National Institute for Health and Care Excellence

Bladder Cancer
Guideline Consultation Table
3rd September – 15th October 2014

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Abbott Molecular	1	NICE	13	1.2.3	Replace "FISH" with "UroVysion" or "UroVysion FISH". *Suggested wording:* 'Offer white-light-guided TURBT with photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker (**UroVysion FISH**, ImmunoCyt or NMP22) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.' OR 'Offer white-light-guided TURBT with photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker (**UroVysion**, ImmunoCyt or NMP22) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.' *Rationale:* • The other urinary biomarkers (ImmunoCyt and NMP22) are referred to using brand names; • FISH just refers to a technology (e.g. PCR) whereas UroVysion refers to a proprietary set of four specific FISH probes which comprise the UroVysion test;	We have made this change.

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						• FISH is spelled out as UroVysion in the other NICE draft documents specifically (e.g. line 7 of page 102 from draft evidence review); • All the evidence reviewed in the NICE guidelines on FISH relates to the UroVysion FISH test; • Most healthcare professionals using the test refer to the test as UroVysion rather than FISH. We would therefore like to suggest adding the brand name 'UroVysion' referring to the FISH test. Calling the test 'UroVysion FISH' or 'UroVysion' would provide some clarification as to what test to use and be consistent with the wording in the other draft guidelines documents.	
SH	Abbott Molecular	2	NICE	13	1.2.1	Break up sentence because it is unclear. *Suggested wording:* '**Urinary biomarkers may be offered and used in conjunction with cystoscopy**. **But** do not substitute cystoscopy **with urinary biomarkers to investigate suspected bladder cancer**, except in the context of a clinical research study.' *Rationale:* We suggest breaking up sentence in the draft guidelines as we found the sentence unclear and misleading. We agree with the statement related to not substituting urinary biomarkers for cystoscopy. For example, results from UroVysion are intended for use, in conjunction with and not in lieu of current standard	Our clinical question did not investigate the addition of urinary biomarkers to cystoscopy. As such the evidence has not been appraised in this area and we are not able to make any recommendations.

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						diagnostic procedures, as an aid for initial diagnosis of bladder carcinoma in patients with haematuria and subsequent monitoring for tumour recurrence in patients previously diagnosed with bladder cancer. The combined sensitivity of cystoscopy and UroVysion has been shown to be significantly more sensitive than cystoscopy alone. (1)	
SH	Abbott Molecular	3	NICE	13 -14	1.2.3	Replace "FISH" with "UroVysion" or "UroVysion FISH". *Suggested wording:* 'Offer white-light-guided TURBT with photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker (**UroVysion FISH**, ImmunoCyt or NMP22) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.' OR 'Offer white-light-guided TURBT with photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker (**UroVysion**, ImmunoCyt or NMP22) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.' *Rationale:* • The other urinary biomarkers (ImmunoCyt and NMP22) are referred to using brand names;	We have made this change.

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						• FISH just refers to a technology (e.g. PCR) whereas UroVysion refers to a proprietary set of four specific FISH probes which comprise the UroVysion test; • FISH is the other NICE draft documents specifically spelled out as UroVysion (e.g. line 7 of page 102 from draft evidence review); • All the evidence reviewed in the NICE guidelines on FISH relates to the UroVysion FISH test; • Most healthcare professionals using the test refer to the test as UroVysion rather than FISH. We would therefore like to suggest adding the brand name 'UroVysion' referring to the FISH test. Calling the test UroVysion FISH or UroVysion would provide some clarification as to what test to use and be consistent with the wording in the other draft guidelines documents.	
SH	Abbott Molecular	4	NICE	16	1.3.7	Suggest adding a bullet referring to the use of urinary tumour markers like UroVysion during BCG therapy for high-risk patients. *Suggested wording:* • 'Offer induction and maintenance intravesical BCG to people having treatment with intravesical BCG.' • **'As follow-up during BCG therapy, offer monitoring with UroVysion.'** *Rationale:* BCG therapy produces a highly inflammatory immune response that can make visual	The evidence reviewed resulted in the GDG making a 'do not use' recommendation for the use of urinary biomarkers in follow up of low-risk disease. The quality of the evidence was insufficient to support making any additional recommendations for clinical practice, but the GDG did make recommendations for research in this area on p109 of the full version of the guideline.

