age-adjusted mortality risk. The risks of moving from remission to recurrence, or remission to dead, persist for people in RFS for the lifetime horizon of the Markov model. All patients in either the Synergo or MMC arm received 12 treatments of MMC (20 mg x 2 per treatment); all were delivered in year 1. (Source: Colombo [2011] for dose, and number of administrations was advised by Dr Lev [General Manager, Medical Enterprises Europe B.V], who witnessed this trial). Patients using Synergo also incur Synergo-specific costs. Utilities for people in remission are applied.

For patients in recurrence/cystectomy, patients may transition to either post-cystectomy or dead. The risk of moving to dead is based on age-adjusted general population norms plus an additional risk of perioperative mortality associated with cystectomy. The risk of moving from recurrence/cystectomy to post-cystectomy is 1 minus the combined mortality risk. Patients cannot remain in recurrence/cystectomy for more than 1 cycle. In recurrence, patients incur the costs of RC and experience a 0.2 decrement in quality of life (baseline of remission).

In post-cystectomy, the risk of moving to dead is associated with an annual mortality risk, calculated using a 10-year mortality risk specific to patients who have incurred a cystectomy. The risk of remaining in post-cystectomy is 1 minus the mortality risk. Costs of post-cystectomy are stoma cost related. People in post-cystectomy also experience a 0.2 decrement in quality of life (baseline of remission).

In the dead health state people are assumed to incur palliative care costs.

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Annual lease cost: £9,500
Consumables per administration: £490

Cost of Synergo per patient: £317
Cost of Synergo plus training costs per patient: £327

The average annual number of patients at a site using Synergo + MMC is assumed to be 30. To a large extent this number will depend on the extent of centralisation of the service and the patient selection criteria.

To put the 30 into perspective, Afshar (2018) reported in 2014 only 60 sites conducted RC and or prostatectomies in England (down from over 130, 10 years earlier). There are about 1,800 RCs performed a year (NHS Digital).

If the list price is not used in the model, provide the price used and a justification for the difference.

Not applicable

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

When NMIBC recurs, despite bladder installations with chemotherapy agents (usually MMC) or immunotherapy (BCG), urological guidelines recommend surgical removal of the bladder or some form of bladder sparing treatment (See NICE NG2, 2015).

Cystectomy

The HRG codes for 'Cystectomy with Urinary Diversion and Reconstruction' are LB39C-D. We used a weighted average cost for elective inpatients (£11,743) from NHS Reference costs (2018/19). These patients would normally be managed as electives, not non-electives. This cost was indexed to 2021 prices.

In the NHS, reinterventions after cystectomy are about 30% (Afshar, 2018). These were costed using HRG codes LB19C and 19D 'Ureteric or Bladder Disorders with intervention' at a cost of £2,773 (2018/19 prices). This cost was indexed to 2021 prices.

Other costs related to cystectomy include:

- One visit to a stoma clinic pre-surgery £49 (Source NHS Reference costs; Specialist Nursing, Stoma Care Services, Adult, Face to face N24AF £46, indexed to 2021 prices)
- Two home visits £102 (2 hours of band 6 nurse from Curtis and Burns indexed to 2021 prices)
- Four attendances at a stoma clinic (1, 3, 6 and 12 months) at £46 each
- Two telephone contacts with stoma nurse at £17 each (Code N24AN)
- One year of stoma products £2,244 (see later section)

The total cost of RC in year 1 was £16,168.

The NHS tariff values for cystectomy are £10,018 and £7,827 for a combined day case/ordinary elective spell tariff for codes LB39C and LB39D respectively. Note tariff costs are not used in the model, but are provided here for transparency.

The OPCS codes are:

M34.3	Cystectomy NEC
M34.4	Simple cystectomy
M34.8	Other specified total excision of bladder
M34.9	Unspecified total excision of bladder

MMC chemotherapy

The costs of administering MMC chemotherapy were taken from NHS Reference costs:

Day care	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£385
Outpatient	SB15Z	Deliver Subsequent Elements of a Chemotherapy Cycle	£223

Patients receiving MMC via Synergo require a slightly longer procedure time (about 30 minutes longer) than patient receiving MMC alone. No staff presence is required and thus the cost relates to the use of the room only. This was costed using the allocated cost per attendance at an oncology consultant-led outpatient clinic of £116 at 2019/20 prices (ISD R044:Speciality Group Costs- outpatients). This cost covers accommodation, utilities, rates and other overheads but excludes all direct costs such as staff and consumables.

Each standard attendance was assumed to take about 1 hour. This gives a cost per 30 minutes of £58, rising to £61 when indexed to 2021 prices.

The cost of the MMC drug was taken from BNF being £135 per mitomycin 40mg powder and solvent for intravesical solution vials.

Follow-up costs

Follow-up costs for those in RFS were derived using the recommendations from NICE clinical guideline (NICE, 2015). For patients at intermediate risk, the guideline recommends cystoscopic follow-up at 3, 9, and 18 months and annually thereafter, discharging patients after 5 years of disease free follow-up. Patients at high risk should be followed up every 3 months for 2 years, every 6 months for next 2 years and then annually.

The patient mix was assumed to be in the ratio 77% intermediate and 23% high (see Colombo 2003).

The unit cost applied was £250 (2018/19 cost) for 'Diagnostic Flexible Cystoscopy, 19 years and over LB72A' (NHS Reference costs 2018/19). This is equivalent to £267 in 2021 prices.

Applying the unit costs to the number of cystoscopy follow-ups and assuming patients attend all follow-ups gave annual costs £406 in years 1 to 5 and £160 thereafter.

Palliative care

The cost of palliative care was extracted from Cox (2020) and updated to 2021 prices. Before indexing the cost was £12,968 (2017 prices), equivalent to £14,167 in 2021 prices. Note the original source was an earlier health technology assessment (Mowatt, 2010). This adopted an

NHS only perspective. Hence this cost is likely to understate the relevant costs which should include social care. This cost was applied to all people dying in the final year of their lives.

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

NHS Digital reported a mean length of stay of 11.2 days for patients undergoing RC in 2019/20

The annual cost of stoma products across NHS Commissioning Groups in England was reported at £2,008 (£2,144 at 2021 prices) by East of England NHS Collaborative Hub (2019). The provision and cost of undergarments was found by web searches. Women are able to get on prescription annually up to 6 pairs of underwear (around £10 each) and 3 support garments (around £40 each) and men can get 3 belt supports at an average cost of £80 to £90 each. A value of £100 per patient was used, assuming some people may buy their own undergarments.

In addition to these costs each patient was assumed to attend a stoma clinic (£49) and have two telephone contacts (£36). Hence the total NHS cost for managing a stoma after year 1 was £2,329.

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

The resources required are the cost of leasing the machine and the consumables. In addition all healthcare professionals must undertake training before using Synergo. This consists of a 4 to 5 hours (5 hours costed) training course and supervision by a company representative of the operator's initial procedures. Each site was assumed to train 3 band 7 nurses and 1 consultant at an hourly cost of £61 and £122 respectively (Curtis and Burns, 2020). Assuming each person practises for 5 years on average, the annual cost per site for training was £306.

No additional staff are required to operate the Synergo system. It would be operated by the band 7 nurse administering the intravesical chemotherapy. The patient would require to be on site for an extra 30 minutes but this does not require any staff input (Source: Dr Lev, General Manager, Medical Enterprises Europe B.V).

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

No additional resources will be required; rather the interventions will delay or obviate the need for radical cystectomies.
The main changes will be fewer radical cystectomies with associated reduction in the need for reinterventions post initial surgery events and attendances at stoma clinics. The mean length of stay for RC was 11.2 days in 2019/20 (NHS Digital) for this procedure and the procedure was associated with a 30% re-intervention rate (Afsher, 2018).

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

See previous answer.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

Costs	Synergo + MMC	MMC	Difference
MMC drug and administration Cost per patient	£5,381	£4,649	£732 (Cost of 30 mins extra wait x 12)
Synergo per patient	£6,308	£0	£6,308
Total costs per patient	£11,689	£4,649	£7,040

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

A detailed analysis of adverse events was reported in Brummelhuis (2021) and is used to inform this section.

AEs post Synergo treatment	Number %
Spasms	183 (62%)
Pain	82 (27%)
Catheter problems	52 (18%)
Dysuria	156 (53%)
Hematuria	88 (30%)
Urinary tract infection (all grade 2 or 3)	46 (16%)
Nocturia	43 (15%)
Incontinence	18 (6.1)

The paper reports that most events were mild to moderate and transitory, with only 6 (2%) of patients requiring medication for moderate incontinence.

Colombo (2003) provided a comparative analysis with Synergo + MMC versus MMC. The authors noted most local side events were identical in both groups, with the only significant difference being pelvic pain. Although higher pain was reported, no patients terminated the treatment because of pain. The authors added that these events were localised and transitory during delivery and resolved with no residual effects.

This evidence is consistent with the evidence synthesised across more studies and reported in Section 6 of Part A.

The model included treatment for all UTIs (16%) and the 2% of patients requiring treatment for incontinence.

UTIs were assumed to require treatment with amoxicillin (as recommended by the NHS)

The recommended dose is 500 mg 3 times a day for 7 days at a cost of £1.72 per treatment (British National Formulary). In additional a cytology test, at a cost of £7.47 (Reference costs DAPS01 updated to 2021 prices) and one GP attendance at a cost of £33.73 (Curtis and Burns [2020] cost of £33 updated to 2021 prices). Applying these costs to 16% of patients receiving Synergo + MMC gave a mean cost per patient for UTIs of £6.87.

Incontinence is managed in the NHS by duloxetine twice a day and assess after 2 to 4 weeks at a cost of £9.96. In addition 2 GP attendances are assumed at a cost of 2 x £33.73 (Curtis and Burns [2020] cost of £33 updated to 2021 prices). Applying these costs to 2% of patients receiving Synergo + MMC gave a mean cost per patient for incontinence of £1.55 and a total cost for adverse events of £8.42 per patient receiving Synergo + MMC.

Adverse events common to both arms arising from the use of MMC have not been costed.

The Scope included 3 outcomes related to adverse events:

- Treatment tolerability
- Treatment delivery rates in inpatient or outpatient settings
- Rates of failed treatment delivery due to device-related issues.

Tolerability is linked to the adverse events. Brummelhuis reported about 15% of patients in each arm developed an allergy to MMC and were switched to epirubicin. This was delivered by the Synergo machine. The rates were balanced across the arms. The authors also report 11.4% of patients discontinued treatment due to side effects but no further analysis was provided. In the model it has been assumed all patients had a mean of 12 treatments. If some received less due to stopping treatment then the cost per patient may be overstated; the efficacy and safety reflects the doses administered in practice so are correct.

No patients discontinued treatment in Colombo (2003). The Brummelhuis patients were intensively pre-treated with multiple TURBs and intravesical installations which could explain the different discontinuation rates.

Treatment delivery was in outpatients across the studies.

Neither study reported any other data pertaining to failed treatment due to device-related issues.

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Adverse event	Items	Cost	Source
UTI	Drug, cytology and GP	£6.87	See above
Incontinence	Drug and GP x 2	£1.55	See above

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

There were no other costs.

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

Yes People with certain co-morbidities, particularly mental health disorders or dementia who live alone are likely to require support from social services to manage their stoma safely. These costs have not been included in the base case because of gaps in evidence sources. However we have included a sensitivity analysis based on the following.

The biggest risk factor for dementia is age, with 7.1% of all people over the age of 65 years having dementia, rising to one in five for those aged between 85 to 89. (Source https://www.dementiastatistics.org/statistics/prevalence-by-age-in-the-uk)

We cannot establish the percentage of these who live independently and hence would require support. (The number living alone is 37% but that is across the population. Source http://www.ageuk.org.uk/globalassets/age-uk/documents/reports-and-publications/later_life_uk_factsheet.pdf)

People who are in a wheelchair or have very limited mobility, living alone, may also require assistance.

Costs for homecare vary across the country, but average around £15 per hour (source Age UK https://www.ageuk.org.uk/information-advice/care/paying-for-care/paying-for-homecare/).

If 5% of people with a stoma require 15 minutes help every second day to change their bag the cost would be an average of about £35 across all people with stomas a year.

People with a stoma are likely to experience a range of problems such as depression, anxiety, sexual disorders, pain, rashes etc (Ayaz-Alkaya, 2018). Hence it can be deduced that they are more likely to require support in primary and secondary care. However, no cost for these events in people with a stoma were identified.

Sensitivity analyses report the impact that higher costs post stoma have on the base case results.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per patient over lifetime of device (device is leased so have no lifetime to hospital)	£11,150 is cost per patient for Synergo + MMC for drug and its administration over a lifetime	Model
Consumables per year (if applicable) and over lifetime of patient	£5,880 for first year and £5,690 lifetime (included in cost of £11,150)	Model
Maintenance cost per year and over lifetime of device	NA	Model
Training cost over lifetime of patient	£10 (included in £11,150)	Model
Other costs vary per year and are reported over lifetime of patient	£25,391	Model
Total cost per patient over lifetime	£36,541	Model

Table 8 Total costs for the comparator in the model

Description	Cost	Source
Cost per patient over lifetime of device (device is leased so have no lifetime to hospital)	£4,013	Model
Consumables per year (if applicable) and over lifetime of patient	NA	Text
Maintenance cost per year and over lifetime of device	NA	Text
Training cost over lifetime of patient	NA	Text
Other costs vary per year and are reported over lifetime of patient	£36,994	Model
Total cost per patient over lifetime	£41,007	Model

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator (£)**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***
Remission	£12,762	£4,095	£8,667
Recurrence	£6,972	£11,049	-£4,077
Post-cystectomy	£8,940	£17,431	-£8,491
Dead (palliative care)	£7,867	£8,432	-£565
Total	**£36,541**	**£41,007**	**-£4,466**
Outcomes per patient			
Number of RCs	24.28	33.26	-8.98
Life years	12.93	11.77	1.16
QALYs	10.16	8.41	1.75
Cost /QALY	Synergo + MMC dominant		
Length of stay			
Total number of bed days	272	372	-101
Number of bed days per patient	5.4	7.4	-2.0

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

No scenario analyses were done. Rather we tested aspects such as number of patients per site through deterministic sensitivity analysis. We adopted +/-20% values, ranges wider enough to capture the impact of any credible variation in patient numbers per year

Describe the differences between the base case and each scenario analysis.

NA

Describe how the scenario analyses were included in the cost analysis.

NA

Describe the evidence that justifies including any scenario analyses.

NA

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator (£)**	**Difference in cost per patient (£)***
Scenario 1 (total costs)	Text	Text	Text
Scenario 2 (total costs)	Text	Text	Text
* Negative values indicate a cost saving. Adapt this table as necessary.			

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Deterministic sensitivity analyses were undertaken of the clinical and cost variables. No probabilistic sensitivity analyses were undertaken because the clinical data were point estimates only, with no measure of variance reported in the studies.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

This table provides the sensitivity analysis and results. These in the main changed the base case value by +/- 20%. Exceptions are age, sex and discount rates. The clinical studies reported no confidence intervals to provide more meaningful analyses. A Tornado diagram is presented later.

Base case incremental cost per patient	-£4,466	Low value		High value	
Parameter	Base case value	Value	Incremental cost	Value	Incremental cost
Average starting age (years)	64	54	-£4,103	74	-£3,963
Proportion male	75.0%	60.0%	-£4,456	90.0%	-£4,473
Discount rate - costs	3.5%	2.8%	-£4,670	4.2%	-£4,263
Synergo annual recurrence risk (years 0-4)	6.3%	5.0%	-£5,691	7.5%	-£3,309
Synergo annual recurrence risk (years 5-9)	2.7%	2.2%	-£5,364	3.2%	-£3,634
MMC annual recurrence risk (years 0-4)	24.6%	19.7%	-£1,976	29.6%	-£6,325
MMC annual recurrence risk (years 5-9)	1.4%	1.1%	-£4,288	1.6%	-£4,637
Perioperative cystectomy annual mortality risk	2.1%	1.7%	-£4,495	2.5%	-£4,437
Post-cystectomy annual mortality rate (years 0-4)	5.0%	4.0%	-£5,057	6.0%	-£3,917
Post-cystectomy annual mortality rate (years 5-9)	5.0%	4.0%	-£4,898	6.0%	-£4,054
Cost per patient for Synergo	£11,689	£9,351	-£6,696	£14,027	-£2,236
Cost per patient for MMC	£4,649	£3,719	-£3,663	£5,579	-£5,268
Cost per patient for cystectomy	£16,168	£12,934	-£3,709	£19,401	-£5,223
Cost of stoma management beyond year 1	£2,329	£1,863	-£2,768	£2,794	-£6,164
Short-term cystoscopy follow-up cost	£406	£325	-£4,608	£488	-£4,324
Long-term cystoscopy follow-up cost	£160	£128	-£4,572	£192	-£4,360
Annual cost of palliative care	£14,167	£11,333	-£4,353	£17,000	-£4,579

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

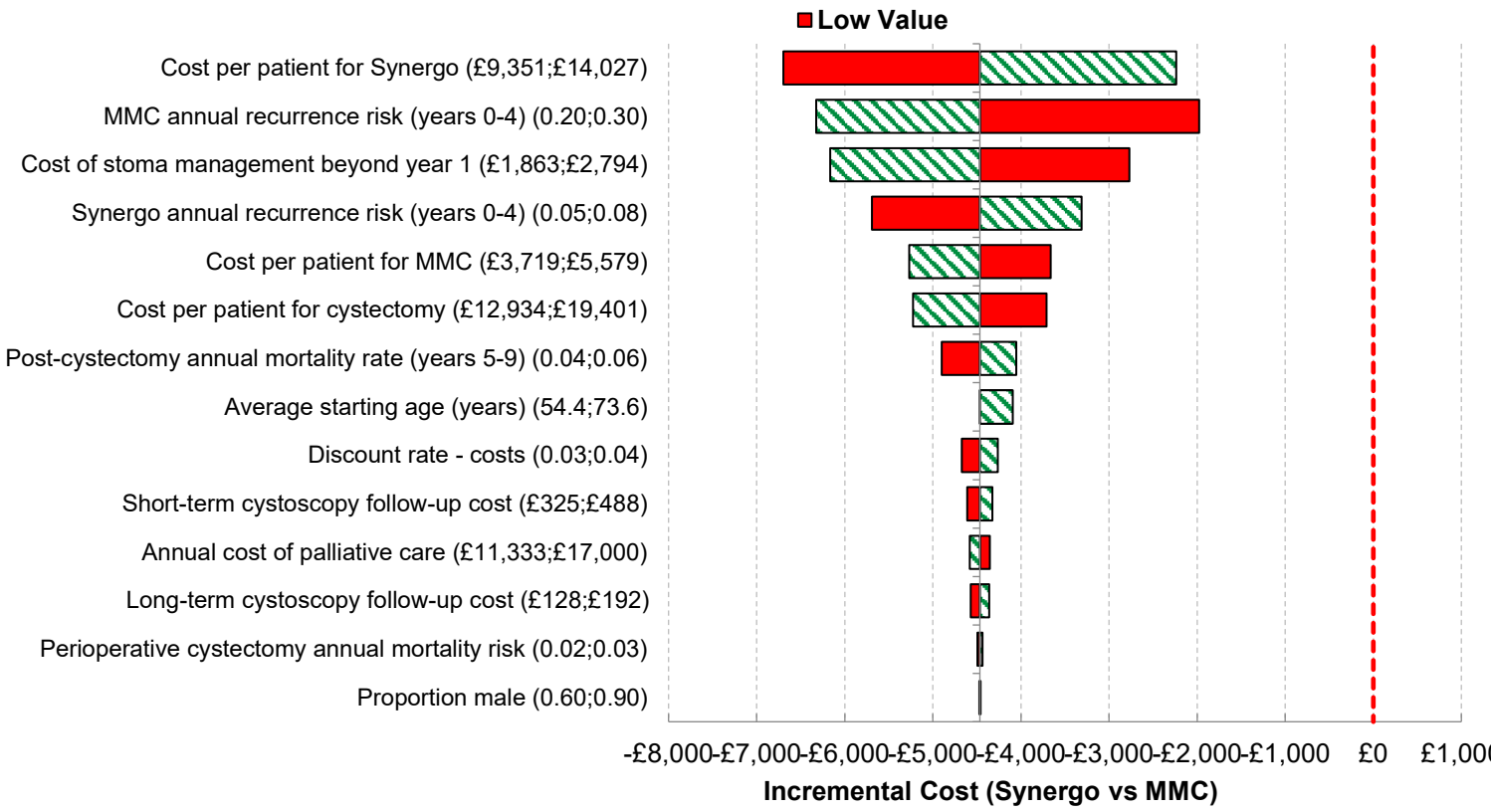
Any variable that did not impact cost savings was excluded, including benefit discount rate, length of stay and HRQoL input.

