National Institute for Health and Care Excellence

Medical technologies evaluation programme

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

Consultation comments table

Final guidance MTAC date: 17 September 2021

There were 21 consultation comments from 1 consultee:

- Company

The comments are reproduced in full, arranged in the following groups:

- Recommendations (comments 1 to 3)
- Synergo care pathway (comment 4)
- Clinical evidence (comments 5 to 10)
- Economic modelling (comments 11 to 14)
- Future research – comparing Synergo to other device-assisted chemotherapy technologies (comments 15 and 16)
- Future research – Synergo mechanism of action (comment 17)
- Consultation question responses (comments 18 to 21)

#	Consultee ID	Role	Section	Comments	NICE response
Recommendations					
1	1	Company	1.1	Please refer to our reply to subsection 1.2- the data already exist and only need to be collected. We believe that the data from routine treatments that were already done in the NHS is vast, and should suffice. [Please see comment #2]	Thank you for your comment. The committee agreed that the collection and analysis of local audit data may help address some of the uncertainties around the potential clinical and cost benefits of Synergo compared with standard care. The committee decided not to change the recommendations in response to this comment. Final guidance recommends collecting and analysing local audit data. Please also refer to NICE's response to consultation comment 2.
2	1	Company	1.2	According to numerous unaffiliated consultants, collected data should only focus on the evaluation of the treatment's success- disease progression, cystectomy, BC related death. Collected data should include patients' gross raw data, and treatment protocol for evaluation of the integration of Synergo® as a viable treatment for NMIBC. The company suggests analysing available data from the two major NHS treating centres (St. Georges and Darent Valley), that will cover some 80% of all routinely treated patients in The UK, in order to gain better understanding on the implementation of Synergo® in the NHS system while saving precious time.	Thank you for your comment. The external assessment centre's assessment report conducted a comprehensive literature search identifying all relevant peer-reviewed published studies, all of which were appraised and discussed in detail in the report. This included published data involving St George's and Darent Valley NHS centres. The committee agreed that if centres have collected more data than is reported in their published studies and that this could be made available either through new published studies or for audit purposes, it may help address some of the current uncertainties around the patient pathway and the potential clinical and cost benefits of Synergo compared with standard care. The committee decided not to change the recommendations based on this comment. Final guidance recommends collecting and analysing local audit data.

				We believe that such accelerated analysis is imperative in order to help patients that have dissipated all other treatment alternatives, and are otherwise referred to cystectomy (standard of care for BCG failures. Associated with high morbidity and mortality rates within 90 days post-op). We also take into consideration patients that can't be cystectomised due to comorbidities, inability to be anaesthetized, or objection to undergo such surgery, and are left w/o other treatment options. We will gladly supply a list of suggested data to collect, that was composed by unaffiliated consultants.	
3	1	Company	1.2	The seeming equivalence in the text between Synergo® and conductive hyperthermic intravesical chemotherapy, despite the previous statements by NICE about the adverse events and poor clinical evidence of the latter, is a conundrum to us. While RITE has 4 RCTs* (of which 2 compare to MMC and BCG and both reach statistical significance), HIVEC does not have even one published randomised study. It does not seem relevant to compare warm MMC to Synergo® while efficacy of warm MMC comparing to MMC alone is yet to be confirmed. The flagship study of Combat (HIVEC II) required increasing patient number from 191 to 259 (on 2015). Recruitment ended 4 years ago.	Thank you for your comment. Section 1.2 of the guidance has been amended to remove the comparison to other device-assisted chemotherapy options from the recommendations. The committee noted that published evidence on the efficacy of other device-assisted chemotherapy options is limited at present. However, it agreed that information on the benefits and costs of Synergo, compared with other device-assisted chemotherapy technologies available in the NHS would be helpful and, although not featured in the recommendations, remains a consideration for future research. This is discussed in section 4.14 of the guidance, which has been amended to improve clarity.
Synergo care pathway					
4	1	Company	2.4	Also in cases of patients that cannot sustain radical procedure (due to comorbidities, old age etc.), and patients	Thank you for your comment. Based on advice sought from clinical experts, the committee agreed that section 2.4 of the guidance accurately reflects the