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						inspection of the bladder for tumour recurrence by cystoscopy difficult during BCG treatment. We would suggest adding information about urinary tumour markers in the BCG section because tests like UroVysion have demonstrated to be beneficial in the BCG setting and may provide increased sensitivity to detect recurrence. UroVysion is a genomic test, and DNA is not affected by BCG therapy unlike other diagnostic methods. UroVysion provides a Negative Predictive Value of 94.1% and a clinical sensitivity of 92.3% and therefore may add value to patient management at this time. (2) Therefore, we would suggest adding a bullet which speaks to the role of urinary biomarkers during patient monitoring. During BCG therapy patients can be monitored by UroVysion for risk of recurrence or progression of disease. UroVysion can be used for bladder screening in high-risk patients and adjunct to cystoscopy to detect invisible tumours for CIS (100% sensitivity in CIS) and tumours that are high grade. Cystoscopy in combination with UroVysion has been shown to be significantly more sensitive than cystoscopy alone. (1) Evidence to support this addition: • **Draft Evidence Review (page 829, box "Rationale"):** "Recurrence of a positive UroVysion test following intravesical BCG treatment has recently been shown to be associated with disease progression (Kamat et al, 2012).	

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						This marker holds the best prospect in diagnosis as well as follow-up of bladder tumours in conjunction with a high quality urine cytology service." • **Kamat et al., 2012 – Prospective study demonstrating that FISH (UroVysion) can identify patients at risk for tumour recurrence and progression during BCG immunotherapy** Kamat *et al.* found positive FISH results identified patients who were 3 to 5 times more likely to develop tumour recurrence as compared to patients with negative FISH results. The authors concluded results of FISH assays correlated with the risk of tumour recurrence. The earlier a FISH result converted to positive from a negative baseline, the higher the risk of recurrence and progression (a positive FISH result at 6 weeks indicated a 50% overall risk of recurrence and a 30% overall risk of disease progression). The authors' conclusions from this study were *"patients can be counselled with even greater accuracy based on individual history of FISH results"*. Finally, in patients who do not respond to BCG therapy, radical cystectomy can improve bladder cancer patient survival by 20% in patients when performed within 24 months after diagnosis. • In addition, multiple studies evaluated the use of FISH (UroVysion) in monitoring the response to intravesical therapies in	

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						patients with high-risk superficial bladder tumour (HRSBT). Each study (described below) concluded that a positive FISH test at the end of intravesical therapy was predictive of eventual relapse, with one study also showing higher chance of progression of disease: a. **Kipp et al. (2005)** studied US patients prospectively and concluded that patients with a positive FISH test at the end of treatment were at high risk for progression to muscle invasive bladder cancer (3) b. **Mengual et al. (2007)** studied Spanish patients prospectively and concluded FISH appeared to be useful for the surveillance of patients with HRSBT following BCG therapy. HRSBT patients could be monitored more carefully and treated more aggressively to prevent tumour relapse, progression and metastasis (4) c. **Whitson et al. (2009)** studied US patients retrospectively and concluded that in patients with high-risk superficial bladder tumours undergoing intravesical therapy, a positive UroVysion test after treatment is highly predictive of recurrence, even in a multivariate mode. (5)	
SH	Abbott Molecular	5	NICE	19	1.3.24	Suggest adding a bullet referring to the use of urinary tumour markers like UroVysion for monitoring for high risk bladder cancer patients as an adjunct to cystoscopy.	The evidence reviewed resulted in the GDG making a 'do not use' recommendation for the use of urinary biomarkers in follow up of low-risk disease. The quality of the evidence