The variables in table 3 were all addressed in sensitivity analysis.

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

See table above for results. The associated tornado diagram is now presented.



What were the main findings of each of the sensitivity analyses?

The main finding is Synergo + MMC avoids RCs. In this cohort of 50 patients in each arm, 24 required RC in the Synergo + MMC arm, a 27% reduction from the 33 who required RC in the MMC only arm. Avoiding RCs reduced NHS costs and improved quality of life.

All of the sensitivity analyses show that Synergo + MMC is cost saving over a lifetime time horizon compared with MMC in this patient group. The main drivers are listed in the tornado diagram.

The results are most sensitive to the additional cost per patient of using the device. This cost comprises the drug cost, cost of consumables, cost of attendances at outpatients plus the cost of the device itself. The last element is quite a small element of the cost per patient (£327 out of £11,689). Hence results are more sensitive to a change in the number of administrations of MMC than the number of patients at each site. We used the mean number of administrations reported for the study. If these are lower in clinical practice then the savings would have a materially greater impact in reducing costs in the Synergo + MMC arm. For example, a 20% reduction in these costs driven by a 20% reduction in the number of planned cycles (12) to around 10 would increase savings to around £6,700 per patient.

The model is much less sensitive to the cost of MMC. Reducing these by 20% reduces the potential savings to £3,663 per patient.

If the annual risk of recurrence with MMC is less than that reported by Colombo (2011) then this reduces the relative benefit of Synergo + MMC. If the annual risk of recurrence with Synergo + MMC reduces from that reported then the cost savings increase. This is the major clinical effectiveness variable driving the results.

Unsurprisingly the results are sensitive to the annual cost of stoma products. As noted earlier the cost used in the base case is an underestimate of the true cost to the NHS and social care because it assumes no-one with a stoma requires assistance from social services. An increase in cost to around £2,800 per patient would increase the savings from Synergo + MMC by 38% to £6,164 per patient.

The model is also sensitive to the cost of cystectomy and the mortality rate post-cystectomy. A 20% change in cystectomy costs alters the base case savings by a similar percentage change. Reducing annual mortality from the 5% assumed in the base case increase the cost savings as more patients are alive for longer and hence require stoma products.

If one defines parameters that change baseline costs by less that 10% in either direction as having little impact on results then the following parameters fall into that category: starting age, male/female split, discount rates, perioperative cystectomy annual mortality risk, post-cystectomy annual mortality rate, palliative care unit costs cystoscopy follow-up costs and discount rates.

What are the main sources of uncertainty about the model's conclusions?

The main sources of uncertainty are around the clinical data and their generalisability to UK practice. The treatment regimens are consistent with the Synergo + MMC protocols, as advised to each site, so in principle the results from these studies should generalise. But simple deterministic sensitivity analysis by changing RFS by +/- 20% has limited information content because we do not know what the actual confidence intervals are.

Miscellaneous results

Include any other relevant results here.

None

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

Model was quality assured by a YHEC consultant who is independent of the team working on the submission. He used the relevant checklists developed by YHEC for decision trees, Markov models and sensitivity analysis. No external references sources are available to provide external validation.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

No clinical experts were involved with validating the model.

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The economic model has identified that using Synergo + MMC is bladder-saving for patients and in consequence cost saving to the NHS compared with administering further sessions of MMC in patients who have already failed MMC. Initially, the NHS has a higher cost for the device and consumables but the relatively higher remission rate associated with this form of administration, particularly in the first 5 years, reduces the number of patients requiring RC and some avoid the need for RC altogether. Delaying the procedure brings material benefits in quality of life and reduces the pathway costs by avoiding the cost of managing stomas. It also reduced the mean bed days per patient by 2 days (27%).

Briefly discuss the relevance of the evidence base to the scope.

Evidence is judged relevant to the scope in terms of indication.

The population is narrower than the scope being those that are intolerant to or cannot have BCG. Thus it has not modelled BCG as a comparator nor people who have failed BCG. This positioning reflects the company's suggested positioning for Synergo + MMC which is not directly against BCG (see NICE, 2020) and the comparative evidence base against MMC. There are several studies of Synergo + MMC in patient groups who have been pre-treated with BCG and have recurrent tumours or who proved refractory to BCG (for example Brummelhuis (2021), van Valenberg (2018), Nativ (2009), Ayres (2018) and Tan (2020)). However, the only RCT has such material weaknesses that it could be not used to populate the model. The difficulty was finding a comparator using MMC in this patient group.

There are also no well-conducted studies comparing Synergo + MMC with other device-assisted chemotherapy options (hyperthermic or electromotive drug administration). In all Synergo studies RC is a clinical outcome not a comparator.

Many of the outcomes listed in the scope have been modelled. Exceptions are complete response rates for CIS and papillary NIMBC and disease specific survival. The studies used in this Part do not record complete response rates. Several of the clinical studies reported in Part A do report the values for these parameters.

The costs reported matched the scope except it was not possible to estimate robustly the mean cost to social care to manage patients with stomas.

No subgroup analysis of CIS only, papillary only or by risk group, stage and grade, or by intravesical agent was possible due to the absence of comparative clinical data limit in these groups.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

Not applicable

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

Yes cost analysis is relevant to the patient groups in England that match those included in the studies. Doses and follow-up in the trials are consistent with those adopted in NHS clinical practice. Unit costs were taken from national databases and data on resources used during and after RC were taken from recent publications informed by patients managed in the NHS (Afshar [2018] and NHS East of England [2019]).

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

The strengths of these analyses are they use the best available clinical evidence to match the patients in the scope (Colombo 2011). THE NICE bladder cancer pathway has informed the pathway. We have modelled drug doses and number of administrations consistent with UK practice, with follow-up in line with the NICE guideline (NICE, 2015). UK costs from national datasets are used, with the cost of palliative care being the only exception. However, this did come from an HTA conducted in the UK. Quality of life measures were informed by EQ-5D scores reported by patients in England. Survival post RC used linked HES and ONS data and thus are generalisable. (Asher, 2018). We are able to report the values for many of the outcomes listed in the scope. The weaknesses are we could not find clinical data to model all of the subgroups and interventions listed in the scope.

Detail any further analyses that could be done to improve the reliability of the results.

The key to improving the reliability and confidence in the results would be to have 95% confidence intervals, or a similar measure of dispersion, around the single point values used to report the clinical outcomes in the studies. Without a better understanding of these it is not possible to do robust probabilistic sensitivity analysis.

5 References

Please include all references below using NICE's standard referencing style.

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6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	01 Feb 2021
Date span of search:	Search dates: 01-Jan-2000 to 01-Feb-2021
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Search strategy: 1 - cancer 2 - neoplasm 3 - tumour 4 - tumour 5 - #1 OR #2 OR #3 OR #4 6 - transitional 7 - urothelial 8 - urinary 9 - bladder 10 - #5 OR #6 OR #7 OR #8 11 - #9 AND #10 12 - thermochemo*[tw] 13 - thermo-chemo*[tw] 14 - chemotherm*[tw] 15 - chemo-therm*[tw] 16 - chemohypertherm*[tw] 17 - hypertherm* 18 - #12 OR #13 OR #14 OR #15 OR #16 OR #17 19 - #11 AND #18 20 - non-muscle-invasive 21 - non-muscle invasive 22 - non-invasive 23 - superficial 24 - nmibc 25 - stcc 26 - papillar* 27 - CIS 28 - in-situ 29 - #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 30 - #19 AND #29 31 - synergo[tw] 32 - microwave[tw] 33 - radiofrequency[tw] 34 - radio-frequency[tw] 35 - #31 OR #32 OR #33 OR #34	

36 - #30 AND #35
Databases:

1. PubMed – US National Library of Medicine (NLM)
2. Embase – Elsevier
3. Cochrane Library – Cochrane Collaboration

PubMed

Original query:

(((((cancer) OR neoplasm) OR tumour) OR tumour)) AND (((((transitional) OR urothelial) OR urinary OR bladder)) AND (((((((thermochemo*[tw]) OR thermo-chemo*[tw]) OR chemotherm*[tw]) OR chemo-therm*[tw] OR chemohypertherm*[tw] OR hypertherm*) AND (((((non-muscle-invasive) OR non-muscle invasive) OR non-invasive) OR superficial) OR nmibc) OR stcc OR papillar* OR CIS OR in-situ)) AND ((((synergo[tw] OR microwave[tw]) OR radiofrequency[tw]) OR radio-frequency[tw])))) AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]) AND English[lang]

Translations:

cancer	"cancer's"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]
neoplasm	"neoplasm's"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]
tumour	"cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumour"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumours"[All Fields]
tumour	"cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumour"[All Fields] OR "tumour's"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumours"[All Fields]
transitional	"transit"[All Fields] OR "transited"[All Fields] OR "transiting"[All Fields] OR "transition"[All Fields] OR "transitional"[All Fields] OR "transitionals"[All Fields] OR "transitioned"[All Fields] OR "transitioning"[All Fields] OR "transitions"[All Fields] OR "transits"[All Fields]
urinary	"urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]
bladder	"bladder's"[All Fields] OR "urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields] OR "bladders"[All Fields]
invasive	"invasibility"[All Fields] OR "invasible"[All Fields] OR "invasion"[All Fields] OR "invasions"[All Fields] OR "invasive"[All Fields] OR "invasively"[All Fields] OR

	"invasiveness"[All Fields] OR "invasives"[All Fields] OR "invasivity"[All Fields]
superficial	"superficial"[All Fields] OR "superficially"[All Fields] OR "superficials"[All Fields]
nmibc	"nmibc"[All Fields] OR "nmibcs"[All Fields]

Translated query:

("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] OR ("neoplasm s"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumour"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumours"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumour"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumours"[All Fields])) AND (("transit"[All Fields] OR "transited"[All Fields] OR "transiting"[All Fields] OR "transition"[All Fields] OR "transitional"[All Fields] OR "transitionals"[All Fields] OR "transitioned"[All Fields] OR "transitioning"[All Fields] OR "transitions"[All Fields] OR "transits"[All Fields] OR "urothelial"[All Fields] OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("bladder s"[All Fields] OR "urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields] OR "bladders"[All Fields])) AND ((((("thermochemo*"[Text Word] OR "thermo chemo*"[Text Word] OR "chemotherm*"[Text Word] OR "chemo therm*"[Text Word] OR "chemohypertherm*"[Text Word] OR "hypertherm*"[All Fields]) AND ("non-muscle-invasive"[All Fields] OR ("non-muscle"[All Fields] AND ("invasibility"[All Fields] OR "invasible"[All Fields] OR "invasion"[All Fields] OR "invasions"[All Fields] OR "invasive"[All Fields] OR "invasively"[All Fields] OR "invasiveness"[All Fields] OR "invasives"[All Fields] OR "invasivity"[All Fields])) OR "non-invasive"[All Fields] OR ("superficial"[All Fields] OR "superficially"[All Fields] OR "superficials"[All Fields]) OR ("nmibc"[All Fields] OR "nmibcs"[All Fields]))) OR "stcc"[All Fields] OR "papillar*"[All Fields] OR "CIS"[All Fields] OR "in-situ"[All Fields]) AND ("synergo"[Text Word] OR "microwave"[Text Word] OR "radiofrequency"[Text Word] OR "radio-frequency"[Text Word]))) AND 2000/01/01:3000/12/31[Date - Publication] AND "English"[Language]

Embase–Elsevier

No.	Query	Results	Date
#1	cancer OR neoplasm OR 'malignant neoplasm'	4703463	01-Feb-21
#2	'transitional cell carcinoma'/exp OR 'urothelial bladder cancer' OR 'urothelial cancer' OR 'urothelial carcinoma of the bladder'/exp OR 'urothelial carcinoma of the bladder' OR 'bladder carcinoma'/exp OR 'bladder cancer'/exp OR 'bladder tumour'/exp OR 'non muscle invasive bladder cancer'/exp	111067	01-Feb-21
#3	#1 AND #2	94213	01-Feb-21

#4	thermochemotherapy OR 'thermo chemo*' OR thermochemo* OR chemotherm* OR 'chemo therm*' OR chemohyperthermia OR thermotherapy	22537	01-Feb-21
#5	#3 AND #4	370	01-Feb-21
#6	synergo OR 'microwave thermotherapy' OR 'radiofrequency therapy' OR 'radiofrequency-induced'	5833	01-Feb-21
#7	#5 AND #6 AND [humans]/lim AND [english]/lim AND [2000-2021]/py	71	01-Feb-21

Cochrane Library – Cochrane Collaboration

Column1	Column2	Column3
Search Name:	MEL	
Date Run:	01/02/2021 11:48:48	
Comment:		
ID	Search	Hits
#1	cancer	185558
#2	neoplasm	26196
#3	tumour	66018
#4	#1 OR #2 OR #3	210553
#5	transitional	2606
#6	urothelial	1168
#7	urinary OR bladder	52832
#8	#5 OR #6 OR #7	54431
#9	#4 AND #8	9711
#10	thermochemo*	35
#11	thermo NEXT chemo*	11
#12	chemotherm*	10
#13	chemo NEXT therm*	4
#14	chemohypertherm*	37
#15	hypertherm*	2209
#16	#10 OR #11 OR #12 OR #13 OR #14 OR #15	2250
#17	#9 AND #16	107
#18	non NEXT muscle NEXT invasive	652
#19	non NEXT "muscle invasive"	652
#20	non NEXT invasive	11852
#21	superficial	7703
#22	nmibc	382
#23	stcc	15
#24	papillar*	1645
#25	CIS	10035
#26	in NEXT situ	6655
#27	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	36494
#28	#17 AND #27	67
#29	synergo	11
#30	microwave	828
#31	radiofrequency	4602

#32	radio NEXT frequency	441
#33	#29 OR #30 OR #31 OR #32	5409
#34	#28 AND #33 with Cochrane Library publication date Between Jan 2000 and Jan 2021, in Cochrane Reviews	6

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Medical Enterprises continuously monitors the published literature for the presence of studies related to Synergo, as part of its clinical evaluation efforts. Medical Enterprises is not aware of any ongoing studies of Synergo other than those previously published or sponsored by Medical Enterprises. Nonetheless, a search was performed to identify all relevant published works using the general specifications.

Inclusion and exclusion criteria:

Inclusion criteria

Population: People with intermediate or high-risk non-muscle-invasive bladder cancer (NMIBC) who are a) BCG-unresponsive/resistant or b) indicated for BCG after failing previous instillations other than BCG but either cannot tolerate it, do not wish to be treated with it, contra-indicated to it, or cannot be administered it due to shortage in supply.

Interventions: Radiofrequency-induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 System

Outcomes:

- Recurrence rates and time to recurrence
- Disease progression and changes to treatment indicative of advanced disease
- Rates of cystectomy
- Complete response rate for carcinoma in situ
- Disease-specific and overall survival
- Health-related quality of life
- Treatment tolerability
- Length of hospital stay
- Treatment delivery rates in inpatient or outpatient settings
- Device-related adverse events

Study design: Original clinical research.

Prospective and retrospective studies with one or more arms that report outcome data by target population.

Language restrictions: Publications in English only

Exclusion criteria:

Population: NA

Interventions: NA

Outcomes: NA

Study design: Insufficient detail of methods and results to enable data extraction, such as:

- dosage of the drug administered with the device not reported clearly or at all

□ number of administered treatments not reported Language restrictions: NA Search dates: NA
Data abstraction strategy:
Single abstraction. Juxtaposition of study article PDFs to electronic data abstraction forms

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

A search was conducted for studies reporting QoL using a generic tool for people with a stoma. Searches were conducted in google and google scholar from 2015 using the following approach:

Stoma + quality of life or QoL or utility or HRQoL
then
Stoma + quality of life or QoL or utility or HRQoL + england or united kingdom
then
Stoma + cost-effectiveness or cost effectiveness + england or united kingdom
then
cystectomy + stoma + quality of life or QoL or utility or HRQoL
then
cystectomy + Stoma + cost-effectiveness or cost effectiveness

In addition the NIHR Health Technology Assessment database was searched for HTAs including people with bladder cancer. The NICE website was also searched for evidence on relevant economic decision problems.

Inclusion and exclusion criteria:

Studies were included if they reported QoL scores using a measure which was derived from a generic and validated tool (SF or EQ-5D). Three studies were included Cox (2020), Mason (2018) and Mowatt (2010).