				that refuse to have cystectomy (e.g. younger patients)	patients who are most likely to receive Synergo in the NHS. No substantial changes to the guidance were made in response to this comment, however section 2.4 was reworded slightly to improve clarity based on clinical expert advice.
Clinical evidence					
5	1	Company	3.4	the study of Synergo + MMC vs. MMC alone was stopped by DSMB after two reviews. the first allowed additional recruitment to see if the benefit of Synergo remains. once additional recruitment completed and the benefits remained, DSMB recommended to stop the study	Thank you for your comment. Colombo et al. (2011) stopped early due to significantly better efficacy of Synergo over that of MMC alone. This is stated in section 5.2 of the external assessment centre's assessment report and in section 3.4 of the draft guidance. The committee agreed that the level of detail presented in the guidance was sufficient. The committee did not make any changes to the guidance in response to this comment.
6	1	Company	3.6	Conflict of interest- [redacted]	Thank you for your comment. The HYMN trial was assessed by the external assessment centre based on details reported in the published manuscript only. The committee agreed that declarations of interest not reported by the study could not be considered. The committee agreed that in addition to the reported conflicts of interest, substantial limitations of the study existed which impacts the certainty of results. The limitations in the study methodology have been reported in Sections 8 and 9.2 of the Assessment Report. They have also been discussed in sections 3.6 and 4.3 of the guidance. The committee decided not to change the guidance in response to this comment.
7	1	Company	3.6	only for CIS	Thank you for your comment. The committee considered section 3.6 of the guidance to adequately summarise the key limitations of the HYMN trial. The committee decided not to change the guidance in response to this comment.
8	1	Company	3.6	1. CIS treatments were done with low dosage of MMC comparing to Synergo® protocol (2*20mg vs. 2*40mg). 2. Treatment of papillary tumours showed clear advantage for Synergo®	Thank you for your comment. The committee considered that section 3.6 of the guidance accurately reported the dosage of MMC used in the HYMN

				treatment though not reaching statistical significance due to small number of patients. *[see also consultation comment #9]* 3. Central pathology found that 1/3 of the allegedly recurring CIS patients were false positive, and only 1/3 were confirmed CIS	trial. No change was made to the guidance in response to point 1 of this comment. The committee agreed that in people with papillary tumours only, the HYMN trial showed a non-significant difference in disease-free survival with Synergo compared with BCG (53% compared with 24%; p=0.11). Section 3.3 of the guidance has been amended to include details of results for people without baseline carcinoma in situ. See also NICE response to consultation comment 9. The committee were not able to verify point 3 of the comment based on details reported in the published manuscript of the HYMN trial. The committee decided not to change the guidance in response to point 3 of this comment.
9	1	Company	3.6	where the HYMN protocol was adequate (adjuvant for papillary tumours) Synergo showed clear benefit (53% vs. 24% DFS), though not reaching statistical significance	Thank you for your comment. The committee agreed that in people with papillary tumours only, the HYMN trial showed a non-significant difference in disease-free survival with Synergo compared with BCG (53% compared with 24%; p=0.11). Section 3.3 of the guidance has been amended to include details of results for people without baseline carcinoma in situ.
10	1	Company	3.8	to overcome this issue the company suggests data collection as proposed by CEDAR and numerous consultants, with specific objectives: 1. Radical cystectomy. 2. BC specific death	Thank you for your comment. Following expert advice, the committee agreed that data collection should include outcomes on bladder preservation rates and bladder cancer specific mortality, as well as the outcomes outlined in NICE's interventional procedure outcomes audit tool. Section 4.13 of the guidance has been amended to include more detail on suggested outcomes to be collected.
Economic modelling					
11	1	Company	3.14	BCG side effects are systemic and far more serious than Synergo SEs.	Thank you for your comment.