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						Suggested wording: • **'Monitoring of patients with high risk disease (e.g. carcinoma in situ, CIS) with urinary tumour markers may be beneficial.'** UroVysion FISH can be used to monitor high risk bladder cancer patients as an adjunct to cystoscopy. For patients with risk of CIS, high sensitivity of UroVysion (100%) allows for patient monitoring where these lesions may not be visible through cystoscopy (UroVysion Package Insert).	was insufficient to support making any additional recommendations for clinical practice, but the GDG did make recommendations for research in this area on p109 of the full version of the guideline.
SH	Abbott Molecular	6	NICE FULL	13 7	1.2.3 11	Replace "FISH" with "UroVysion" or "UroVysion FISH". *Suggested wording:* 'Offer white-light-guided TURBT with photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker (**UroVysion FISH**, ImmunoCyt or NMP22) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.' OR 'Offer white-light-guided TURBT with photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker (**UroVysion**, ImmunoCyt or NMP22) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT.'	We have made this change.

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						Rationale: • The other urinary biomarkers (ImmunoCyt and NMP22) are referred to using brand names; • FISH just refers to a technology (e.g. PCR) whereas UroVysion refers to a proprietary set of four specific FISH probes which comprise the UroVysion test; • FISH is the other NICE draft documents specifically spelled out as UroVysion (e.g. line 7 of page 102 from draft evidence review); • All the evidence reviewed in the NICE guidelines on FISH relates to the UroVysion FISH test; • Most healthcare professionals using the test refer to the test as UroVysion rather than FISH. We would therefore like to suggest adding the brand name 'UroVysion' referring to the FISH test. Calling the test UroVysion FISH or UroVysion would provide some clarification as to what test to use and be consistent with the wording in the other draft guidelines documents.	
SH	Abbott Molecular	7	FULL	20	4	Break up sentence because it is unclear. *Suggested wording:* '**Urinary biomarkers may be offered and used in conjunction with cystoscopy**. **But** do not substitute cystoscopy **with urinary biomarkers to investigate suspected bladder cancer**, except in the context of a clinical research study.'	This is a footnote to one of the algorithms in the guideline. The algorithms have to reflect the wording used in the recommendations. Therefore we are not able to make this change.

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						Rationale: We suggest breaking up sentence in the draft guidelines as we found the sentence unclear and misleading. We agree with the statement related to not substituting urinary biomarkers for cystoscopy. For example, results from UroVysion are intended for use, in conjunction with and not in lieu of current standard diagnostic procedures, as an aid for initial diagnosis of bladder carcinoma in patients with haematuria and subsequent monitoring for tumour recurrence in patients previously diagnosed with bladder cancer. The combined sensitivity of cystoscopy and UroVysion has been shown to be significantly more sensitive than cystoscopy alone. (1)	
SH	Abbott Molecular	8	FULL	109	2	Suggest adding a bullet referring to the use of urinary tumour markers like UroVysion for monitoring for high risk bladder cancer patients as an adjunct to cystoscopy. *Suggested wording:* • **'Monitoring of patients with high risk disease (e.g. carcinoma in situ, CIS) with urinary tumour markers may be beneficial.'** UroVysion FISH can be used to monitor high risk bladder cancer patients as an adjunct to cystoscopy. For patients with risk of CIS, high sensitivity of UroVysion (100%) allows for patient monitoring where these lesions may not be visible through cystoscopy (UroVysion Package Insert).	We have made research recommendations on the use of urinary biomarkers markers to see if this can be confirmed.

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SH	Abbott Molecular	9	FULL	0General	0General	Replace "FISH" with "UroVysion" or "UroVysion FISH". *Rationale:* • The other urinary biomarkers (ImmunoCyt and NMP22) are referred to using brand names; • FISH just refers to a technology (e.g. PCR) whereas UroVysion refers to a proprietary set of four specific FISH probes which comprise the UroVysion test; • FISH is the other NICE draft documents specifically spelled out as UroVysion (e.g. line 7 of page 102 from draft evidence review); • All the evidence reviewed in the NICE guidelines on FISH relates to the UroVysion FISH test; • Most healthcare professionals using the test refer to the test as UroVysion rather than FISH. We would therefore like to suggest adding the brand name 'UroVysion' referring to the FISH test. Calling the test UroVysion FISH or UroVysion would provide some clarification as to what test to use and be consistent with the wording in the other draft guidelines documents.	We have made this change
SH	Abbott Molecular	10	zEVIDENCE REVIEW	106	35	Replace 'FISH' by 'UroVysion' since all the evidence reviewed on FISH pertains to the UroVysion FISH test. *Suggested wording:* 'For detection of CIS the median sensitivity across studies for both **UroVysion** and	This change has been made