Data abstraction strategy:

Data relating to the EQ-5D scores were extracted.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

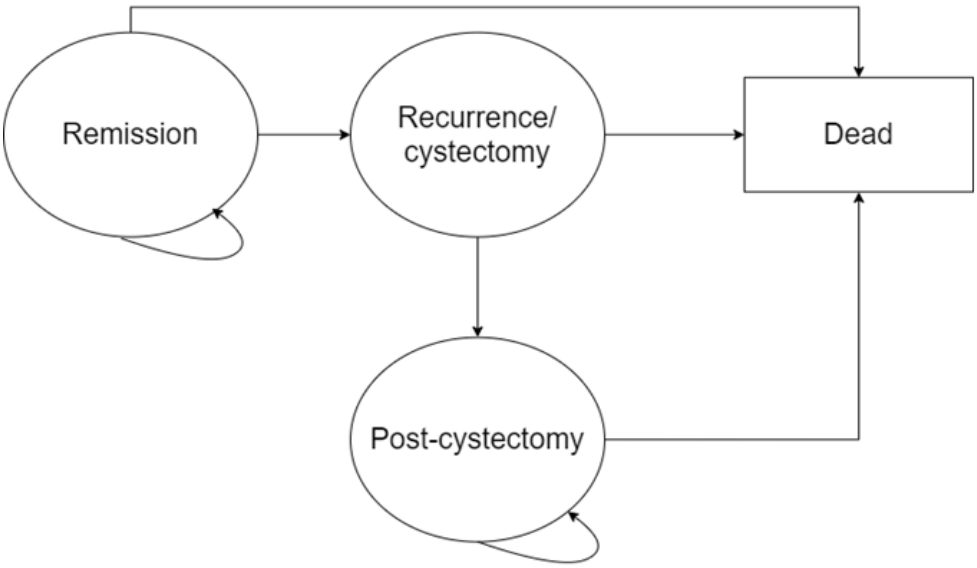
No studies were initially considered and later excluded.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

The PRISMA relates to the systematic search only.

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

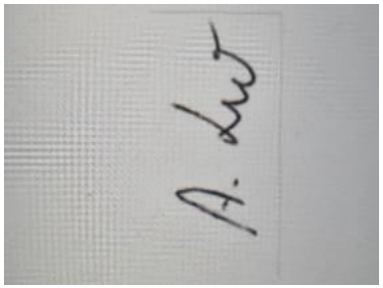
Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	29 March 2021
Print:	Click or tap here to enter text.	**Role / organisation:**	Director

Contact email: [redacted]

NICE National Institute for Health and Care Excellence

Medical technologies guidance

Collated expert questionnaires

Technology name & indication: Synergo for non-muscle-invasive bladder cancer

Experts & declarations of interest (DOI)

Expert #1	Prof Sanjeev Madaan, Consultant Urological Surgeon & Lead Cancer Clinician, Darent Valley Hospital, Dartford
	DOI: Indirect - Currently uses this device
Expert #2	Mr Benjamin Ayres, Consultant Urological Surgeon, St Georges University Hospital NHS Foundation Trust
	DOI: Direct-financial – Funding to attend International Urology Conference by Synergo, Medical Enterprises Europe BV (July 2018 & May 2018; Lecturer fees for teaching on bladder cancer. Kyowa Kirin (May 2017) / Olympus (Nov 2015 – Feb 2019)
Expert #3	Toby Page, Consultant Urologist, Newcastle upon Tyne Hospitals Trust
	DOI: none
Expert #4	Param Mariappan, Consultant Urological Surgeon & Honorary Clinical Senior Lecturer, NHS Lothian & University of Edinburgh
	DOI: none
Expert #5	Ahmed Ali, Consultant Urological Surgeon, Frimley Health NHS Foundation Trust
	DOI: none
Expert #6	Angela Elliott, Urology Clinical Nurse Specialist – Bladder Cancer Nurse, Frimley Health NHS Foundation Trust
	DOI: Non-financial professional - has being treating patients with this since 2009
Expert #7	Chris Backhouse, Macmillan Urology Cancer CNS, St Georges University Hospitals NHS Foundation Trust
	DOI: none

How NICE uses this information: the advice and views given in these questionnaires are used by the NICE medical technologies advisory committee (MTAC) to assist them in making their draft guidance recommendations on a technology. It may be passed to third parties associated with NICE work in accordance with the Data Protection Act 2018 and data sharing guidance issued by the Information Commissioner's Office. Expert advice and views represent an individual's opinion and not that of their employer, professional society or a consensus view (unless indicated). Consent has been sought from each expert to publish their views on the NICE website.

For more in formation about how NICE processes data please see our privacy notice.

1. **Please describe your level of experience with the technology, for example: Are you familiar with the technology? Have you used it? Are you currently using it? Have you been involved in any research or development on this technology? Do you know how widely used this technology is in the NHS?**

Expert #1	Yes, I am familiar with this technology. We have been using this since 2011 when HYMN trial started. We are continuing to use this and are regional referral centre for the high-risk superficial bladder cancer (NMIBC) patients who have failed BCG and are not suitable for cystectomy. We participated in HYMN trial (Tan et al. 2018) This technology is used in limited centres possibly due to set up costs and increased cost of treatment compared to cold mitomycin. E.g in Kent & Medway, we are the only trust who have this facility and other three trusts refer the relevant patients to us.
Expert #2	Yes I have been using this technology as a consultant urologist for the last 7 years. I was first trained in its use as a registrar in 2009. We are currently using it as St George's and have treated 250 patients over the time we have been using it. St George's was involved with the Hymn RCT trial using Synergo for BCG failures (I personally wasn't as still a registrar then). We have published our experience in the following articles: Van Valenberg FJP et al, Intravesical Radiofrequency-induced chemohyperthermia for carcinoma in situ of the urinary bladder: a retrospective multicentre study. Bladder Cancer 2018;4:365-376.

	Ayres B et al, MP08-01 10-year experience of RTE thermochemotherapy for high risk non muscle invasice bladder cancer that has failed BCG. J Urol 2018;199 (4S), e96 Sooriakumaran P et al, Predictive factors for time to progression after hyperthermic mitomycin C treatment for high-risk non-muscle invasive urothelial carcinoma of the bladder: an observational cohort study of 97 patietns. Urol Int 2016;96:83-90. I don't know how widely it is used in the NHS – I am aware of Synergo machines in our unit and Darent Valley, Dartford in the South East.
Expert #3	Familiar and have used Synergo in past No using it at present PI on Hymn trial investigating and evaluating Synergo, trial funded via NIHR and not commercially Not aware of current use in wider NHS aware of local use in Region.
Expert #4	I am familiar with the technology; I have not used it (but have used another device assisted delivery of heated chemotherapy); I have not been involved in any research or development on this technology I do not know how widely it is used in the NHS
Expert #5	I have had multiple lectures and courses regarding he treatment. In addition, I refer patients frequently to have their treatment in other centres and have received good feedback. We are in the process of starting this treatment at our trust and can report our early experience in 6 months. I have not been part of any research with this technology, but from next week we will be collecting the data from our own centre and will carry an internal audit with outcomes

	There are multiple centres that uses this technology in the UK with no reported major adverse events. NICE adoption will help to smooth the process of procurement of this technology in more centres to serve more patients locally.
Expert #6	Yes I have been using since 2009 I have used it regularly since then We are still currently using it I was involoved in the HYMN study 2009 – 20012 in treating the patients Not very widely in South East there are only 2 machines
Expert #7	I have run Synergo Nurse led clinic for 7.5 years at St Georges. I am currently using the Synergo machine on a weekly basis I am involved in the 10yr Synergo study and ongoing data collection for this modality Not widely used at the moment but lots of interest and other units looking to set up their own Synergo service

2. Has the technology been superseded or replaced?

Expert #1	no
Expert #2	No. Other machines are available to provide hyperthermia which heat the chemotherapy solution outside the bladder before pumping it around the bladder – these therefore work in a different way and have not published as widely as Synergo systems on outcomes.
Expert #3	Yes different system (Combat BRS) now in use
Expert #4	There are alternatives
Expert #5	No
Expert #6	We have had software and parts updated
Expert #7	No

Current management

3. How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?

Expert #1	This technology is certainly innovative compared to current SOC although it is not very new and has been around for a long time.
Expert #2	This technology is innovative, particularly for BCG failures. These patients should have a radical cystectomy, which I have outlined above is a major life-changing surgery. Many patients decline it and many are not fit enough for it. Having an alternative for this group of patients, many of whom are elderly, is extremely important and often is a main point of discussion at international academic meetings. Systemic immunotherapy is an alternative novel treatment for BCG failures but in my opinion the emerging clinical data shows higher recurrence rates than Synergo with potential for systemic toxicity. I believe it is expensive too.
Expert #3	Novel concept
Expert #4	It is a significant variation to the standard of care.
Expert #5	The concept of hypethermic induced chemotherapy delivered treatment has been used in the past in managing other types of caner such as intraabdominal tumours for colorectal, gynacolocical and liver ad pancreatic malignancies. Furthermore, the concept of enhanced chemotherapy delivery is not new. Electromotive chemotherapy bladder treatment (EMDA) have been used and data have should that its effective and safe (Di Stasi 2003). Synergo, provide similar concept but with radiofrequency waves to rise the temperature inside the bladder with continuous cooling and temperature monitoring. This is only a minor change from EMDA
Expert #6	Was innovative at start of use but we have been using Years. There have been quite a few articles discussing Synergo. Novel concept based on radiation waves
Expert #6	Totally novel concept in the use of Radiofrequency waves in hyperthermia

4. Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?

Expert #1	There is no competing technology. There were some trials going on with COMBAT system (HIVEC trial) which offers passive hyperthermia instead of RF but I am not sure about their outcome EMDA is another device assisted chemotherapy, which is not being used currently.
Expert #2	Hyperthermia can be provided by heating the chemotherapy outside the bladder and then circulating it in and out of the bladder with a catheter. The COMBAT BRS system (HIVEC trials) is an example of this. It therefore has a different mechanism of action – whether this impacts on effectiveness or clinical outcomes at the moment is unknown as far as I am aware. Clinical data is still immature particularly in the BCG failure group, where I believe additional treatment options are needed. Systematic immunotherapy is now being trialled for BCG failure – more expensive and potential for systematic toxicity and at present appears less effective to Synergo in BCG failure. Intravesical gemcitabine and other chemotherapy agents can also be used in BCG failures, but so far clinical effectiveness is fairly poor.
Expert #3	COMBAT BRS from ACTA company. Combat system is smaller cheaper and simpler to run.
Expert #4	Yes - there are alternatives. The widely used alternatives involves heating the chemotherapy agent itself as it enters the bladder as opposed to heating the bladder.
Expert #5	There are two other devices that has been used to treat similar groups of patients as above. One technology utilises the use of electric current to enhance the delivery of chemotherapy treatment. This has much lower recurrence free survival and cancer progression to Synergo.

	The other type of treatment has the same concept but instead of heating the bladder in situ with radiofrequency, the chemotherapy is being heated outside and delivered to patients. However, the efficacy is again lower than what has been reported with Synergo. As far as I know this technology has now been decommissioned.
Expert #6	I am aware of other systems involving heated Mitomycin but Synergo heats the bladder and cells.
Expert #7	Other devices exist

Potential patient benefits

5. What do you consider to be the potential benefits to patients from using this technology?

Expert #1	Potential benefits are choice of treatment in the setting of BCG failure or intolerance as this is a viable alternative to cystectomy if patient is not fit or not keen for cystectomy
Expert #2	Main benefit is in BCG failure and bladder sparring potential of this treatment. Also has an important role to play if BCG not available as has been the case in recent years.
Expert #3	Additional treatment option for patients who are looking for less invasive treatments for bladder cancer or who are unsuitable for more invasive surgical treatment
Expert #4	Potentially better efficacy in reducing recurrence of cancer and possibly useful in other indications such as high grade non-muscle invasive bladder cancer.
Expert #5	There are multiple benefits for using this technology for patients with non-muscle invasive bladder cancer. It reduces the risk of cancer recurrence in patients with intermediate and high risk of recurrence if they have failed, unable or intolerant to BCG treatment. In addition, it can be used to reduce tumour burden in frail patients that are not fit for major surgery to make it possible to be managed by endoscopic treatment.

Expert #6	It is a viable alternative to Cystectomy so offers treatment to patients are are not fit for this radical surgery, or do not want and are not able to have BCG as they have medical contra-indications. It has also been used in small number of patients when there has been a BCG shortage.
Expert #7	The additional use of radiofrequency waves as well as heat/chemo will give greater scope to prevent bladder cancer recurrence

6. Are there any groups of people who would particularly benefit from this technology?

Expert #1	Yes, patients with high risk NMIBC who have failed BCG are intolerant to BCG
Expert #2	High risk NMIBC that has failed BCG treatment.
Expert #3	patients who are unfit to or unwilling to undergo cystectomy (bladder removal)surgery
Expert #4	Intermediate risk non-muscle invasive bladder cancer; high risk non-muscle invasive bladder cancer and those who have failed intravesical BCG.
Expert #5	There are three groups of patients that this treatment will be indicated in: 1- Patients with high risk non muscle invasive urothelial carcinoma of the bladder (NMIBC) that have failed standard treatment (BCG) 2- Patients with high risk NMIBC that BCG are contraindicated in Patients who are unable to tolerate the BCG treatment
Expert #6	Refractory BCG patients- so non-muscle invasive bladder cancer in the high risk group.
Expert #7	High risk non muscle invasive bladder cancer (NMIBC)patients who cannot have or have failed BCG

7. Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?

Expert #1	Yes, but in selected group of patients. As mentioned before BCG failed or BCG intolerant high risk NMIBC patients are normally offered cystectomy, which is a major operation. Some patients are not fit for this major op or may not be keen for this. In this group use of Synergo will not necessarily reduce visits but will avoid a more invasive treatment
Expert #2	Yes – for BCG failure potential for less invasive treatment – ie reduce number of cystectomies (high morbidity, readmissions, change in quality of life due to loss of bladder and often need for a stoma). Not all BCG failures will be suitable for Synergo and some will still need cystectomies. About 1/3 of our BCG failure patients treated with Synergo do not recur by 5 years. However, 1/3 experience persistent disease or disease progression and so case selection and proper counselling is important. Synergo does not treat disease in the prostatic urethra and upper urinary tracts and unfortunately, a number of patients recur in these areas after failing BCG. Therefore I would advocate prostatic urethral biopsies and up-to-date CT urogram before starting Synergo treatment – unfortunately this has not often been the case with published trials which may explain some of the lack of efficacy. Patients having Synergo treatment still need to attend hospital for treatments and flexible cystoscopy surveillance so it will not impact on hospital visits per se, but most of these will be on an outpatient basis.
Expert #3	some patients may avoid the need for surgical treatment if certain ago system successfully controls their bladder cancer
Expert #4	Yes - potential for all 3
Expert #5	The treatment currently offered for non-muscle invasive bladder cancer patients that fail BCG treatment, have a condition that makes BCG treatment contraindicated or are intolerant to BCG and are unfit for cystectomy or wish to preserve their bladder. Currently, in centres that are unable to offer the treatment, treat their patients with either cystectomy or multiple endoscopic treatments. Having the treatment available to more centres will enable patients to access the treatment and reduce the morbidity of a high morbidity cystectomy and its impact on health and body image or the impact or recurrent general anaesthetic requirement for the other group. The treatment is delivered in an outpatient setting and even in patients that might have tumour recurrence can be managed under local anaesthetic outpatient procedure.

Expert #6	It has the potential after 2 year of induction and maintenance of decreasing cancer of bladder cancer recurrence and progression. However follow-up surveillance is the same for patients in the high risk NMIBC group as patients who receive BCG. However may prevent radical surgery. And frequent general anaesthetics for TURBT
Expert #7	Could prevent the need for cystectomy in high risk recurrent NMIBC patients

Potential system impact

8. What do you consider to be the potential benefits to the health or care system from using this technology?

Expert #1	Reduce the number of patients needing cystectomy
Expert #2	Potentially reducing the number of cystectomies in BCG failure and the impact that this has on the healthcare system as set out above. Having an alternative treatment for patients who fail BCG but are not fit for cystectomy. As mentioned above, treatment of BCG failures remains a current topic of debate in international academic meetings with multiple studies trying to allow a bladder sparing approach. This is therefore a part of the bladder cancer pathway which is likely to change / adapt over the coming years.
Expert #3	this system it is beneficial as it offers patient is a additional treatment option for their non muscle invasive bladder cancer can be delivered in an outpatient or ambulatory setting
Expert #4	Potentially reduced hospital episodes from surveillance and treatment of recurrence; reduce cost, streamlining pathways; dedicated care.
Expert #5	This treatment will provide multiple benefits to the health system, mainly in reducing the risk of cancer progression and its costs and need of multi disciplinary support to those patients. Currently, radical cystectomy (the alternative current therapy) carries high morbidity and mortality that in spite of the adoption of robotic surgery, it still had a morbidity in the

	range of 30% and a 30 day mortality of 3%. Furthermore, The need for urinary diversion using part of bowel does carry its own long term problems such as renal failure, reflux disease, and stone formation. In addition, patients' initial care after radical cystectomy require high dependency care due to the high risk of post operative complications and this always cause a degree of logistical pressure on tertiary referral institutions that main radical cancer surgeries are undertaken at. For elderly and frail patients that are unfit for radical surgery, this treatment will provide clinicians the opportunity to treat such patients in an ambulatory fashion under local anaesthetic.
Expert #6	Unsure – It is a costly system for purchasing of catheter sets. Also procedure takes 1. 30minutes so only able to treat 4 patient in 1 day.
Expert #7	Nurse led clinic saves on time/cost of Doctor. Potentially prevents cost of admission and after care needed for cystectomy. Treatment of bladder cancer to reduce risk of recurrence/ progression in the future

9. Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?

Expert #1	About the same
Expert #2	Synergo is more expensive than standard care if given instead of mitomycin C or BCG to intermediate and high risk NMIBC as a first line treatment. It has a role here in times of BCF shortage though. However, Synergo may be cheaper than standard of care when BCG failures are concerned but I do not know the cost of cystectomy and managing its complications, follow up and cost of stoma bags and support. It also needs to be remembered that Synergo will not prevent all cystectomies in this group of patients and cystectomy may be the more appropriate treatment. There decisions need to be made on a case—by-case basis by a specialist multidisciplinary team.
Expert #3	likely to cost more than current standard of care due to outlay on the machine and single use disposable size as well as need for nurse or medical input during each treatment
Expert #4	Potentially cost neutral.

Expert #5	Having just been involved in adopting this treatment at our centre, I'm able to confirm that based on current tariffs this treatment will provide cost saving from current practice. The cost of treating 5 patients will full course of 12 treatments including induction and maintenance is equivalent to the cost of treating one patient with radical surgery and post-operative care over a year
Expert #6	I would think that is less than cystectomy and after care. But is more costly than BCG treatment. As reduces recurrence it may prevent regular TURBT
Expert #7	Not able to comment on the cost but it would increase Quality of life for patients not willing/ able to have cystectomy

10. What do you consider to be the resource impact from adopting this technology? Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?