				in the HYMN trial one BCG patient had died due to sepsis (not reported. company has the data base)	The external assessment's economic modelling was based on data reported from the HYMN trial. On the basis of the reported results the EAC assumed similar adverse event costs for each arm. Clinical experts agreed that it was reasonable to assume the adverse events costs were similar. The committee decided not to change the guidance in response to this comment.
12	1	Company	3.15	this comparator is incorrect. the gold standard for patients that failed adequate BCG is radical cystectomy, and this should be the comparator.	Thank you for your comment. The committee noted that the external assessment centre had carried out an exploratory scenario analysis using radical cystectomy as a comparator to Synergo in response to expert advice. This analysis was presented to the committee in the form of an addendum to the main assessment report and is described in section 3.17 and 4.10. of guidance. The committee was advised that the analysis was limited by the lack of outcome data on Synergo compared with radical cystectomy. Section 1.2 and 4.13 have been amended to acknowledge that further data collection and analysis should inform a revised cost analysis comparing Synergo to cystectomy or repeat cystoscopies in people who cannot have cystectomy.
13	1	Company	3.17	short and long term side effects associated with cystectomy were drastically under estimated (e.g. over 15% reintervention, around 80% erectile disfunction that many will require implants [especially younger patients] etc.).	Thank you for your comment. The external assessment centre's economic modelling did not include side effects associated with cystectomy. However, the possibility of re-intervention (30%, at £2,897) and routine stoma care products and follow-up (£2,427 per year) were included in the costs of cystectomy. Exploratory analysis done by the external assessment centre in response to this comment suggested that erectile dysfunction (annual cost of £196.76 taken from MTG49) has minimal impact on cost saving estimates. Implantation of penile prothesis (costed at £5,056 in NHS Reference costs 2019/20, not included in MTG49 due to low numbers receiving implants) is also likely to have only a small impact. Section 1.2 and 4.13 have been

					amended to acknowledge that further data collection and analysis should inform a revised cost analysis comparing Synergo to cystectomy or repeat cystoscopies in people who cannot have cystectomy.
14	1	Company	3.17	All the articles show much higher bladder sparing %. for example- van Valenberg et al show 78.5% DFS for at least 36 months, and CIS BCG unresponsive about 50% after 5 years	Thank you for your comment. The 4% quoted in section 3.17 of the guidance is the number of modelled patients who do not require a radical cystectomy within their lifetime. This modelled estimate is based on a 54% disease free survival at 24 months as reported in the HYMN trial for people without baseline carcinoma in situ. Section 3.17 has been amended for clarity to explain that the 4% is a modelled estimate over a lifetime horizon.
Future research – comparing Synergo to other device-assisted chemotherapy					
15	1	Company	4.14	The two technologies are utterly different! 1. conductive heat devices can only change liquid temperature, in a limited range. Synergo® treatment is individualised and the device is tuned during every treatment according to tissue properties and change in blood flow (vasodilation). 2. Synergo shows homogenous tissue temperatures throughout the bladder (measured in real time in different areas). 3. MMC can't reach behind the balloon in the bladder neck, nor heat in the dome, where there are bubbles. With Synergo we have the RF effect throughout the bladder. 4. most of the flow in conductive heat devices is parallel to the tissue, and therefore zero on the boundaries (liquid-bladder wall [fluid mechanics]). 5. conductive heat results in problematic drug absorption (Milla et al, 2014. the company can furnish explanations).	Thank you for your comment. An external assessment centre was asked to review technical documentation supplied by the company and publicly available information, to support the committee with the response to this comment. The committee concluded that although clinical evidence for other device-assisted chemotherapy options was limited at present, further information on the benefits and costs of Synergo, compared with other device-assisted chemotherapy technologies available in the NHS would be helpful to better understand the clinical benefit of Synergo. Section 4.14 and 4.15 of the draft guidance have been amended to improve clarity.

				6. studies show poor energy transfer from warm liquid to tissue, both ex-vivo (van Valenberg et al, 2018) and in-vivo (sent separately by email).	
16	1	Company	4.14	(in reference to emailed graph) *[see appendix 1]* Red line shows liquid inflow (MMC solution). It arrives cooled from the system , and temp' is measured just before entering the catheter. There is a rise in the temp' when MMC is replaced with a fresh solution (not cooled), as routinely done during Synergo treatments. Green curve shows temp' of outgoing MMC solution. We see that it is warmer than the inflow MMC by about 10˚C. This is because the liquid absorbs the heat from the tissue, it travels very slowly through the urethra in and out, the cable inside the catheter is somewhat hotter, and negligible amount of energy is absorbed directly by the liquid (due to its electrolytes). These four phenomena also explain the peek in the red line at the 30-minute mark (when the circulation of cooled liquid is paused). The bold blue curve is the temp' of the bladder wall measured with the Synergo® probes. These are about 6˚C above the liquid in the bladder cavity. Despite the phenomena mentioned, the liquid's absorption of energy accounts for about 2-3W assuming a flow of 6 ml/minute (calculated by the equation $q=mc\Delta T$). That is favorable because it means that the vast majority of the energy is absorbed in the bladder tissue. Blood cooling effect (vasodilation) is clearly	Thank you for your comment. An external assessment centre was asked to review technical documentation supplied by the company and publicly available information, to support the committee with the response to this comment. The committee concluded that although clinical evidence for other device-assisted chemotherapy options was limited at present, further information on the benefits and costs of Synergo, compared with other device-assisted chemotherapy technologies available in the NHS would be helpful to better understand the clinical benefit of Synergo. Section 4.14 and 4.15 of the draft guidance have been amended to improve clarity.