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						ImmunoCyt was 100%.' Since the other urinary biomarkers (e.g. ImmunoCyt) are referred to using brand names and all the evidence reviewed in the NICE guidelines on FISH relates to the UroVysion FISH test, we would like to suggest adding the brand name 'UroVysion' referring to the FISH test.	
SH	Abbott Molecular	11	zEVIDENCE REVIEW	829	Box "Rationale"	*Correction of a typo:* 'Recurrence of a positive UroVysion test following intravesical BCG treatment has recently been shown to be associated with disease progression (**Kamat** et al, 2012). This marker holds the best prospect in diagnosis as well as follow up of bladder tumours in conjunction with a high quality urine cytology service.' *The reference is missing and needs to be added:* Kamat AM, Dickstein RJ, Messetti F, Anderson R, Pretzsch SM, Gonzalez GN et al. Use of fluorescence in situ hybridization to predict response to bacillus Calmette-Guerin therapy for bladder cancer: results of a prospective trial. J Urol 2012; 187(3):862-867	This is a background section giving the rationale for why the clinical question was investigated, rather than a summary of the evidence. Citations have been removed to make this rationale consistent with the others.
SH	Abbott Molecular	12	FULL	108	box "Quality of the evidence"	Current wording: 'There is also uncertainty about the value of adding biomarkers to cystoscopic follow-up in patients with high risk bladder cancer who have been treated with BCG.' The value of adding UroVysion to	Our clinical question did not investigate the addition of urinary biomarkers to cystoscopy. As such the evidence has not been appraised in this area and we are not able to make any recommendations.

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						cystoscopic follow-up in patients that are treated with BCG was investigated and evaluated by Kamat et al. 2012. (2) We suggest to include it into the evaluation: Kamat et al. found positive UroVysion results identified patients who were 3 to 5 times more likely to develop tumour recurrence and 5-13 times more likely to experience disease progression as compared to patients with negative UroVysion results. The authors concluded results of the UroVysion assays correlated with the risk of tumour recurrence or progression. The earlier a UroVysion result converted to positive from a negative baseline, the higher the risk of recurrence and progression (a positive UroVysion result at 6 weeks indicated a 50% overall risk of recurrence and a 30% overall risk of disease progression). The authors' conclusions from this study were *"patients can be counseled with even greater accuracy based on their individual history of FISH results"*. This is of clinical relevance since for patients who do not respond to BCG therapy, radical cystectomy can improve bladder cancer patient survival by 20% when performed within 24 months after diagnosis.	
SH	Abbott Molecular	13	FULL	0General	0General	References 1 Halling KC et al. J Urol. 2000; 164: 1768-1775 2 Kamat AM, Dickstein RJ, Messetti F, Anderson R, Pretzsch SM, Gonzalez GN et al. Use of fluorescence in situ hybridization to predict response to bacillus Calmette-Guerin	Thank you for providing these references to support statements made in your previous comments. We have responded to these comments individually.