Expert #1	Reduce the number of patients undergoing cystectomy and thus needing HDU / ITU bed. Synergo Rx is offered in outpatient setting.
Expert #2	Synergo is delivered in secondary care. It shifts treatment from inpatient to outpatient setting in its role in BCG failure. In its role in first line treatment instead of BCG is does not change the treatment setting. Resource impact is trained nurse and clinic space to deliver it with access to chemotherapy pharmacy.
Expert #3	it is likely that further resource would be required to provide a regular robust sin ago heated mitomycin service particularly with regards the treatment time per patient as well as the need for each treatment to be accompanied by a member of nursing or medical staff
Expert #4	The staff using the device need training. With the potential for reducing recurrence, care could be shifted to an out patient setting, indirectly.
Expert #5	During the initial phase of treatment implementation, specialist bladder cancer nurse can run the treatment with clinician supervision. Once training is complete, this treatment will be run by specialist nurse only with remote supervision.

	In patients managed with endoscopic resection of bladder tumour (frail or elderly having failed BCG or intolerant), this treatment will help reducing tumour burden of the size and number of tumour which makes it suitable to outpatient local treatment ablation with laser or diathermy.
Expert #6	Health professionals/nurses have to have appropriate training to use and need to become highly skilled to deal with patient complications during and after treatment. It is time consuming as nurse needs to remain throughout treatment of 1 hour. Patients need to understand that during induction urinary side effects can be extreme
Expert #7	Need staff/ time for training/room to store equipment and machine/ can be done in outpatient setting/ cost of consumables. Machine is loaned by Company but service contract is required with them on yearly basis

11. Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?

Expert #1	No changes in infrastructure needed Training is needed and is provided by the company
Expert #2	Specific training of doctor(s) and nurse(s) delivering treatment. Can be delivered in outpatient clinic setting (may need space to store the machine but it is not that large)
Expert #3	specific training in the machine is required by or medical nursing staff using it as well as training in the handling of chemotherapy agents
Expert #4	Yes - training of staff
Expert #5	No Major changes to facilities is required. The machine is small in size and can fit in any reasonable size outpatient room. Training will be required to ensure safety of delivery of treatment. This usually could be physical or remote depending on the level of experience
Expert #6	Yes -3 hour theory session with Synergo. At least 4 patients treatments but depends on previous experience and when health professional feels confident to use.

	Chemotherapy safety, reconstituting and administering study and assessment.
Expert #7	Clinical treatment area Warming cupboard useful Need specific training and support before autonomous clinic Chemo pharmacy support

12. Are you aware of any safety concerns or regulatory issues surrounding this technology?

Expert #1	no
Expert #2	No
Expert #3	no
Expert #4	Not to my knowledge
Expert #5	NO
Expert #6	Safety issues re use of chemotherapy – so during pregnancy or lactating. For patients there needs to be a urinary assessment to ensure sufficient bladder capacity, post void residual,- if holding a residual infection risks increased, current urinary symptoms as they most likely become worse. Cannot be used if >3cm diverticulum, caution with enlarged prostate and taking anticoagulants. Monitoring throughout treatment if pacemaker insitu. Unable to be used if patient has Intra cardiac device.
Expert #7	Chemo handling. Being signed off to use machine and be able to trouble shoot to avoid problems impacting patient

General advice

13. Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.

Expert #1	In my experience I have found this very useful in the selected cohort patients with intermediate or high risk NMIBC who have failed or intolerant to BCG and are either not suitable or not keen on a major op like cystectomy with its associated morbidity.
Expert #2	See above
Expert #3	we have stopped using the synergo system and instead use the combat be RS system as the combat system is easier to use more compact and has an easier to use urethral catheter which aids patient comfort. Disposable costs may be cheaper for the combat system vs the synergo system . also double dose of mmc is usually used with synergo, system. Synergo system also requires constant adjustment and monitoring in real time to achieve most effect heating. The cynic go the system he eats the bladder wall rather than the mitomycin itself the manufacturers suggest that this may be a more effective way of increasing the absorption of mitomycin into the urothelial layer however to achieve this a specific catheter with the microwave and transmitter needs to be inserted into the bladder which can be uncomfortable and difficult to introduce and potentially lead to problems with urethral stricturing in some patients
Expert #4	I have used an alternative device
Expert #5	Our centre has just adopted the treatment therefore, we have no major experience. The procurement process was smooth and the company was very professional and co-operative. Hopefully with time to come I can comment on the clinical side of the treatment.
Expert #6	The catheter used is quite big and rigid as houses heating element so increased risk of urethral damage / strictures. Catheterisation therefore is more painful than soft smaller catheter. Catheter sets only available from synergo so issues with Brexit and obtaining stock.
Expert #7	Been running nurse led Hyperthermia clinic for 7.5 years at STG. I order drugs and equipment, book patient s from my hyperthermia diary, treat then, record data and book follow up and inform GP.

	Each tx is one hour on the machine after catheterising so there is time to really talk about all subjects and build a rapor which pts find very therapeutic. Over 2 yrs you get to have a bond with that pt and it is very rewarding for both sides.

Other considerations

14. Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population?

Expert #1	It is difficult to guess at national level but in my hospital which receives referrals from whole of Kent, we start Synergo treatment for 2-3 new patients every month
Expert #2	We have treated 250 patients over about 15 years and many of these are referrals from across the South East. It is therefore a specialist treatment and therefore the number of patients each year will not be too large, although some patients referred to us have declined due to travelling to London etc and so numbers likely to be higher if in more centres. Approx. 80% of bladder cancers are NMIBC and about 30% are high risk requiring BCG treatment. In my experience approx 20% of patients fail BCG treatment and so might be suitable for Synergo but some will be better of being advised to have cystectomy up front.
Expert #3	Small number of patients who are either refractory to bcg treatment or have a contraindication to bcg treatment for high grade superficial bladder cancer.
Expert #4	About 25% of all bladder cancer patients. This could increase if we have evidence of efficacy in those with high grade non-muscle invasive cancer.
Expert #5	Based on our own estimation, We expect to treat 12-15 patients per year. Our trust serves a population of around 800,000 people. Each patient will have around 12-16 treatments depending on risk group.
Expert #6	20-25 patients per year from my trust and east kent trusts
Expert #7	Unsure of numbers due to recent pandemic reducing the number of referrals.

15. Would this technology replace or be an addition to the current standard of care?

Expert #1	Addition to the current SOC
Expert #2	Would replace some cystectomies if used for BCG failure.
Expert #3	Additional
Expert #4	Addition to some areas and replace some areas.
Expert #5	It is an addition to current practice. However, in the past there has been periods of BCG shortage where Synergo will be an alternative to it.
Expert #6	In addition
Expert #7	addition

16. Are there any issues with the usability or practical aspects of the technology?

Expert #1	need to write business case, annual maintenance fee of £5,000, possible inadequate reimbursement from the primary care for the treatment
Expert #2	Need access to chemotherapy pharmacy. Catheterisation can sometimes be challenging as large catheter to allow microwave equipment so having a supervising doctor available is important in our experience but largely specialist nurse delivered.
Expert #3	yes the technology requires the use of a quite large stiff catheter can be difficult to insert and also can be uncomfortable for patients. The technology requires specific training both in insertion of the catheter monitoring and adjustments to the treatment in real time as well as the use of chemotherapy antibiotic agents and their handling and disposal
Expert #4	Not to my knowledge

Expert #5	No
Expert #6	Treatment is labour intensive. The catheters sets are expensive. Patients usually have increased side effects than BCG.
Expert #7	Need a robust training programme

17. Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?

Expert #1	Some of the issues mentioned above.
Expert #2	Cost is likely to be an issue and it needs to be considered by an experience specialist on a case-by-case basis so I would recommend this technology is delivered on a cancer network basis rather than by lots of individual hospitals.
Expert #3	cost and training
Expert #4	Not to my knowledge, apart from an initial capital investment.
Expert #5	There are no main issues in adopting this technology. Having said that, I don't expect that it will be adopted by every trust in the UK. There has to be certain amount of expertise and staff availability to deliver the treatment.
Expert #6	No
Expert #6	No
Expert #6	Time for training and cost of set up

18. Are you aware of any further evidence for the technology that is not included in this briefing?

Expert #1	1. van Valenberg FJP, Kajtazovic A, Canepa G, Lüdecke G, Kilb JI, Aben KKH, Nativ O, **Madaan S**, Ayres B, Issa R, Witjes JA. Intravesical Radiofrequency-Induced Chemohyperthermia for Carcinoma in Situ of the Urinary Bladder: A Retrospective Multicentre Study. Bladder Cancer. 2018 Oct 29;4(4):365-376. doi: 10.3233/BLC-180187.
Expert #2	Yes – papers as listed above (and again below for ease) but not exhaustive – there are many more papers to consider. Arends TJH et al, Results of a randomised controlled trial comparing intravesical chemohyperthermia with mitomycin C versus bacillus Calmette-Guerin for adjuvant treatment of patients with intermediate and high risk non muscle invasive bladder cancer. Eur Urol 2016;69:1046-52. Van Valenberg FJP et al, Intravesical Radiofrequency-induced chemohyperthermia for carcinoma in situ of the urinary bladder: a retrospective multicentre study. Bladder Cancer 2018;4:365-376. Ayres B et al, MP08-01 10-year experience of RITE thermochemotherapy for high risk non muscle invasive bladder cancer that has failed BCG. J Urol 2018;199 (4S), e96 Sooriakumaran P et al, Predictive factors for time to progression after hyperthermic mitomycin C treatment for high-risk non-muscle invasive urothelial carcinoma of the bladder: an observational cohort study of 97 patietns. Urol Int 2016;96:83-90.
Expert #3	no
Expert #4	No
Expert #5	No
Expert #6	No
Expert #7	n/a

19. Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.

Expert #1	We do maintain a prospective database. We have treated more than 50 patients with Synergo. I shall attach an old abstract approximately 4 year ago showing the outcome of 25 patients with at least 12 months follow up.
Expert #2	No current trials on this in the UK. Not sure re Europe or US. Units currently using it should be able to provide local audit data. Ours is in publications listed above. As discussed above – case selection is important for successful treatment including close surveillance of upper urinary tracts and prosthetic urethral biopsies to exclude carcinoma in situ. This does vary between published data and is another limitation along with small numbers and often retrospective data.
Expert #3	no
Expert #4	Not to my knowledge
Expert #5	Each trust that have been delivering the treatment will collect their own data for governance reasons. However, with time and more centres using the treatment there will be the need for UK wide audit and I will be more than happy to participate.
Expert #6	We collect data on all the patients we treat with synergo and keep a database. Professor Madaan will review and has written in conjunction with other medical team members some articles. Synergo in past has reviewed and collected data. Sharing with NICE I would need to discuss with Professor Madaan but I have no objections.
Expert #7	Continuing to collect data of treatment session and work collaboratively with other centres who are starting Synergo service

20. Is there any research that you feel would be needed to address uncertainties in the evidence base?

Expert #1	Yes, research will be useful but there are difficulties in getting funding and trying to recruit enough numbers
Expert #2	A multi-arm RCT comparing different options for BCG failure would be useful but this would need to be international to recruit the number of patients that would be needed and I think will be very expensive and difficult to recruit to.
Expert #3	potentially to assess subgroups of patients and patients with different grades and stages of bladder cancer who were not treated in the NIH R HTA HYMN trial
Expert #4	Yes - a trial to compare all the modalities of delivering heated chemotherapy agents into the bladder.
Expert #5	There has been many studies on Synergo technology in Europe showing the evidence of using radiofrequency in enhancing the efficacy of chemotherapy in the treatment of bladder cancer. Therefore, I don't feel any more studies currently is required.
Expert #6	No
Expert #7	Continue to audit data

NICE National Institute for Health and Care Excellence

Patient expert statement

Synergo for non-muscle-invasive bladder cancer [GID-MT553]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	Evelyn Prokop

2. Are you (please tick all that apply):	☐ **a patient with the condition?** ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Fight Bladder Cancer
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☐ **I don't know**
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **other (they didn't submit one, I don't know if they submitted one etc.)**

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **I have personal experience of the condition** ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Being diagnos4d with bladder cancer (T1 grade 3 CIS) although contained in the bladder is a life changing event. I found the treatment, as a 69-year-old lady, very intrusive until I eventually relaxed and got used to the treatment. I live with the knowledge that bladder cancer is something I will have to live with for the rest of my life. I am aware that if my bladder were removed, I would have a 95% chance of being free form cancer re-occurrence. But that means living with a stoma, and all that entails. Decisions were made basically on my age, BMI and health, plus NICE first line treatments. I did not feel included at any time, like most patients, After two TURBT's I had a course of BCG and another TURBT because of failed BCG. I felt that I had to educate myself on the treatments available.

	This is when I changed hospitals and started Hyperthermic Mitomycin, under [redacted] at Darent Valley Hospital. During a short period of time, I underwent. • 5 TURBOT's altogether • 6 weeks BCG • 8 weeks Hyperthermic Mitomycin • And then I had two years treatment after the above. Having to travel 80 miles each way for treatment is demanding, plus being reliant on family to take me as I needed pethidine for pain relief.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	BCG as a first line treatment for non-invasive bladder cancer, with no choice of other treatments, except bladder removal for T1 Grade 3 CIS, depends on the consultant that you have For patients with little knowledge, they often have to make a choice without the knowledge that trials, and other treatments are available at other hospitals
10. Is there an unmet need for patients with this condition?	The answer is yes Patients with grade 3 T1 do not have many options. They are advised BCG or bladder removal depending on age and fitness for surgery . No real choice is given as consultants differ in their opinions . BCG is a one of course of treatment that cannot be repeated, and side effects in patients differ widely Some patients, like myself, would not be eligible for radiotherapy and some patients are not suitable to undergo surgery .

	Bladder cancer is mainly an older person's disease. Treatment for cancer contained in bladder is sadly lacking in options, and is decided by a post code lottery , making it very difficult to access treatment e.g. only one SYNERGO machine in Kent. In my experience the average patient dos does not realise this treatment exists, it is not offered by consultants. NHS is failing he needs of bladder patients. I am aware that my cancer will come back, but do not know when. I know with SYNERGO that I can have more treatment, plus it gives more time for new treatments to be found. . I am now 72 yrs. young, aware time is not on my side, quality plus time is my priority. So new treatments are especially important.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	My personal experience is of the new technology for new treatments THE SYNERGO technology should be more widely available
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	These include : The distance I had to travel to obtain treatment. The effects on my body once pain relief had worn of My bladder did have burn marks, so I am assuming that the catheter failed and this was damage from microwave Not knowing anyone who had the same treatment plus having to learn and treat the afte reffects in my own way

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Certainly for the older generation with T1 GRADE 3 CIS like myself this treatment is less invasive than bladder removal and has a better recovery time I believe the SYNERGO system has been well trained and tested in all groups of patients in different grades over a period of many years . In the short term for older people whose life span is not considered long the system offers an easier answer to major surgery. If the cancer returns the SYNEWRGO can be used again , unlike BCG BCG side effects against the side effects of Hyperthermic Mitomycin also should be considered against age related illness
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Not to my knowledge**
Other issues	
15. Are there any other issues that you would like the committee to consider?	My personal belief is the system is only as good as the people administrating it. Specialised Bladder Cancer nurses, is so important, I believe without my two nurses I would not have got through treatment, I am aware of people who have not completed the full course. I cannot speak highly enough of the team that treated me, from the specialised cystoscope nurse, through to my own Bladder SYNERGO nurses. They answered every question I asked or found information I wanted. The treatment requires the patient to be relaxed, If I did not have that support and belief from the

	nurses, I don't think that I would have completed the course. The nurses believed in the treatment and helped me believe in it.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- New treatment for contained bladder cancer
- Pain relief needed.
- More SYNERGO machines made available
- Patients being informed of treatment options available to them
- Highly trained bladder cancer nurses who can administer the SYNERGO system

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

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The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies – Synergo for non-muscle-invasive bladder cancer

NICE Medical Technologies Advisory Committee

Please read the guide to completing a submission fully before completing this template.

Information about your organisation	
Organisation name	Fight Bladder Cancer
Contact person's name	[redacted]
Role or job title	[redacted]
Email	[redacted]
Telephone	[redacted]
Organisation type	Patient/carer organisation (e.g. a registered charity) ✔ Informal self-help group ☐ Unincorporated organisation ☐ Other, please state:
Organisation purpose (tick all that apply)	Advocacy ✔ Education ✔ Campaigning ✔ Service provider ✔ Research ✔ Other, please specify:
What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)? Fight Bladder Cancer is a patient advocacy group and charity for bladder cancer, based in the UK. We run a 24/7 private online support that has approx. 5,200 members nationally and internationally, local support groups around the country, online support groups and a national 1 to 1 bladder buddy service. Our website and literature is available worldwide.	

Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies – Synergo for non-muscle-invasive bladder cancer

If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to medtech@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place. Up to 20 places will be available, depending on the size of the venue. Where meetings are oversubscribed NICE may need to limit the number of places we can offer.

Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

We reached out to people on our private online forum of 5200+ patients and carers, as well as being able to collaborate with bladder cancer charities to understand the patient experience. We also were able to conduct private conversations with those having had the Synergo treatment or who would like to be able to consider having it.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies – Synergo for non-muscle-invasive bladder cancer

Impact of the symptoms, condition or disease

1. How do symptoms and/or the condition or disease affect people's lives or experiences?

People diagnosed with intermediate or high-risk non-muscle-invasive bladder cancer know that they have cancer with a high recurrence rate and yet there are currently limited options of treatments. Procedures and check-ups can be lifelong, and due to the recurrence rate the fear is always there that the cancer has progressed into the muscle or further. The treatments are invasive and side effects range from uncomfortable to significant, often with side effects lasting long after treatment has stopped and affecting the quality of life.

2. How do symptoms and/or the condition or disease affect carers and family?

Carers have a lot of pressure and worry when helping support and care for their loved ones, particularly during the many procedures and treatments. High grade bladder cancer carries a lot of fear for them as they know that it could recur and spread and maybe become untreatable. Carers report a substantial impact on their ability to work and enjoy their time alone and with family.

'I am in constant worry, always waiting with my partner for his procedures and results and trying to stay positive. I want to enjoy some time away from it all, but my partner can't escape things so I feel guilty even thinking this way'

3. Are there groups of people that have particular issues in managing their condition?

The treatments for bladder cancer can cause significant pain and damage of the bladder wall for some time, for some this can mean they are unable to hold their urine, for others it can mean that the bladder itself can cramp and have spasms. Less mobile people can have issues getting to the toilet and managing any incontinence issues. The uncertainty of life with a high-grade bladder cancer diagnosis, coupled with bladder problems has been seen to exacerbate underlaying mental health conditions on top of the understood emotions of having a cancer diagnosis. With bladder cancer having such a large amount of older patients, the thought of lifelong treatments and check-ups is very hard as well as the difficulties in getting to the hospital. Many people don't feel comfortable talking about personal things, so a bladder cancer diagnosis in itself is very upsetting for them.