				evident and can be overcome with increased power.	
Future research – Synergo mechanism of action					
17	1	Company	4.15	The company possesses a review document with an abundance of studies that prove and explain the effect of microwave energy on cancer cells, including specific work on bladder cancer cells. For Example, one study showed that: "RF treatment caused declines in cancer cell viability and proliferation. RF treatment also affected mitochondrial function in cancer cells more than HT treatment did and, unlike HT treatment, was followed by the elevation of autophagosomes in the cytoplasm of cancer cells. Importantly, the effects of RF treatment were negligible in nonmalignant cells. Conclusion: The obtained data indicate that the effects of RF treatment are specific to cancer cells and are not limited to its hyperthermic property."	Thank you for your comment. An external assessment centre was asked to review technical documentation supplied by the company and publicly available information, to support the committee with the response to this comment. The committee concluded that further research would be welcomed on demonstrating the additional benefit of Synergo's mechansim of action. Section 4.14 and 4.15 of the draft guidance have been amended to improve clarity.
Consultation question responses					
18	1	Company	General	*Has all of the relevant evidence been taken into account?* only clinical evidence. pre-clinical evidence has not been taken into account	Thank you for your comment. The published scope provides the framework for assessing the technology. It defines issues relevant to the evaluation, addresses the clinical and resource impact questions that need to be answered, and sets the boundaries for assessing the evidence and the committee's decision making. Section 5 of the MTEP methods and process guide states the scope may also include technical questions raised by the committee or the programme team at selection stage but these technical questions do not extend to a full technical evaluation of the device.

					No technical questions were raised during scoping and therefore preclinical evidence on technical aspects of the technical were deemed out of scope of the evaluation by the external assessment centre. The committee did, however, accept the comment and assigned an external assessment centre to review the technical documentation supplied by the company and publicly available information, to support the committee with the response to consultation comments 15 to 17 above.
19	1	Company	General	*Are the summaries of clinical and resource savings reasonable interpretations of the evidence?* no. patients that are candidates for immediate radical cystectomy vs. Synergo + MMC were not fully evaluated for QOL, death risk, and 10 year follow-up . intermediate-risk patients treated with Synergo vs. MMC failure that are up-risked were not evaluated properly.	Thank you for your comment. A cost comparison with radical cystectomy was included by the external assessment centre. This was presented to the committee as an additional exploratory analysis in an addendum to the main assessment report. Additional life years, avoidance of radical cystectomy and QALYs were reported for the lifetime horizon. This is described in section 3.17 And 4.10 of the guidance. The external assessment centre's assessment report conducted a comprehensive literature search identifying all relevant peer-reviewed published studies in line with the published scope. The clinical evidence includes people with intermediate risk non-muscle invasive bladder cancer that has failed intravesical treatment. The committee decided not to change the guidance in response to this comment.
20	1	Company	General	*Are the recommendations sound and a suitable basis for guidance to the NHS?* No. they do not offer a solution for: - patients that are BCG intolerant - BCG contra-indicated patients - BCG shortage - Patients that are contra-indicated to cystectomy - patients that refuse to be cystectomised	Thank you for your comment. The scope of the evaluation covered these patient subgroups. The committee acknowledged the limited treatment options for these patients in section 4.1 of the draft guidance. However, the committee did not believe that the current evidence supports the case for routine adoption in the NHS. The committee decided not to change the guidance in response to this comment.
21	1	Company	General	*Are there any equality issues that need special consideration and are not*	Thank you for your comment.

				covered in the medical technology consultation document? no	

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."

Appendix 1: Tissue and drug temperature dynamics during Synergo treatment (graph supplied by company) [academic in confidence]