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						therapy for bladder cancer: results of a prospective trial. J Urol 2012; 187(3):862-867. 3 Kipp BR, Karnes RJ, Brankley SM, Harwood AR, Pankratz VS, Sebo TJ et al. Monitoring intravesical therapy for superficial bladder cancer using fluorescence in situ hybridization. J Urol 2005;(173):401. 4 Mengual L, Marin-Aguilera M, Ribal MJ, Burset M, Villavicencio H, Oliver A et al. Clinical utility of fluorescent in situ hybridization for the surveillance of bladder cancer patients treated with bacillus Calmette-Guerin therapy. Eur Urol 2007; 52(3):752-759. 5 Whitson J, Berry A, Carroll P, Konety B. A multicolour fluorescence in situ hybridization test predicts recurrence in patients with high-risk superficial bladder tumors undergoing intravesical therapy. BJU Int 2009;(104):336.	
SH	Action On Bladder Cancer (ABC) Charity	1	NICE	11	1.1.1 - 1.1.9	The emphasis on the role of the clinical nurse specialist is welcomed. In most trusts the CNS coordinates the management of bladder cancer. The guidance puts further pressure on the CNS to deliver this care. Financial support would need to be ear marked to underpin the delivery of the CNS lead service.	We agree, but this will be a matter for implementation of the guideline
SH	Action On Bladder Cancer (ABC) Charity	2	NICE	11	Table	The WHO performance status table does not include WHO PS 0 or 5 and uses the definition for 0 under 1.	This table has been removed from the guideline.
SH	Action On Bladder Cancer (ABC) Charity	3	NICE	13	1.2.3	The enthusiasm for PDD, NBI, urinary biomarkers and cytology will be welcomed by many clinicians. The economic and clinical efficacy of these tests are still undergoing evaluation however, e.g. the forthcoming PHOTO trial.	Thank you.

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SH	Action On Bladder Cancer (ABC) Charity	4	NICE	14	1.2.7	The statement to offer patient intravesical mitomycin-c at the time of TURBT is welcomed by the ABC. The implementation of this recommendation may be difficult as pharmacy guidelines and ordering of the agent often preclude the drug being offered in theatre or recovery.	Thank you. This recommendation was heavily supported by the GDG, clinical experience and the cost effectiveness analysis. In addition the cost of delivering a single instillation in theatre was compared against the cost of later delivery by a nurse on the ward. Delivering it in theatre was found to be the cheaper of the two options (£23.83 cheaper). This was primarily a result of the shorter time taken by the urologist to deliver the drug in theatre. The GDG considered instillation at the time of TURBT to be more convenient for clinicians and patients. It also ensures that patients receive the full benefit of this time-dependent treatment. The GDG considered the main benefit of giving a single instillation of MMC to be a reduced risk of recurrence. Giving MMC in theatre should improve access to the treatment and be more convenient for patients. We hope that these points will be taken into consideration when implementing the recommendation, to help overcome any potential barriers.
SH	Action On Bladder Cancer (ABC) Charity	5	NICE	13 & 14	1.2.2 & 1.2.12 4 (under Diagnosin	"Consider CT or MRI staging before.." The MRI and CT imaging modalities should be used for the staging of muscle invasive and high-risk non-muscle invasive bladder tumours. This recommendation is strongly supported. There is evidence to show that MRI is superior	Thank you.

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					g and staging bladder cancer: 1.2.2 & 1.2.12)	to CT in evaluating the T stage of bladder cancer and that should be clarified in the guidance. Whilst the modality will probably be determined by availability within different Trusts.	Due to the lack of high quality evidence, the GDG could not recommend one type of imaging (CT or MRI) over the other. This was documents in the Linking Evidence to Recommendations section in the full version of the guideline.
SH	Action On Bladder Cancer (ABC) Charity	6	NICE	14	1.2.11	ABC feel strongly that a CT thorax should be mandated for patients undergoing radical treatment, palliative chemotherapy or palliative radiotherapy and that the recommendation within the guidance should be changed to 'offer'.	The use of the word 'consider' reflects the strength of the evidence (please see page 6 of the NICE version for further information on the wording of NICE recommendations).
SH	Action On Bladder Cancer (ABC) Charity	7	NICE	14	0General	The current recommendations for staging investigations should include a bone scan in all patients with clinical features, including a raised plasma ALP level, consistent with possible bony metastatic involvement who would otherwise be considered for radical therapy.	No recommendation was made on detecting bone metastases because there was insufficient high quality evidence on techniques looking primarily at bone metastases, and because the GDG felt that the other recommendations made for CT and MRI would likely pick up those people with bone metastases in any event. This was documented in the Linking Evidence to Recommendations section in the full version of the guideline. We would expect that in patients with symptoms, appropriate imaging will be performed, which may include a bone scan.
SH	Action On Bladder Cancer (ABC) Charity	8	NICE	14	1.2.6	Consider using a bladder map to record location, size and number of tumours as this can help with further management e.g. pathological evaluation, re-resection and follow up.	We would consider recording of intraoperative observations to be a routine part of good clinical practice, and therefore have not made a recommendation on this.
SH	Action On Bladder Cancer (ABC) Charity	9	NICE	14	1.2.8	Consideration of further TURBT at 6 weeks should be clarified to apply to patients with; 1] high risk non-muscle invasive bladder cancer	This comment relates to 3 recommendations (1.2.4 Obtain detrusor muscle during TURBT; 1.2.8 Consider further TURBT within 6 weeks if the first specimen does not include detrusor