Experiences with currently available technologies

4. How well do currently available technologies work?

There is very limited amount of choice for patients with this diagnosis, BCG or a bladder removal is suggested, along with Mitomycin C for intermediate grade. BCG if successful can prevent the cancer returning and prevent a radical cystectomy, although there can be a lot of fear during and after treatment that the cancer will have returned and possibly progressed making an RC difficult.

5. Are there groups of people that have particular issues using the currently available technologies?

Although for those that complete the course many will have suffered side effects, some people have even found their bladder has become too painful and have gone on to have a full removal. Many elderly people are scared of the side effects but either are not suitable for a bladder removal or don't want to go through such a big life changing procedure. Many younger people struggle with BCG but don't want the alternative of a removal, alternatively some don't want to wait to see if BCG will work and have a removal as their first option. Due to the lack of options many don't tell the nurse about their side effects as they are worried it might be stopped.

'I daren't tell my CNS how much pain I have been feeling this week as I'm scared they will stop it (BCG) and then what?'

About the medical technology being assessed

6. For those <u>with</u> experience of this technology, what difference did it make to their lives?

The Synergo treatment gives patients more options and hope at the outset. With BCG failing to work the only other option was for the patient to have a full bladder removal, this treatment which worked for them, has given them many more quality years with their bladder and no long lasting side effects. The only issue for the patient was that they didn't know of any others at the time having the same.

'I would have liked to have talked to someone else having this treatment. I did have some side effects, not bad really but I would have liked to have been able to share experiences'

7. For those without experience of the technology being assessed, what are the expectations of using it?

There is a lot of hope that another treatment could be suitable, with many people interested in an alternative to BCG. There is a huge unmet need for treatment options within this group of bladder cancer patients, and I have spoken to many people that would like the opportunity to have another method to try as many are concerned that a recurrence could mean going straight to a removal. The hope is that this treatment would be available easily as another option for those with a high risk situation.

'I've heard of this new method but I would have to travel a long way. I want to be able to try it but am nervous there won't be time, BCG hasn't worked for me and I feel I may be a bit old to handle such a large operation'

8. Which groups of people might benefit most from this technology?

Those with an intermediate or high-risk bladder cancer, as well as those who don't respond to BCG.

Those who are unsuitable for BCG due to other health issues, e.g. eye problems, arthritis.

People who have been recommended a bladder removal who either don't want one and would like to try another option first, or those that aren't suitable for a removal for health reasons or age.

It could be an alternative treatment when the BCG supply becomes limited

Additional information

9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

Urothelial cancer has come near the bottom of the annual NHS cancer patient experience survey since its launch. This treatment offers a ray of hope for this much ignored cancer. The high risk of recurrence and progression has led to this cancer seeing one of the highest associated suicide rated for cancer patients due to the emotional strains of the treatments and quality of life issues.

Key messages

10. In up to five statements, please list the most important points of your submission.

- There are currently few options on treatment for those diagnosed with intermediate or high-risk bladder cancer
- For those unsuitable or unable to have an RC this alternative could be considered
- For those who have recurrences after BCG this could prevent the need for a bladder removal
- With more options for such a high recurring cancer the patient would feel less anxiety, for example when discussing options after a recurrence and for those who can't tolerate BCG at the outset.
- This treatment could see an improvement in which this much ignored cancer is treated for many

Thank you for your time. Please return your completed submission to medtech@nice.org.uk

Using your personal information: The personal data submitted on this form will be used by the National Institute for Health and Care Excellence for work on Medical Technologies (including Diagnostics Assessment) and will be held on the Institute's databases for future reference in line with our privacy notice.

External Assessment Centre correspondence log

GID-MT553 Synergo for Non-Muscle Invasive Bladder Cancer

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*

		Why were they contacted? (keep this brief)		
1.	05/03/2021	Company engagement meeting - Clinical	Start-up videoconference with the company. A list of questions was sent to the company in advance of the meeting covering key topics such as • Terminology and definitions • Use of Synergo in the NHS • Specific clarifications on the clinical submission	Full responses, verified by the company are detailed in Appendix 1
2.	09/03/2021	E-mail from the company	E-mail request to clarify search dates	YHEC undertook searches on 19th February 2021 of the: • MHRA https://www.gov.uk/drug-device-alerts database. The terms used were: thermochemo, chemotherm, chemohypertherm, hypertherm and Synergo. There were no matching results for any of the searches. • MAUDE https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm databases for Manufacturer: Medical Enterprise, Brand Name: Synergo, Report Date From: 02/01/2000. No records were found.

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3.	12/03/2021	Expert engagement meeting	Videoconference conference with a range of clinical and patient experts to discuss topics relating to • Clinical pathway • Use of Synergo in the NHS • Relevant patient population • Terminology and definitions	Full responses verified by experts are detailed in Appendix 2.
4.	30/03/2021	E-mail from company	EAC sent an e-mail requesting some clarification on the numbers reported in the PRISMA charts	The difference between your totals are the 5 systematic reviews. As explained in the text we could not use these but we did retrieve them and checked their included studies, in part to ensure the search had not missed any but also to see if they had relevant info. Hence we included them in the PRISMA. *'In addition, 5 reviews were identified Bahouth (2016), Colombo (2016), van Valenberg (2016), Soria (2015) and Lammers (2011) which included overlapping groups of the above studies. None of these was comprehensive and up to date, so the data are reported for each of the primary studies separately*.' From page 47.

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5.	06/04/2021	Company engagement meeting - Economics	A short description of the clinical evidence was given by the EAC. A list of questions was sent in advance to the company.	Full responses, verified by the company are detailed in Appendix 3
6.	07/04/2021	Clinical Experts	An e-mail with additional questions relating to the economics was sent to all clinical experts.	Responses were received from 3 experts These are detailed in Appendix 4
7.	07/04/2021	Company	E-mail to the company to request clarification on the inflation approach used in the model: My understanding is that all prices were inflated to 2020/21 using the PSSRU indices and assuming that the index for 2019/20 could also be applied to 2020/21. For some of the prices, it appears to us that the index has been applied an additional time (as if inflating to 2021/22 at the same rate). Examples of this are costs taken from NHS	you are correct, we indexed to 2021/22. Here are the values we used.

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			reference costs 2018/19 e.g Costs for initial and subsequent chemotherapy. As these calculations are not included in the model, could you confirm if this is actually what has happened, or if there is an alternative explanation	2021/2022 102.21% 2020/21 102.21% 2019/20 102.21% 2018/19 102.31% 2017/18 101.16% 2016/17 100.35% 2015/16 101.30% 2014/15 100.90% 2013/14 101.10% 2012/13 101.70% 2011/12 102.10% 2010/11 103.00% 2009/10 100.60%
8.	15/04/2021	Clinical Experts	An e-mail with additional questions relating to the economics was sent to all clinical experts.	Responses were received from 5 experts These are detailed in Appendix 5
9.	15/04/2021	Company	An e-mail requesting clarification on the HRQL data used in the model: The 0.85 value is taken from Cox 2019, and they say that the HRQOL was measured using EQ-5D-3L as	sorry but we cannot enlighten you on this inconsistency

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			part of the BOXIT trial. However when we looked at the paper by Kelly (2018) reporting BOXIT, they do not mention EQ5D-3L, but state that HRQOL is measured using EORTC QLQ-C30 and EORTC QLQ-BLS24. Can you shed any light on this discrepancy?	
10.	19/04/2021	Clinical Experts	An e-mail requesting clarification on the BCG regimen used in the UK	One expert responded to say Standard BCG doses in UK are - Oncotice 12.5mg in 50ml N saline - Connaught 81mg in 50 ml N saline

Appendix 1: Notes from Company Post Clinical Submission Meeting for MT553 Synergo for Non-Muscle Invasive Bladder Cancer

This document summarises the discussions that took place at the company post clinical submission meeting for MT553 Synergo, which took place on Friday 05th March 2021, 11:00-12:00am

Attendees

NICE

1. Lizzy Latimer, Health Technology Assessment Adviser
2. Rebecca Brookfield, Health Technology Assessment Analyst
3. Federica Ciamponi, Health Technology Assessment Analyst
4. Lee Berry, Programme Manager
5. Victoria Fitton, Project Manager

Cedar (EAC)

6. Susan O'Connell
7. Laura Knight

Company

8. James Wright, MedTech Connect Ltd
9. Avigdor Lev, Medical Enterprises Ltd
10. Gad Lev, Medical Enterprises Ltd
11. Igal Ruvinsky, Medical Enterprises Ltd
12. Ilan Schleisne, Medical Enterprises Ltd
13. Lisa Deutsch, Medical Enterprises Ltd

14. Naama Reich, Medical Enterprises Ltd
15. Sam Harper YHEC
16. Joel Russell, YHEC
17. Joyce Craig, YHEC

Population

1. NICE guidance states that: 'There is no widely accepted classification of risk in non-muscle-invasive bladder cancer.' The 3 RCTs in the MIB used the risk criteria from 'European Association of Urology guidelines'. Can the company comment on this?

   The company agreed that most of the evidence used the European Association of Urology guidelines risk classification. Overall, the question around the generalisability of the RCTs to UK practice according to the risk stratification set out in NG2 would be better suited for the clinical experts and therefore, no further discussion was had around this.

Intervention

2. Can the company give us some guidance as to the terms/elements that we should be looking for when reviewing the evidence?
3. Is there likely to be any other system available which will be the same/similar to Synergo (Is RITE unique to Synergo)?
   - Not all papers describe Synergo as RITE (radiofrequency induced thermo-chemotherapy effect) as in Arends 2016, in the title/abstract, in this case 'chemo-hyperthermia' and no mention of RF element.
   - The company confirmed that some studies use different terminology to explain Synergo. They noted that the term RITE was introduced later in the evidence base to distinguish between the 2 main chemo-hyperthermia techniques (heating the bladder wall directly using RF vs. heating chemotherapy outside the body).
   - The term RITE is related to the use of RF and is not specific to the device used. However, at the moment only Synergo delivers RITE and no other system uses RF to treat bladder cancer.
   - Other relevant terms include Radiofrequency, RITE, Microwave, Synergo, Thermochemotherapy. The company advised that the term ‘Microwave’ might bring up alternative technologies which are not Synergo.

- Then there is the Combat BRS system V2.0 (Hyperthermic Intra-Vesical Chemotherapy, HIVEC™) which doesn't have the RF element but it might not be obvious until looking at full text which system has been used.

Comparator

4. Are there any obvious comparator systems available?
    - The company advised that there are no direct comparator devices to Synergo. Synergo uniquely heats the bladder wall while cooling closed loop circulating chemotherapy outside the body. This is a different approach to other hyperthermic chemotherapy approaches which heat the MMC outside the body.

5. Is cystectomy a reasonable comparator? So far the evidence suggests that cystectomy would be something that patients might get after any chemotherapy which failed?
    - The company noted that with regard to current published evidence, direct comparisons exist only in particular cases/groups such as patients who have recently failed BCG? Synergo can be a treatment option in this situation as may delay/reduce radical cystectomy
    - Some patients cannot undergo cystectomy and some patients cannot tolerate BCG/contraindicated. Synergo provides an alternative treatment option for these patients.
    - Synergo can be a first line or second line treatment option.

6. Is MMC always the chemo and the comparison is how it is being delivered (e.g. via the synergo system).
    - The company stated that the choice of treatment/chemotherapy might depend on the nature of the tumour. t~~umours~~ In patients with has CIS or multiple recurrences or large tumor spread an ablative dose will be chosen.
    - MMC is most commonly used chemotherapy agent suitable for these patients but Epirubicin is a possible alternative, particularly where MMC is contraindicated (For example due to allergy). The company also noted that other, less common, chemotherapy agents are being used but primarily in a research setting.
    - Synergo can be used with other chemotherapy drugs however there is currently limited evidence for this.
    - The effectiveness of MMC via Synergo is due to the radiofrequency approach which has a twofold effect:
        - More active MMC because of temperatures it operates at

    - Help MMC get deeper into target tissue/higher concentration of drug in the tumour
- Due to limited evidence, it is not clear whether using other chemotherapies would have the same impact however the company advised that they believe there is no difference in efficacy and safety between MMC and epirubicin delivered via Synergo.
- One study looks at multiple different chemotherapies

Versions

7. Does the company have any information on the newer version to be installed in the UK?
    - Software specifically needs to be updated but it is a minor change that does not change efficacy or safety of device. All updates will be done as soon as Covid restrictions on hospital visits are lifted.
    - Version A_133 of the software will be installed
    - The system undergoes constant upgrades on both software and hardwar and Covid permitting, the next hardware improvement will be done may/June 2021.
    - The values in the table are for the updated, planned versions.

    Question on the version numbers for Transurethral Radiofrequency Ablation Applicator and Tubing Line Disposable Set
    - Version one (LI932B) is currently in use while the second (LI92B-S) will start distribution in 2022. The difference between the two versions is that the catheter tip is softer in the newer version.

Component	Version	Year
Required		
Radiofrequency Hyperthermia Device	SB-TS 101.3	2014
Transurethral Radiofrequency Ablation Applicator and Tubing Line Disposable Set	LI932B LI92B-S	2002 2020

Synergo System Software	A _132	2019
Optional		
Closed Drainage Set	CDS932B	2013

Economics

8. What software is the economic model in?

- Excel
- QALYs are being considered but post cystectomy QALYs are difficult to find

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Appendix 2: Notes from Expert Engagement Meeting for MT553 Synergo for Non Muscle Invasive Bladder Cancer

This document summarises the discussions that took place at the expert engagement meeting for MT553 Synergo, which took place on Friday 12th March 2021, 9:00-10:30am

Attendees

NICE

18. Lizzy Latimer, Health Technology Assessment Adviser
19. Rebecca Brookfield, Health Technology Assessment Analyst
20. Federica Ciamponi, Health Technology Assessment Analyst

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21. Susan O'Connell, Senior Healthcare Scientist
22. Laura Knight, Senior Healthcare Scientist
23. Megan Dale, Senior Healthcare Scientist

Clinical Experts

24. Ahmed Ali, Consultant Urological Surgeon, Frimley Health NHS Foundation Trust
25. Mr Benjamin Ayres, Consultant Urological Surgeon, St Georges University Hospital NHS Foundation Trust
26. Angela Elliott, Urology Clinical Nurse Specialist – Bladder Cancer Nurse, Frimley Health NHS Foundation Trust
27. Prof Sanjeev Madaan, Consultant Urological Surgeon & Lead Cancer Clinician, Darent Valley Hospital, Dartford
28. Param Mariappan, Consultant Urological Surgeon & Honorary Clinical Senior Lecturer, NHS Lothian & University of Edinburgh,

29. Toby Page, Consultant Urologist, Newcastle upon Tyne Hospitals Trust,
30. Chris Backhouse, Uro–Oncology Nurse Specialist, St George's University Hospitals NHS Trust
31. Eve Prokop, patient expert

Additional expert invited to the expert engagement only:

32. Leyshon Griffiths, Associate Professor/Consultant Urological Surgeon, Leicester Medical School

Themes for Discussion

1. **The clinical pathway**
2. **Synergo in clinical practice**
3. **Definition of BCG Failure**
4. **Patient population**
5. **Terminology and potential competitors**

The clinical pathway

The EAC requested input from the clinical experts relating to the current clinical pathway and how the clinical pathway might change with the addition of Synergo.

The EAC shared a graphical representation of the current clinical pathway, with and without Synergo as a treatment option, based on the recommendations outlined in NG2 Bladder Cancer: Diagnosis and Management (Figures 1 and 2).

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Figure 1: EAC interpretation of the current NICE Pathway

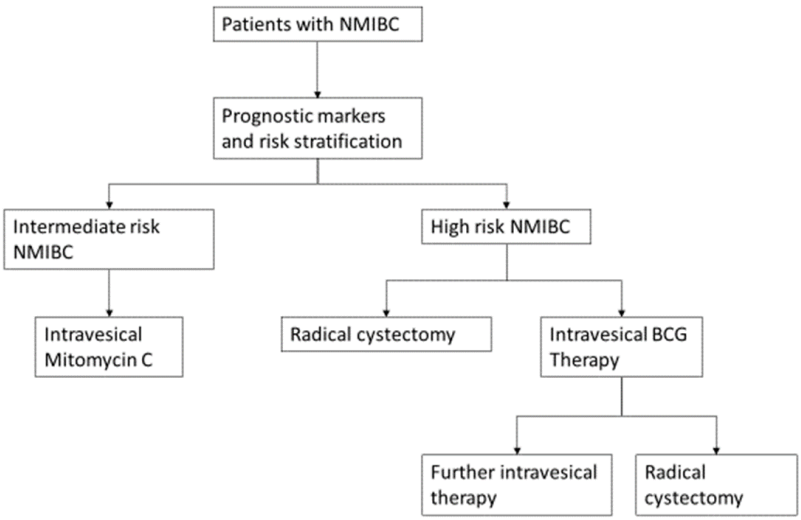
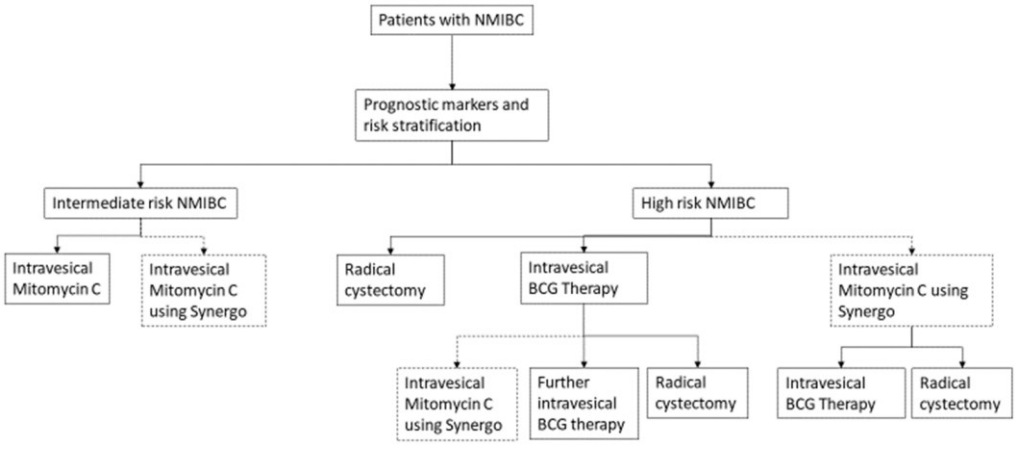


Figure 2: EAC proposed pathway with Synergo



The clinical experts discussed both pathways in detail and broadly considered that the proposed pathway with Synergo was an accurate representation of the clinical pathway and treatment options available for patients with intermediate and high-risk non-muscle invasive bladder cancer (NMIBC) also referred to as transitional cell carcinoma (TCC) or urothelial carcinoma. One expert noted that non-muscle invasive bladder cancer is superficial (not in Muscle of bladder wall).TCC type urothelial cancer may be a better term than TCC

The patient expert noted that it is very important that the clinical pathway makes both clinicians and patients aware of all of their potential treatment options, particularly options alternative to a radical cystectomy.

Intermediate risk

On the intermediate risk pathway specifically, the clinical experts noted that there have been issues with availability of mitomycin C (MMC) and as a result many have been using epirubicin and/or gemcitabine as alternatives. The experts noted that although there is no longer a problem with MMC supplies, the option of alternative chemotherapy drugs could be added to the pathway in case of future shortages. One clinical expert noted that the effectiveness of MMC and epirubicin are similar while one expert noted results were inferior to BCG and hyperthermia.

One expert noted that they used epirubicin only if allergic to MMC or if re-inducting. Gemcitabine is not used at all.

High risk

One expert noted that high risk NMIBC are a heterogenous group of patients. Multiple elements determine the prognosis such as (size, number of lesions, concomitant CIS and stage of cancer). In the highest risk group the risk of progression reaches 45%. Therefore, fit and healthy patients in this group are offered cystectomy up front.

On the high-risk pathway specifically, the clinical experts noted that radical cystectomy may be offered as first line treatment but noted that most patients will opt for BCG unless contraindicated (e.g. allergy/immunocompromised). One expert noted that decision is dependent on likelihood of progression due to amount of tumour in bladder especially if it was a T1. Age is a factor because you are at more risk of missing progression outside the bladder if you have a patient with extensive NMIBC under 40. One expert noted however that there is not more risk of missing

progression in young patients as they are assessed and monitored as regularly as any other patient.

Most people with high risk NMIBC will be offered BCG as first line.

Approx. 5-10% of people with high-risk NMIBC will be offered cystectomy as first-line therapy. This is usually determined by characteristics of the cancer indicating severe disease for example, micropapillary, multifocal or large tumours.

One expert also noted that cystectomy might be offered to younger people with high risk cancer as well.

One expert noted that the option of radical cystectomy is available to all high-risk patients but it is typically used in <10% with unfavourable features like high volume, multifocal, extensive involvement of lamina propria (G3pT1), associated CIS. Obviously, threshold is lower in younger patients.

Some of the he clinical experts questioned the addition of Synergo as an option after BCG, noting there is a lack of evidence however one expert challenged this, stating there was evidence to support use after BCG.
The EAC noted that the lack of evidence, while relevant to making recommendations does not mean that Synergo should not be placed as an option after BCG if it could be used there.

The clinical experts also discussed whether Synergo could be offered as an alternative to first-line cystectomy in high-risk patients with severe disease but said there was no strong evidence that it is an effective treatment option. Cystectomy would be offered first line for high-risk with severe disease. They added however, that some of these patients don't want or are not fit for surgery. In this case BCG or Synergo could be considered as first-line for severe disease.

Further discussion between EAC and experts elicited information which indicated that the intermediate risk pathway may not easily be isolated from the high-risk pathway.

Clinical experts noted that patients with intermediate risk NMIBC who's cancer does not respond to Mitomycin C, will be managed according to the high-risk pathway.

The EAC has redrafted the proposed clinical pathway based on feedback from the experts (figure 3).

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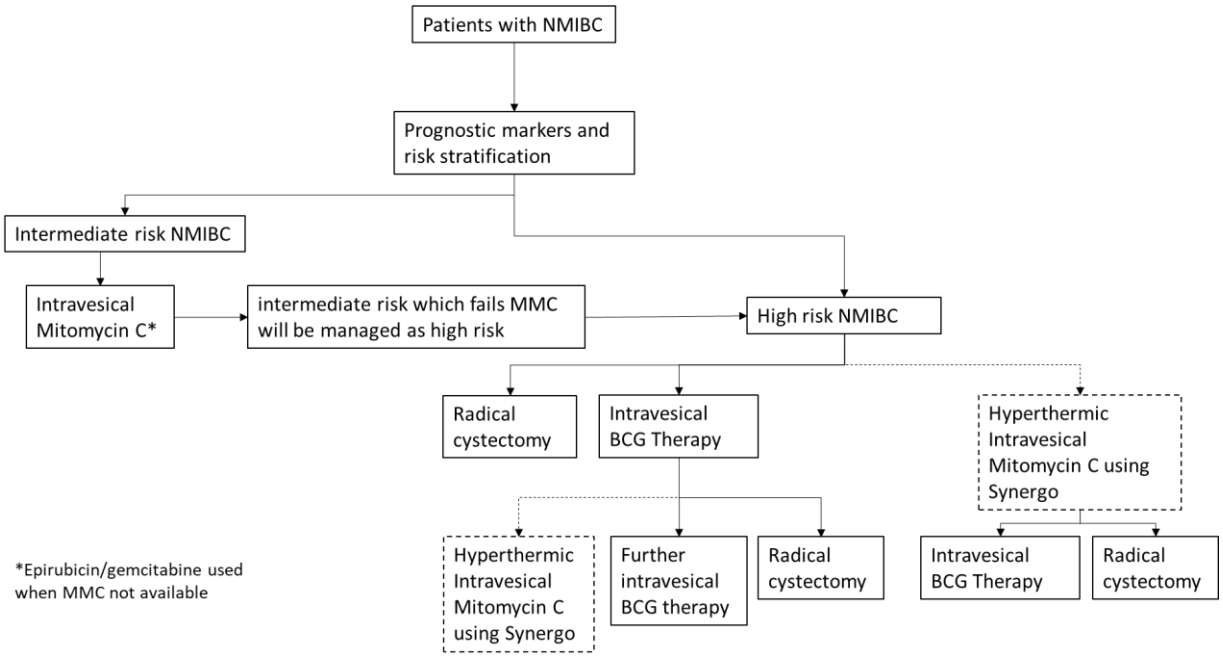
Figure 3: Revised clinical pathway with Synergo



One expert stated they feel it is best to leave Synergo for high risk NMIBC only.

One expert stated that patients were unlikely to need hyperthermic MMC first line so the reflected pathway is accurate. One expert supported the approach not to use hyperthermic MMC as an alternative to intravesical MMC for intermediate risk as it is not practical in terms of time/staff/resources (hyperthermia takes 1.5 hrs per session v intravesical MMC 10 mins.

For Intermediate risk which fails MMC, the arrow should not go to high risk NMIBC as radical cystectomy will not be recommended here unless the histology has progressed to high risk. Therefore, it will be better if the arrow points to intravesical BCG therapy under high risk NMIBC

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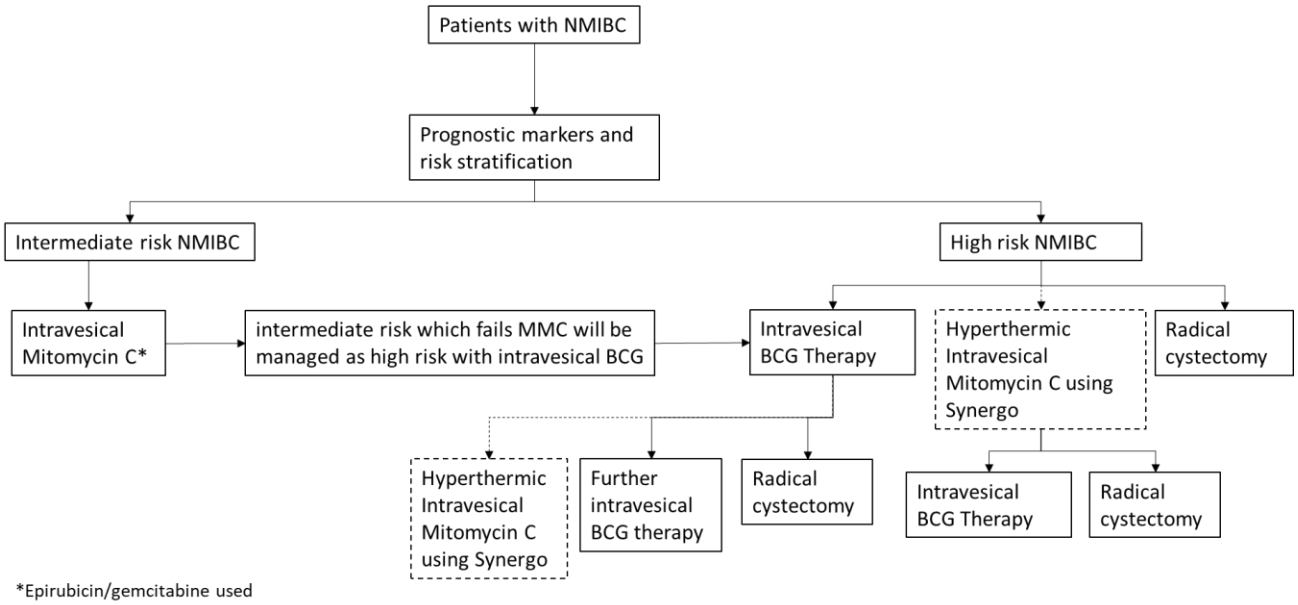
Pathway adjusted by EAC in response to clinical expert comment



Synergo in Clinical Practice

Two experts noted that they use Synergo only after failed BCG, with one expert agreeing that is could be used at other points in the pathway if considered appropriate.

One expert noted that in one unit, hyperthermic chemotherapy using the Synergo system was introduced as a result of BCG shortages and not wanting radical cystectomy to be the only treatment option for patients.

A second expert noted that in their unit hyperthermic chemotherapy using COMBAT BRS was introduced in response to BCG shortages. Audited data on high risk patients at 2 years suggested hyperthermic chemotherapy was at least as good as BCG and showed promise but they have moved back to BCG in line with NICE clinical guidelines. A large proportion of the patients had CIS and these patients are often excluded from studies. The clinical expert noted that side effects with hyperthermic chemotherapy (COMBAT BRS device) are less than with BCG.

One expert noted they use epirubicin with Synergo when there was a shortage of MMC but do not routinely use it.

One expert noted they had problems accessing funding for Synergo based on the evidence. The patient expert noted that with only 9 or 10 machines in the country, clinical evidence will be difficult to come by.

Several experts noted that Synergo uses approximately 1.5 hours of clinical time for the CNS as they need to sit with the patient and monitor them throughout treatment (compared with approx. 5-10 minutes for MMC or BCG) and only one patient can be treated per device.

Experts noted the EAC need to pay attention to company recommended doses of MMC with Synergo, particularly for carcinoma in situ (CIS).

The patient expert noted that access to Synergo is limited to a small number of centres and that many clinicians do not seem aware of Synergo as a treatment option which disadvantages some patients. The patient expert noted that having a clinical team who are fully versed in the available treatment options and the advantages and disadvantages of each is crucial to being able to decide. Without the option of Synergo, many patients may be looking at regular (6 monthly) procedures requiring general anaesthetic.

Experts agreed that a Network approach is needed with full staging/histology etc to ensure the bladder is clear before Synergo is offered.
This is because clinical experts noted that there can be noted that there can be disease recurrence in the time between referral from elsewhere and start of treatment. One expert suggests repeat bladder investigations to ensure Synergo is the appropriate option. Experts agreed that they would recommend an up to date cystoscopy and repeat TURBT before Synergo. This is because bladder needs to be cleared of disease and the prostatic urethra needs to be assessed and free of disease before treatment.
Clinical experts also discussed carrying out additional new assessments, for example bladder capacity or contraindications to treatment.
Clinical experts had a brief discussion about the HYMN trial noting that while it had some methodological flaws and didn't give the results 'we all hoped for', we need to have treatment options for patients who cannot or won't have a radical cystectomy. One expert said that there is now promising data coming from centres that use Synergo a lot and these are seeing better results than those in the trial.

Another expert said that HYMN trial did not show benefit in CIS but that the company recommend a different protocol for CIS than what was used in the trial.

Definition of BCG Failure

One expert said the inclusion criteria was 'BCG failure' and represents a heterogenous population. The terminology has now changed to 'BCG-unresponsive'

Further discussion around what constitutes BCG failure suggested that high-risk patients will get 9 to 12 BCG doses before it's considered a failure. They would have 6 doses initially, have a look (assume cystoscopy) and then another 3 to 6 doses more before being offered cystectomy.

If after 6 doses cancer has progressed or stage has changed then might consider cystectomy. Another expert said that if T1 after 6 doses then strongly consider cystectomy.

One expert offered the following definitions for BCG treatment outcomes:

- BCG-refractory (unresponsive): Muscle-invasive disease at 3 month cystoscopy Persistence or recurrence of high-risk disease at 6 months (either after 6+3 or 6+6)
- BCG-resistant: Low-risk or intermediate risk disease by 6 months
- BCG-relapsing: Recurrence after achieving disease-free state at 6 months

The patient expert and the clinical experts agreed that the role of the Clinical Nurse Specialist (CNS) was crucial. The CNS has a relationship with the patient and can help patients manage expectations of the treatment and side effects. It can be harsh for patients for the 8 weeks of treatment but much easier once moved on to maintenance. One expert noted they had moved from 42 degrees to 40.5/41 degrees which helps with some of the side effects. As the member of the clinical team delivering the chemotherapy via Synergo, the CNS has experience of the system and can limit the discomfort of elements such as catheter insertion.

The patient expert noted that for 5 days they did nothing but bed/sleep/eat etc but this was time limited and worth it. Synergo was mentally and physically a good treatment decision because while there were quality of life issues during treatment but resolved after treatment.

Discussion around how Synergo was used in clinical practice indicated that both Synergo and COMBAT BRS system (another technology that delivers hyperthermic chemotherapy) are being used in the NHS for treatment of NMIBC. It was stated that COMBAT could be used to treat multiple patients at a time whereas Synergo could only treat a single patient, however one clinical expert providing clarity on this noted that the COMBAT machine can only treat one patient at a time. The expert noted that the doctor or CNS should monitor the Synergo monitor throughout

treatment, modifying radiofrequency and pump speed to adjust temperature depending on patient symptoms and urethral temperature. They stated they would not be comfortable leaving any patient unmonitored on any type of treatment.

Population and Risk Classification

The EAC and NICE had a question on how bladder cancer risk stratification happens in clinical practice given NICE guidance stating: 'There is no widely accepted classification of risk in non-muscle-invasive bladder cancer.'
The clinical experts noted that there are clearly defined risk stratification guidelines (grade, depth, multifocality and other features) for risk classification as well as definitions provided in NICE and EAU guidance.
Experts noted that there may be some subtle differences between intermediate and high risk which will need teasing out. The clinical experts noted for example patients assessed as high risk according to EAU guidelines would be classified as intermediate risk NMIBC in the UK.
The experts and EAC agreed that, where reported in the evidence, the evidence assessment will clearly report the grading system used in the study and, if available, specific definitions of intermediate and high risk.
One expert noted that that trials can have a mix of intermediate and high-risk pts and there is a heterogenous population in data. It is also possible that muscle invasive patients are included because trials don't always do a repeat TURBT.

One expert provided a reference for risk classifications:
Kamat AM, Sylvester RJ, Böhle A, Palou J, Lamm DL, Brausi M, Soloway M, Persad R, Buckley R, Colombel M, Witjes JA. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. J Clin Oncol. 2016 Jun 1;34(16):1935-44. doi: 10.1200/JCO.2015.64.4070. Epub 2016 Jan 25. PMID: 26811532; PMCID: PMC5321095.

There was some discussion around the tolerability of treatment for men and women and what specific issues might be experienced.
One expert noted that in men there have been some urethral injuries due to difficulties inserting the rigid catheter. One expert noted that it can be more difficult to insert the catheter in men but it is manageable if you take your time and use plenty of gel. There are some things which you need to be specifically aware of such as enlarged prostate or use of anticoagulants. One expert said the catheter has gotten smaller over the years which makes using it easier
The patient expert noted that it is also intrusive for women and there can be issues resulting from leaking chemotherapy when the catheter is removed.
The patient expert noted that there may have been a fault in the device that they were treated with which caused burns to the bladder wall however the clinical experts provided reassurance that a

burn on the bladder is a fairly common occurrence with Synergo and that the burn is superficial and heals with time. The patient expert noted that no device is 100% and would be interested to see information on any problems with the device. The EAC noted that the assessment process would include searches of databases which would provide this information if available.

Terminology and Competitor Devices

Synergo and COMBAT BRS system are both approaches to Hyperthermic Intravesical Chemotherapy.

NICE asked the clinical experts to comment on the difference between Synergo and COMBAT. Briefly, COMBAT heats MMC outside the bladder and circulates around the bladder whereas Synergo uses radiofrequency to heat the bladder wall which then heats the MMC. The experts noted that the decision process is the same decision process for both Synergo and COMBAT and that COMBAT would therefore be added to the clinical pathway at the same points as Synergo. The clinical experts identified a practical difference between the technologies, that multiple patients can be treated at the same time with COMBAT and with Synergo, a single patient is treated at a time.

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Appendix 3: GID-MT553 Synergo for non-muscle-invasive bladder cancer

Company Engagement Meeting

This document summarises the discussions that took place at the company engagement meeting for MT553 Synergo, which took place on Wednesday 6th April, 13:00-14:30. Written responses were supplied by the company in advance of the meeting on 6 April 2021.

Attendees

NICE

33. Lizzy Latimer, Health Technology Assessment Adviser
34. Rebecca Brookfield, Health Technology Assessment Analyst
35. Federica Ciamponi, Health Technology Assessment Analyst

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36. Susan O'Connell, Senior Healthcare Scientist
37. Laura Knight, Senior Healthcare Scientist
38. Megan Dale, Senior Healthcare Scientist

Company

39. Joyce Craig, YHEC
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42. Gad Lev, Medical Enterprises Ltd
43. Igal Ruvinsky, Medical Enterprises Ltd

44. Ilan Schleisne, Medical Enterprises Ltd
45. Naama Reich, Medical Enterprises Ltd
46. Sam Harper YHEC
47. Joel Russell, YHEC

Themes for discussion

1. **De novo economic model structure**
2. **Comparators for Synergo**
3. **Ablative versus Adjuvant Doses**
4. **Technology and Training Costs**

De novo economic model structure

1. The model excludes BCG from the pathway, focusing on patients or circumstances where it would not be appropriate. There are reasons discussed in the submission for this, but could you tell us more about this decision, as the scope includes BCG as a possible comparator, and this is a potential treatment for patients at high risk as described in the NICE pathway?

Written response:

This positioning is consistent with the MIB which stated:

'The company states that Synergo could be used:

- *as first-line treatment for intermediate and high-risk non-muscle-invasive bladder cancer if BCG immunotherapy is not available*
- *as second-line treatment for intermediate and high-risk non-muscle-invasive bladder cancer patients if previous treatment has failed*
- *in people with high-risk non-muscle-invasive bladder cancer who cannot have or do not want to have a cystectomy*
- *in people with intermediate or high-risk non-muscle-invasive bladder cancer who are either intolerant to, or cannot have, BCG immunotherapy. '*

The only comparative information for Synergo + MMC after failing BCG (unknown kind of failure) Vs site's preference is Tan (2019)[1]. This was a poorly conducted RCT and the company judges the results have no validity and cannot be modelled (See Witjes AJ (2019[2])).