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						2] likely incomplete resection eg large tumours, mutifocal tumours (especially if intravesical therapy is being considered) 3] imaging and pathological evaluation that do not correlate. It would generally be considered unnecessary to perform re-resection for low risk disease. Recommendation 1.3.5 does emphasise high risk cases only – the guidelines should ensure consistency throughout.	muscle; 1.3.5 If the first TURBT shows high-risk non-muscle-invasive bladder cancer, offer another TURBT as soon as possible and no later than 6 weeks after the first resection). The aim of these recommendations is to promote a high quality TURBT at the first procedure, to ensure high-quality staging, by repeating the procedure if there is no detrusor muscle, and to ensure high-quality management of people with high-risk disease. The wording of recommendation 1.2.8 allows the MDT to decide if the repeat TURBT to obtain detrusor muscle is appropriate for the individual patient with low or intermediate risk. Whereas recommendation 1.3.5 requires that the TURBT be repeated if high-risk disease is found.
SH	Action On Bladder Cancer (ABC) Charity	10	NICE	14	1.2.12	PET CT is not widely utilised for bladder cancer although some centres do so in selected cases. This recommendation places a high resource demand on centres and funding may remain a limiting factor. We would suggest that alongside a guideline this should be supported as a research priority especially for the role of PET scanning in image defined locally advanced disease. The role of imaging within bladder cancer (including the use of PET scanning) should form part of a research recommendation.	The GDG did not think that the use of PET-CT was a priority area for further research. Finding resources to enable this recommendation to be carried out will be a matter for local implementation.
SH	Action On Bladder Cancer (ABC) Charity	11	NICE	15	TABLE	The risk categories table is useful. However the table is based on the WHO 1973 grading. Many MDT's are moving to the WHO 2004 system. It should be commented that the 2004 grading system may be used and will move	We disagree. It was the consensus of the GDG that the 1973 grading system, or a hybrid of that and the 2004 system, are more commonly used and therefore the risk definitions were based on this. We have

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						some tumours from intermediate to high risk categories (eg TaG2 high grade)	added brackets to the definitions to try to make them clearer.
SH	Action On Bladder Cancer (ABC) Charity	12	NICE	15	1.3.1	The proposed allocation of a risk category within the details to be recorded is useful.	Thank you
SH	Action On Bladder Cancer (ABC) Charity	13	NICE	16 and 17	1.3.4 and 1.3.8	Both of these points suggest referral to a bladder cancer specialist multidisciplinary team if a patient relapses after intravesical therapies. ABC feels that all potentially curative treatment decisions should be made in this context (i.e. widen this to other aspects within the guidelines that are radical in intent.)	The requirement for all radical treatments to be discussed at the specialist MDT is already covered by the Improving Outcomes in Urological Cancers guidance.
SH	Action On Bladder Cancer (ABC) Charity	14	NICE	16 and 17	1.3.6 and 1.3.8	We would support the recommendation that a urologist who performs BCG and cystectomy should discuss management in these circumstances. We would suggest that it is recommended that all intermediate and high-risk disease be discussed at specialist MDT and that treatment should be managed by a urologist with special interest in bladder cancer.	The recommendations we have made for people with intermediate risk disease can all be performed by local MDTs and therefore it is unnecessary for a referral to the specialist urology MDT, unless the person develops recurrence. Involvement with the specialist urology MDT for people with high-risk disease is part of the Improving Outcomes in Urology guidance and associated peer review measures. We have therefore not specified this in the recommendations as it would be expected to happen.
SH	Action On Bladder Cancer (ABC) Charity	15	NICE	18	1.3.10 to 1.3.12	The group felt that the guidelines have not gone far enough to address quality issue in radical bladder cancer surgery: 1. Although practice is fairly consistent in the UK ABC felt a description of an acceptable standard operation could be made in men and women undergoing radical cystectomy in	NICE guidelines focus on areas of uncertainty and variation in clinical practice. Consequently the issues you have raised were not prioritised for inclusion in the guideline. However, recommendation 1.3.6 does cover discussion of issues around impact on quality of life, body image and sexual and urinary