Additional discussion: Further discussion with the company around why a UK trial with BCG as a comparator had not been used in the model indicated a number of possible issues with the Tan (2019) trial which the company felt meant the data could not be used.

Tan (2019) issues stated by the company were:

- Issues with patient selection with insufficient information provided on previous BCG exposure (duration and doses) and the timing thereof. The inclusion criteria were very vague and allowed for example the inclusion of patients who failed maintenance BCG as well as patients who got partial induction BCG of those who got BCG years ago etc. Each of these examples is considered very different risk that ranges from intermediated to very high risk.
- There is no medical history of patients before randomisation and therefore no information about when pts last received BCG therapy.
- Comparator was site preference (institutional standard of care), so not a consistent treatment used (not all patients in the comparator arm were treated with BCG)
- No ablative dose was used for high risk patients, hence patients with CIS to be undertreated. All CIS patients were supposed to get ablative dose and ablative treatment regimen (8 weekly treatments) as specifically stated in the company labelling. As also shown in Brummelhuis 2021 it is of significant contribution. Also stated in Prof. Witjes letter to the editor.
- Study terminated early due to higher than expected CIS recurrence in Synergo arm. This is more difficult to identify than papillary tumors.CIS identification is quite tricky and many errors might be introduced. Readers of the article should note the reverse effect in papillary tumours which instead can be easily identified by a pathologist. For patients

[1] Tan WS, Panchal A, Buckley L, Devall AJ, Loubiere LS, Pope AM, et al (2019) Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guerin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guerin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial. European Urology 75(1):63-71

[2] Witjes AJ (2019) Radiofrequency-induced Thermochemotherapy for Recurrent Non-muscle- invasive Bladder Cancer: A New Treatment for an Unmet Need? European Urology 75(1):72-73

with the latter there was a higher disease free survival with Synergo at 24 months (53% and 24% respectively).
- Authors use alternative technologies to Synergo, leading to a conflict of interest
- Study was underpowered for the total population and subsequently for any subgroup analysis

The company further explained that they investigated using data from single arm studies to populate the model. The company explained that while there were some good single arm studies for Synergo post BCG (e.g. Brummelhuis 2021), however there were issues with single arm studies for MMC (e.g. small sample size and non-comparable survival outcomes). As a result, none were stable when modelling and were not suitable for submission.

Comparators for Synergo

2. Would you expect Synergo ever to be used as an alternative to offering BCG if both were available and clinically suitable?

Written response: In high-risk patients we expect that BCG would be offered initially, with Synergo +MMC the option for those who fail BCG before radical cystectomy. In intermediate-risk patients we expect Synergo + MMC to be offered before BCG.

Additional discussion: Further discussion around the number of patients who cannot tolerate BCG.
Patients in the model couldn't get BCG in subsequent lines of treatment (as the model is for when BCG is not available / not tolerated) and therefore are going back to MMC.
The company stated that there are a high percentage of patients who are intolerant of BCG, with large studies showing that 27% of patients tolerated BCG for the whole 3-year duration.[3] The company state that according to clinical guidelines, it is advised that BCG therapy is given for at least 1 year, but that many people cannot tolerate therapy for 1 year.

3. Is MMC a normal clinical option at the time points modelled? The EAC's understanding is that it would not normally be offered as an option for high risk patients, and it wouldn't be offered as an option if intermediate risk patients have failed the first round of MMC.

[3] Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000;163:1124–9

Written response: Several studies provided in the part 1 evidence, related to patients who had failed on MMC and were then treated with Synergo + MMC (see Table 1). Arends (2016)[4] also included patients who had been treated with MMC provided there was a gap of 12 months.

There is also in vitro evidence of the greater efficacy in impairing NMIBC cell proliferation of Synergo + MMC versus MMC or epirubicin only (Brummelhuis, 2021; attached).

Table 1: Studies using Synergo + MMC post MMC and other treatments

Article	No. of patients
Combined Chemohyperthermia: 10-Year Single Center Experience in 160 Patients with Nonmuscle Invasive Bladder Cancer. Tom J. H. Arends 2014	MMC- 8 MMC + BCG- 74 MMC, BCG + other- 4
Neoadjuvant combined microwave induced local hyperthermia and topical chemotherapy versus chemotherapy alone for superficial bladder cancer. Renzo Colombo 1996	MMC- 11 MMC + BCG- 1
Local microwave hyperthermia and intravesical chemotherapy as bladder sparing treatment for select multifocal and unresectable superficial bladder tumors. Renzo Colombo 1998	MMC- 8 MMC + BCG- 4
Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). Renzo Colombo 2010	7
Intravesical mitomycin C combined with hyperthermia for patients with T1G3 transitional cell carcinoma of the bladder. Sarel Halachmi 2011.	5

[4] Arends TJH, Nativ O, Maffezzini M, De Cobelli O, Van Der Heijden AG, Witjes JA (2015) 944 Results of the first randomized controlled trial comparing intravesical radiofrequency induced chemohyperthermia with mitomycin-C versus BCG for adjuvant treatment of patients with intermediate- and high-risk non-muscle invasive bladder cancer. European Urology 14 (Suppl. 2): e944

Thermo-chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients. B. Moskovitz 2005	11
10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer. B Moskovitz 2012	22
Preliminary European Results of Local Microwave Hyperthermia and Chemotherapy Treatment in Intermediate or High Risk Superficial Transitional Cell Carcinoma of the Bladder. A.G. van der Heijden 2004	MMC- 7 MMC + BCG- 10 MMC + Epirubicin- 3 MMC + BCG + Epirubicin- 3
Intravesical hyperthermia and mitomycin-C for carcinoma in situ of the urinary bladder: experience of the European Synergo® working party. J. Alfred Witjes 2009	11

Additional discussion:

Company agreed with the EAC statement that MMC would not typically be offered as an option for high-risk patients. But stated that the clinicians in the study (Arends et al. 2016) saw this as a valid position in clinical practice for MMC and MMC+Synergo, and there is clinical evidence. The company explained that currently, patients with high-risk bladder cancer would be offered radical cystectomy or nothing. For these patients, synergo+MCC offers an alternative treatment option that can be considered before cystectomy.

In some cases, MMC can be substituted by Epirubicin and there is some evidence to show it is safe and effective. The company enquired as to whether this data could be considered given it is not recommended by NICE Clinical Guidelines?

- NICE responded that economic models should be built on the best evidence available. But, further scenarios/ deviations can be introduced in the economic models. NICE confirmed with the company that it can consider data using synergo+ epirubicin if there is evidence in the relevant population that is in line with the published scope.

Ablative versus Adjuvant doses

4. Could the model be applied for ablative as well as prophylactic use of Synergo?

Written response: Yes.

Additional discussion: It is possible to use the model for ablative and prophylactic use but would need to change the dose information, number of cycles and years in which the cycles took place and clinical outcomes information in the model

Technology costs and training

5. Is there a purchase option for Synergo, or is it always leased?

Written response: Synergo is always leased.

6. Do Synergo provide training free of charge?

Written response: Yes
Additional discussion: During the meeting the company also confirmed that training time was included in the model.

7. Are there any routine maintenance costs for Synergo, and are these included in the lease cost?

Written response: All maintenance costs are included in the lease costs

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Appendix 4: Collated Email responses (07/04/2021)

No.	EAC Question	Expert Adviser 1	Expert Adviser 2	Expert Adviser 3
1	If a patient at high-risk was unable to tolerate BCG, or BCG were unavailable, what treatment options would be considered?	Hyperthermia treatment with SYNERGO	1. Radical cystectomy 2. Heated chemotherapy 3. Consider clinical trial participation	If available Synergo RITE. Other options are cold MMC, Gemcitabine or cystectomy
2	How does treatment for patients with Carcinoma in situ differ from those without CIS?	We at STG give 8 induction treatments of Hyperthermia with SYNERGO instead of 6 if CIS present	A stronger emphasis on early cystectomy upon failure to respond to BCG and also less likely to be considered for chemotherapy instillation	Both are same CIS = carcinoma in situ
3	Is disease free survival time the inverse of time to recurrence, or is there a difference in the definitions?	My understanding is: Disease free survival time is a way of measuring time after treatment that the patient is cancer free Time to recurrence to a way to describe a patient whose cancer has recurred	Based on these 2 terminologies, they appear to be the same. Disease Free survival is computed by Kaplan Meir curve analysis.	Disease free survival and time to recurrence essentially mean the same thing
4	Approximately how many patients are treated with Synergo at your site each year?	2019 38 patients were treated	0	10-12 new patients each year. The treatment will continue for 2 years.

No.	EAC Question	Expert Adviser 1	Expert Adviser 2	Expert Adviser 3
5	Can you provide a brief description of the difference between the adjuvant and ablative dose of MMC and situations where each dose would be used?	We only use MMC occasionally x1 after first TURBT. We also use MMC with SYNERGO Hyperthermia after bladder cleared – STG doesn't chose to use Hyperthermia as ablation	The adjuvant course of MMC is 40mg once a week for 6 weeks. I am not familiar with the standard use of MMC for 'ablation' beyond a trial setting (such as CALIBER). PS: By 'ablative' do you mean use of a single instillation of MMC post TURBT?	Adjuvant dose is 20 + 20 mg MMC - for papillary lesions which have been surgically cleared Ablative dose is 40 + 40 mg MMC - for CIS
6	Is there and adjuvant and ablative dose of BCG or is it just for chemotherapy (MMC and epirubicin)?	BCG is always same dose and after treatment. Only for Chemo	BCG is always used in the adjuvant setting.	For BCG there is no difference.
7	Would the first treatment visit be as a daycase for: • Synergo with MMC • MMC alone • BCG	All treatments are classed as daycase visits but done in outpatients in nurse led clinic. First TURBT might have MMC single dose in Day surgery/ recovery	The patient would be expected to be in the treatment area for at least 4 hours.	First treatment visit is as outpatient
8	Would subsequent treatment visits be as an outpatient for: • Synergo with MMC • MMC alone • BCG	All treatments are classed as daycase visits but done in outpatients in nurse led clinic.	The patient would be expected to be in the treatment area for at least 4 hours.	Yes

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Appendix 5: Collated Expert Responses (15/04/2021)

No.	EAC Question	Expert Adviser 1	Expert Advisor 2	Expert Advisor 3	Expert Advisor 4
1	What proportion of people can't tolerate BCG treatment?	5-10%	Most can tolerate it. 0.5% get BCGosis (type of TB from Tx)	20% don't tolerate full treatment with BCG	Approximately 15%
2	What proportion of people with intermediate and high-risk NMIBC who might be treated with BCG or Synergo have carcinoma in situ?	<5%	Less than 1/3 for Synergo	None of those with Intermediate risk because if cis is found, the classification becomes high risk. 10% of patients with High grade Ta/T1 cancer have concomitant cis.	Approximately 30%
3	What would be offered to people who couldn't have BCG if there was no option of Synergo? Would you expect all patients to have a radical cystectomy?	If patients are fit for cystectomy then that's the preferred option. Unfit patients, will be managed with endoscopic resection.	Radiotherapy is an alternative to radical surgery if they are not fit/ or keen	1. take part in clinical trials 2. Heated chemotherapy using COMBAT 3. cystectomy	Radical cystectomy will be first option. Other options will be cold MMC, Gemcitabine'

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

GID-MT553 Synergo for non-muscle-invasive bladder cancer

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from CEDAR to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **4 May 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

28 April 2021

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 25 Arends 2016	Patients were not all BCG naïve	See paper	Thank you for your comment. The EAC has made this correction to table 5 on page 28.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 26 Colombo studies	Follow-up was 10 years	See paper	Thank you for your comment. The EAC has checked this against the information recorded in table 5. Colombo 2001: No change made, a follow-up duration is not reported as this is a pilot/feasibility study. Colombo 2003: No change made – follow-up time for outcomes was 24 months Colombo 2011: Additional follow-up details added.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 42 Erturham (2015) and Kiss (2015)	Both are described as prospective studies on p38 but retrospective on this page	Wrong study type	Thank you for your comment. The EAC cannot find mention of these studies on the listed page numbers. Then EAC has made corrections to study type in tables 6 (page 35) and 8(page 45).

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 51 DFS Volpe 2012	For adjuvant group DFS at 2 years should be 58% not 46%. (Page 6 of study)	Consistency	Thank you for your comment. The EAC has made this correction on page 54.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 52 Recurrence	1.2% should be 41.2%	Typo	Thank you for your comment. The EAC has made this correction on page 55 (van der Heijden 2004)

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 55 patients with epirubicn in Gofrit	N = 4 not 3	See paper	Thank you for your comment. The EAC has made this correction in table 10..

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 61 Witjes 2009	Add ‘because of recurrent tumor’ after ‘cystectomy’	6 patients had RC	Thank you for your comment. The EAC has added this clarification in table 10, in the text, page 55 and in Appendix B.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 64 Brummelhuis 2021	Bladder pain was 27.1% not 27.8%	Table 6 of paper	Thank you for your comment. The EAC has not made any change as the text of the paper states 27.8% and checking the calculations in the table suggests that 27.1% is an error (82 patients of 294 patients reported pain).

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Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 68 line 6 Also • the majority of people had intermediate risk NMIBC and would not be offered BCG as a 1st line treatment in the UK is incorrect. Arends 2016 Letter reports 85 patients were high risk under 2016 classification	Arends 2016 not 2011 Remove the bullet	typo Incorrect- the majority of patients are high risk under current definitions	Thank you for your comment and clarification. The EAC has corrected the year of publication and adjusted the text of this bullet point. Table 13, adjusted to read: Intermediate (69%) high risk (31%) reported in publication using 2001 guidelines. 60% high risk in ITT group using 2016 guidelines.(Arends 2017) Appendix B table has a note amended to state: Risk groups were classified using 2001 guidance. A letter (Arends 2017) subsequently stated that 85 of the ITT patients (n=142) were high risk using the 2016 classification. The letter has been added to the references.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 69 Comparison with epirubicin	Arends 2016 should be Arends (2014)	Correction	Thank you for your comment.

			The EAC has made this correction.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 120 '3.8% had received CHT as initial treatment '	Should this be 3.8% had no previous treatment?	See Table 1 in paper	Thank you for your comment. The text in Appendix B for Arends (2014) has been changed to 3.8% had no previous treatment.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 143 33% (7/21) patients died of metastatic disease	This is all cause death. 2/7 died of metastatic disease	See study	Thank you for your comment. The EAC has added this result to Appendix B, Kiss 2015

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 144 • 76.2% of patients (n=2) completed treatment	N = 32	See study	Thank you for your comment. The EAC has corrected this typo (Appendix B, Maffezzini 2014)

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 57; 150 • Probability of recurrence was 85% at one year and 56% at two years	It is recurrence-free probability	See study	Thank you for your comment. The EAC has corrected the data tables 10 and Appendix B (Nativ 2009) but made no change to the text where it was reported correctly as a recurrence-free probability

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 155 Sri	Median ages not means are reported and these are 72 for RITE and 69 for non- RITE groups	See study	Thank you for your comment. The EAC has corrected this in Appendix B (Sri 2020)

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 157 Tan	Add '40 mg MMC in total' after 'maintenance RITE'	See study and to improve transparency	Thank you for your comment. The EAC has added this text in Appendix B for clarification.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 162 Van Valenburg (2018)	'Other BCG treated patients: mean 40.6 months'. This rate was for BCG naïve patients	See study	Thank you for your comment. The EAC has corrected this in Appendix B

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 171 Halachmi 2009 or 2011?	Halachmi 2009 is reported but Halachmi 2011 has slightly later data- eg recurrence was 17/51 vs 16 in 2009	For information	Thank you for your comment. Halachmi 2011 was not identified by the EAC searches. As this is an abstract the EAC does not consider it makes a material difference to the evidence and therefore has not made any changes.

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Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 173 Ludecke 2015	I cannot find the data in paper to support the bullets starting: • '*41.7% tumour free in BCG failure patients with BCG-resistance stay tumor-free* ….'	Double check please	Thank you for your comment. The EAC has not changed the results as these are reported in the abstract. We have edited the text for clarity.

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 82	'After year 5, the model takes the high-risk annual cost from years 0-5 (£679)...' where cost in the model is actually £694.	Correction	The cost in the submitted model was £694. After EAC corrections to inflation, but still using 13 visits over 5 years, the cost was £679. The text has been amended for clarity to reflect all EAC changes (inflation and 11 visits) to: "…cost from years 0-5 (£575 after all EAC changes) and applies to the proportion of people….."

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Exec Summary parag 1	Synergo is a …..which uses radiofrequency-induce thermo-chemotherapeutic effect (RITE)	Should be 'induced'	Thank you for your comment. The EAC has corrected this typo

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 2	Please revise LI92B-S to LI932B-S	correction	Thank you for your comment. The EAC has corrected this typo and corrected the number in the corresponding text.

Issue 23

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 13 3rd last line	'local anaesthesia' should be 'local anesthetic lubricating gel'	Correction	Thank you for your comment. The EAC has added this clarity

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 25 Arends 2016	Arends 2016 reply (attached) gives number of high risk patients using 2016 classification	Consistency across studies in treatment of risk	Thank you for your comment. The EAC has used data reported in the peer reviewed publication only and has not made any change to table 5. Additional information has been added to Appendix B and a note added to table 13

Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 38 Sri 200	Not all patients in Sri trial had failed BCG before cystectomy: 'Overall 102 patients underwent either primary cystectomy or cystectomy post BCG failure'	Accuracy	Thank you for your comment. The EAC has added clarity to table 4, 5, Section 5.1 (page 41), page 48 (complete response rate)

Issue 26

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 43 Sri 2020	The text refers to 19.6% of patients treated with standard MMC. This is incorrect. The comparator group did not get standard MMC but were cystectomised directly.	Accuracy	Thank you for your comment. The EAC has checked this study and made appropriate corrections to the text.

Issue 27

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 40 list of studies including subgroups of patients with concomitant CIS, patients with papillary disease only	List is incomplete. Please add studies by Arends 2014, Witjes 2009, Tan 2019 and van Valenburg 2018.	Accuracy	Thank you for your comment. The studies have been added to the list

Issue 28

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 40 list of studies including subgroups of people treated with MMC and Epirubicin	List is incomplete. Please add Brummelhuis 2021	Accuracy	Thank you for your comment. The study has been added to the list

Issue 29

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 40 list of studies including subgroups by BCG treatments	List is incomplete, please add Nativ	Accuracy	Thank you for your comment. The EAC has added this information.

Issue 30

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 44 last parg on Sri	Sri refers to recurrence following cystectomy and this is not comparable with the other studies with are recurrence pre-cystectomy	Clarity	Thank you for your comment. The EAC has clarified this

Issue 31

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 46 Arends 2016	Disease progression was reported at 0%.	Correction	Thank you for your comment. The EAC has added this result

Issue 32

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 46 Colombo 2003	The study reported no progression to muscle disease. The patient in table 9 had worsening of grade of NIMBC	Accuracy	Thank you for your comment. The results relating to progression are reported as they are outlined in the text of the paper (Colombo 2003 and 2011). No change has been made

Issue 33

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 47 Sri 2020	Study not relevant here as recurrence is after cystectomy not post Synergo or comparator. Also, 'metastatic disease in the no MMC group' is incorrect. This should read 'metastatic disease in the no RITE-MMC group'.	Aid interpretation. Accuracy.	Thank you for your comment. The EAC has corrected information relating to Sri.

Issue 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 47 Tan 2019	In Study column please add *'Prophylactic dose of' intravesical MMC*	Aid interpretation	Thank you for your comment. The EAC has not added this information as it is included elsewhere in the report and has not been included in this table for any study.

Issue 35

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 49 ‘All patients’	All synergo treatment articles present recurrence rates / disease free survival. Depends how the writer wishes to present the data. The only article not relevant is Sri 2020 which compares cystectomy outcomes. Articles presenting ablative regimen also include “response”. Please explain purpose of the adjuvant and ablative (neo-adjuvant) treatments before presenting data.	Aid understanding and clarity	Thank you for your comment. This section titled ‘All patients’ relates to results reported for whole study cohorts as reported in the individual papers. Subgroups comparisons of relevance are reported in later sections. The EAC has highlighted the difference between adjuvant and ablative doses earlier in the report. No changes have been made.

Issue 36

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50 heading ‘Treatment response’	More accurate to use ‘Treatment response after ablative (neo-adjuvant) regimen’	Accuracy	Thank you for your comment. The EAC has added some clarity to the section ‘treatment response’ on page 53.

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Issue 37

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 51 Bladder Preservation Rate	The following studies have been omitted: Witjes 88.9% Halachmi 88.2% Ayres (Ayres BE, Connor A, Corbishley C, Bailey MJ. 3-year single-centre UK experience of radiofrequency hyperthermia and mitomycin C in BCG failures [abstract]. BJU Int 2010;106(Suppl s1). - 81.6% Colombo 2011: "The bladder preservation rate after 10 years was 86.1% and 78.9% for HT + MMC and MMC-alone groups, respectively" Sooriakumaran 2016: 81.4% "the bladder preservation rate for the entire cohort was 81.4%" Sri 2020: "Approximately a third of patients at our centre go on to have cystectomy due to RITE-MMC failure" Gofrit 2004: At a median follow-up of 15.2 months ..The bladder preservation rate was 86.5%. The prophylactic protocol was administered to 24 patients. After a mean follow-up of 35.3 months, the bladder preservation rate was 95.8%. … The bladder preservation rate for the ablative group was 78.6%.	Studies omitted	Thank you for your comment. The text reports the key results therefore no results from abstracts are listed in the main text. Bladder preservation rates for Colombo et al are reported in table 9 however for consistency the EAC has added the rates to the main text relating to comparative studies. As cystectomy is essentially the comparator in Sri et al, the bladder preservation rate was not considered a useful outcome in this context. Bladder preservation rates for Gofrit are reported in the section comparing Adjuvant and Ablative regimens (page 55) Bladder preservation rate for Sooriakumaran et al has been added to the report. Witjes reports RC numbers and these are reported in the subsequent section.

Issue 38

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 51 Sooriakumaran (2016)	The text is misleading. The correct % is 18/97 went on to have cystectomy (table 4) = 18%. Authors report bladder preservation rate of 81.4%	Correct misleading text	The EAC considers the text to be accurate as it is the percentage of patients with recurrence who had a radical cystectomy however for additional clarity has added the number of patients that relates too, and figures for the whole cohort..

Issue 39

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 51 Adjuvant versus Ablative Regimens	Data from Brummelhuis 2021 are missing	Accuracy	Thank you for your comment. This information has been added.

Issue 40

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 51 Recurrence	Text difficult to follow as ordering of ablative and adjuvant regimens switches. Also Brummelhuis data should be added	Improve understanding	Thank you for your comment. The EAC has re-ordered the sentence for ease of reading. Data from Brummelhuis has been added

Issue 41

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 52 previous BCG treatments	Studies omitted include: Arends 2014 80.6% failed BCG treatment prior Synergo Moskowitz 2015: 59% failed BCG in the prophylactic (adjuvant) group and 80% in the ablative (neo-adjuvant) group Moskowitz 2012 59.1% failed BCG in the prophylactic (adjuvant) group and 76.9% in the ablative (neo-adjuvant) group Maffezini 2014: 19% failed BCG & 45.3% failed previous chemotherapy Soouriakumaran 2016: previous "BCG only" 69.1%, previous "BCG + other": 13.4% Volpe 2011: 100% failed BCG Halachmi 2011: 19 had BCG (19/ 56 T1G3 patients = 33.9%) Kiss 2014: 57% had previous BCG	Accuracy	Thank you for your comment. The EAC acknowledges that patents in all of these studies reported previous BCG treatment use however the purpose of this section was to report studies where results specifically addressed the possible impact from previous treatments. No change has been made.

Issue 42

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 40 Subgroup results for people with intermediated versus high risk NMIBC (Nativ 2009)	Should be 'intermediate'	Typo	Thank you for your comment. This typo has been corrected.

Issue 43

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 52 *Intermediate Risk compared with High Risk NMIBC*	The following studies present relevant analyses: van der Heijden 2004 in Table 2 and text. Colombo 2011 – although rates are not provided. Text states: 'There were similar results for both the intermediate- and high risk NMIBC subgroups. Even tumour multiplicity (i.e., ≥ 5 concurrent tumours), which was a severe negative prognostic factor in the MMC-alone group, did not significantly influence the efficacy of the HT + MMC treatment. ' Arends 2014: see Table 2		Thank you for your comment. The EAC has not included narrative results in this section. Data for van der Heijden 2004 has been added.

Issue 44

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 58 Sooriakumaran 2016	Bladder preservation reported as 81.4%. Also 51.4% in final column is misleading. Rate of cystectomy was 18/87 = 18%	Correction	Thank you for your comment. See response to previous comment relating to this.

Issue 45

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 61 Wijtes	Add 49% (n=22) of responders had a recurrence at mean follow up of 27 months. Also, 6 patients had a cystectomy, not 5 as stated in the final column.	Adjustment/correction	Thank you for your comment. The EAC has added clarity.

Issue 46

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pages 63 and 64 Table 11	Brummelhuis: please add number of patients so 30/299 and 34/299. Tan: same change so 5/48 Native 6/111 Gofrit 2/52 Maffezini: 5/42 Arends: 5/92 Van de Heijden 2004 – One case of severe, prolonged posterior wall thermal reaction with a lesion >2cm which took 3 months to heal. Please add 'asymptomatic' Witjes 2009: 1/49	Context required	Thank you for your comment. The EAC has made these changes

Issue 47

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Glossary BCG-Refractory	'People with stage or grade progression at 3 months despite BCG therapy.' This is inaccurate as progression is not necessary, recurrence of tumor alone is sufficient	Accuracy	Thank you for your comment. The EAC has not made any change here as the clinical experts have reviewed the glossary.

Issue 48

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Hyperthermic intravesical chemotherapy Definition is factually incorrect. If you use heated chemo for the term "hyperthermic intravesical chemotherapy" than it would be only the Combat. It is a critical error to state that RF heats the drug which in turn heats to tissue. The drug with RITE is cooled so that in the bladder it is tepid! The drug circulates in and out the bladder in closed circuit, passing in a heat exchange chamber which is at about 5DegC. it keeps the drug in the bladder tepid. The RF heats the tissue.			Thank you for your comment. It is unclear from this what correction is required. The glossary definitions were reviewed by clinical experts. The EAC has made adjustments to the glossary definitions to add clarity using the proposed amendment from the next comment.

Issue 49

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Radiofrequency-induced chemohyperthermia (RF-CHT) Definition is inaccurate as drug is only heated when inside the tissue	A type of hyperthermic chemotherapy treatment approach which involves heating the bladder wall to 42-44C through controlled delivery of radiofrequency (non-ionising microwave radiation) using the Synergo device.	Accuracy. We can send a labelled image of the device if this will assist.	Changes made to glossary

Issue 50

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Figure 2 EAC pathway	Addition to pathway is required to include patients that cannot tolerate or are contra-indicated or when BCG is unavailable	Relevant subgroup that should be addressed in EAC pathway	Thank you for your comment. The Pathway was agreed with the clinical experts. The EAC has not made any changes.

Issue 51

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 28 Tan study. The intervention and comparator are identified as appliable to the decision problem.	The intervention is not applicable to the decision problem because adjuvant dose used and only for 6 treatments. Neither are UK practice		Thank you for your comment. The applicability in this context relates to the population, the intervention the comparator, and the outcomes specifically. The relevant limitations of the Tan study and the impact on the evidence certainty are acknowledged and discussed in the report in detail. The EAC has not made any changes.

Issue 52

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 53 MMC Vs epirubicin	Please add comparative efficacy from Brummelhuis		Thank you for your comment. The EAC had added the following text to page 57: Multivariate analysis results from Brummelhuis 2021 indicated no significant difference in recurrence free survival and durable response for MMC vs Epirubicin (adjusted HR: 1.23 (0.71-2.14, p=0.46).

Issue 53

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 66 8 Interpretation Use of term 'hyperthermic chemotherapy' here as elsewhere in the report is incorrect.	Synergo should not be described as hyperthermic chemotherapy' but RITE or similar. This change should be applied throughout the assessment report.		The definition has been amended following an earlier comment. The EAC has amended the Assessment report to ensure all references to Synergo specifically are stated as 'Synergo' and all references to hyperthermic chemotherapy have been changed to 'device assisted chemotherapy' for clarity.

Issue 54

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 67 Tan 2019. Duration of dose also wrong.	After 'an adjuvant dose.' Dosage was also only for 6 instillations, rather than the recommended 8.' And same addition after (2x40mg). in second bullet	The description of the undertreatment should be correct .	Thank you for your comment. The EAC has made this change in section 8.

Issue 55

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 67 Quality of results also impacted by no reporting of type of BCG failure at entry for randomisation.	Please add a bullet. 'The study did not report type of BCG failure and whether this was random between the groups.'	Improve accuracy.	Bullet point added in Section 8: The trial recruited a heterogenous group of BCG refectory, resistance, and intolerance. These groups are not included in patient demographic results, although the numbers receiving less or more than 6 instillations are reported.

Issue 56

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 68 last paragraph line 3. In In UK practice settings also treat patients at intermediate risk but considered high risk after failing first line MMC.	'treat only high-risk NMIBC and those who fail first line MMC.'	Accuracy	Thank you for your comment. The EAC has not made any change here as this is a reflection of the information provided by the clinical experts.

Issue 57

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 69 3rd paragraph – omits Brummelhuis	Reported only in two studies (Arends 2016…) Then please add findings from Brummelhuis	Accuracy	Thank you for your comment. The EAC has made this change.

Issue 58

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 57: Disease progression column states 'not reported'.	The progression rate was 3%.	Accuracy.	Thank you for your comment. The authors (Nativ 2009) report that 3% experienced recurrent muscle invasive disease, and in the abstract state the progression rate is 3%. For clarity the EAC have moved this from recurrence to progression in table 10.

Issue 59

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 57: Survival column states 'not reported'.	The Kaplan-Meier estimated disease-free survival rate was 85% and 56% after 1 and 2 years, respectively.	Accuracy.	Thank you for your comment. This is reported in Nativ (2009) both as disease-free survival and recurrence free survival. It is already included in table 10 as recurrence free survival. No changes made

Issue 60

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Typography error throughout, ‘van Valenburg’.	‘van Valenberg’	Accuracy.	Thank you for your comment. This has been corrected.

Issue 61

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 20 The EAC has excluded two studies that were included in the company submission (Colombo 1995 and Colombo 1996) as the study dates overlap and it was unclear whether there was patient overlap.	The articles of Colombo are not overlapping. The first was to see ablation of existing tumours. The later one was: randomized with marker lesion.	Accuracy.	Thank you for your comment and clarification. The EAC has not made any changes.

Issue 62

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is unclear why the Tan 2019 study has been used in the EAC additional analysis, and for CIS specifically.	Please describe why Tan 2019 was used in place of other relevant studies, e.g. van Valenberg was not used, which specifies the type of BCG failures.	Accuracy.	Tan 2019 was used to inform the part of the pathway where BCG would be the most appropriate comparator. Tan 2019 was the only available comparative study for BCG where information was available for non-CIS patients treated with adjunctive protocol. There are limitations to this paper, and these were discussed in the assessment report. The additional analysis was specific to non-CIS only. The following text has been amended to ensure that this is clear: "There is a subgroup analysis of patients without CISC who did receive the recommended Synergo regimen. This subgroup of 33 patients is used for the EAC scenario of Synergo vs BCG for 2nd line treatment for patients with no CIS. Data was extracted from the Kaplan Meier graph in Tan (2011) using webplot digitizer. The EAC did not identify any comparative study that would have been better able to inform modelling for patients with CIS using for any comparator" Clarifications have also been added to the results and conclusions that these apply only to patients with no CIS, as follows: P90: Due to limitations of available evidence, the EAC have restricted remodeling to recurrence of NMIBC following treatment with BCG or other standard care in patients with intermediate or high risk NMIBC and no CIS, with the intervention and comparator arm as shown. p94: "The EAC model using Tan (2019) for Synergo vs BCG for patients with no CIS" P101: "The EAC amended the submission to use an alternative clinical source data (Tan, 2019) to model the Synergo vs BCG as 2nd line treatment for patients with no CIS" p.105: "The economic model for Synergo compared to BCG as a 2nd line treatment for patients with no CIS, found that it was cost incurring," Van Valenberg (2018) is a retrospective, non-comparative paper that considers the use of Synergo in patients with CIS that have previously had BCG treatment. This could potentially inform one arm of a model, however the complexities of the patient selection and pathways would make populating the comparator arm very uncertain.

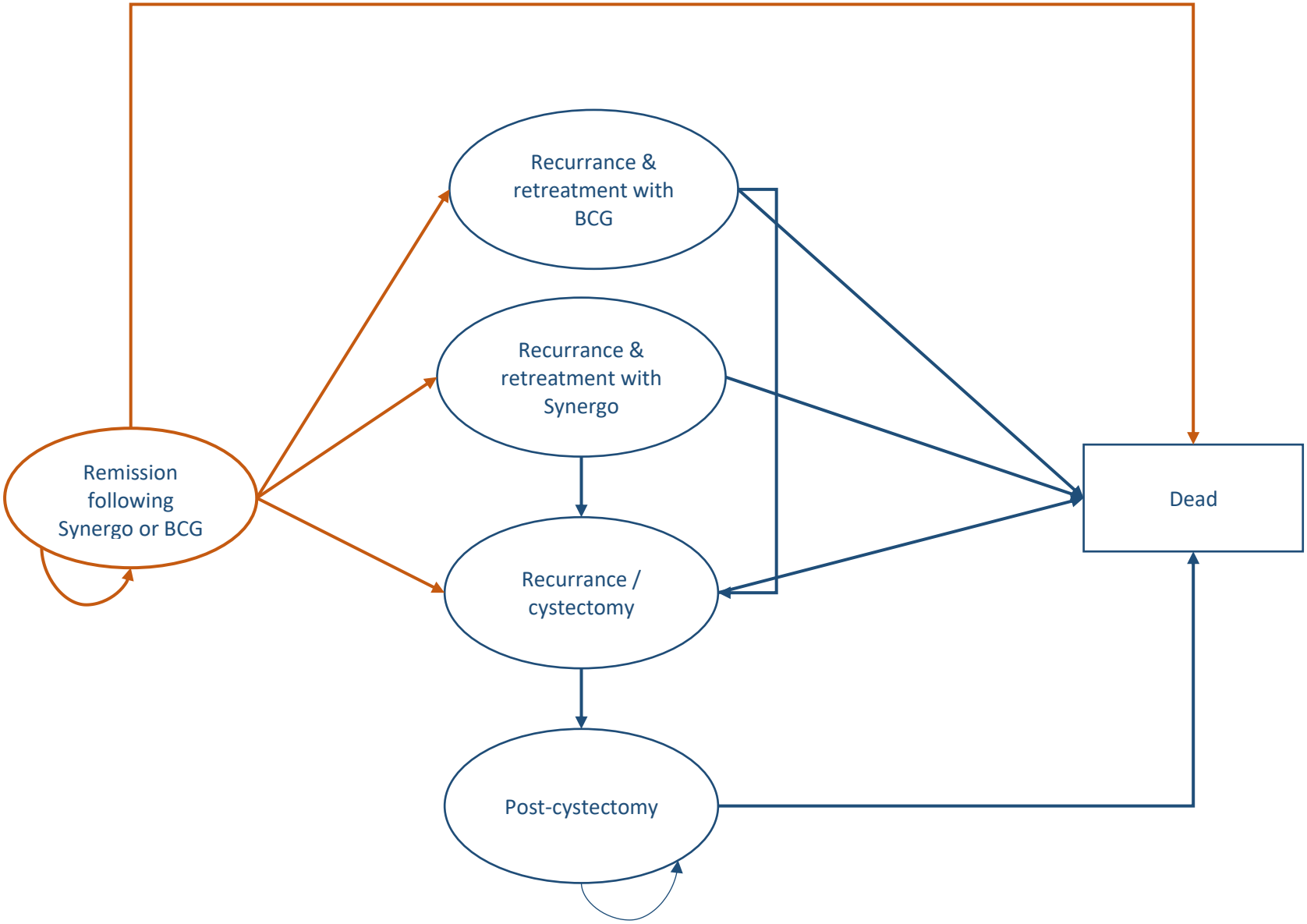
Additional error corrections identified by NICE / EAC:

Table 16: the lifetime horizon total costs for Synergo vs BCG were incorrectly entered and have been amended as shown in blue text

EAC model for Synergo vs BCG (Tan 2019)				
Short term (<=5 years)	£32,081	£27,431	-£4,649	0.49
Longer term (post years)	£23,004	£20,153	-£2,852	0.30
Lifetime horizon	**£55,085**	**£47,584**	**-£7,501**	**0.79**

Figure 11: Horizontal axis corrected to read Incremental cost (Synergo vs BCG)

Figure 5: One arrow had moved during editing of the document, this has been corrected to connect “retreatment with BCG” to “recurrence / cystectomy”, as shown below


Recurrance & retreatment with BCG
Recurrance & retreatment with Synergo
Remission following Synergo or BCG
Recurrance / cystectomy
Dead
Post-cystectomy