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						terms of its extent. 2. No mention is made of who should or should not be a candidate for neobladder 3. No mention is made of how to manage the bladder neck/prostate prior to neobladder 4. No mention is made of the role of urethrectomy 5. No mention is made about counselling after cystectomy for ED/sexual dysfunction in both men and women 6. No mention is made regarding lymph node dissection and its extent	function related to treatment. In addition recommendations 1.1.4 refers to holistic needs assessment which should be carried out after first treatment; and recommendation 1.1.5 covers discussing the impact of treatment on sexual health and body image. Recommendation 1.1.7 offers people opportunities to discuss care with healthcare professionals including those who can provide psychological support.
SH	Action On Bladder Cancer (ABC) Charity	16	NICE	18	1.3.13	ABC agrees that a less aggressive approach may be appropriate for some types of NMIBC. The figure of 3 mm is less than widely used in the literature and we would be happy for low risk NMIBC to be managed conservatively up to 5 mm. We would like to see a recommendation that active surveillance and management using local anaesthetic cystoscopic surveillance be considered in patient with low risk NMIBC and comorbidity.	The GDG used clinical experience to make a conservative recommendation about the criteria for fulguration without biopsy. The criteria were more conservative than those reported in the evidence because the GDG could not be confident in the low quality evidence presented. This was documented in the Linking Evidence to Recommendations section in the full version of the guideline. We have made recommendations (1.4.1 – 1.4.6) that cover follow-up of patients with low-risk NMIBC.
SH	Action On Bladder Cancer (ABC) Charity	17	NICE	19	1.3.20	The recommendation regarding discharge of low risk cases at 12 months is of interest. This will reduce the burden of follow up cystoscopy to patients and the health service and for this	The potential benefits of the recommendation for patients with low risk disease result from the reduced burden of cystoscopic follow-up. The GDG balanced this against the potential

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						reason would be welcome. However, it is a bold change in practice that is not currently in any national or international guidance. In general, not many patients would be expected to come to harm if it is adopted. However, it is likely that some of the inevitable recurrent disease will be of larger volume or multifocal and potentially more difficult to resect if we wait for haematuria before offering cystoscopy. More rarely patients can develop grade progression from low to high risk. We are interested in this change but would propose that it is a research question currently and that the strength of the recommendation should be altered to 'consider' at most. We would not view the current level of available evidence to be acceptable to proscribe longer or more intensive follow up by specialist MDTs/urologists.	for harm resulting from a possible small increase in the late detection of disease recurrence and that patients may experience anxiety after discharge from follow-up. The GDG considered that reducing the burden of follow-up (which is associated with anxiety and discomfort of cystoscopy) in this low-risk group strongly outweighs the possible increase in late detection of recurrence. Reduced frequency follow-up was shown to be the most cost-effective strategy in low risk patients. It was substantially cheaper and the strategy was found to be cost-effective. Moreover, significant opportunity costs were identified specifically the opportunity to focus scarce cystoscopy resource on people at higher risk who have the greatest benefit. Given the evidence to support making this recommendation we do not consider that a research recommendation was warranted.
SH	Action On Bladder Cancer (ABC) Charity	18	NICE	20 (and page 10)	1.4.2	Neoadjuvant chemotherapy in non-TCC bladder cancer has virtually no evidence. Non-TCC bladder cancer should not receive neoadjuvant chemotherapy.	We agree. Recommendation 1.5.2 only refers to urothelial bladder cancer.
SH	Action On Bladder Cancer (ABC) Charity	19	NICE	20	1.4.3	For muscle invasive TCC a choice of cystectomy or chemoradiotherapy is appropriate advice. However, chemoradiotherapy for other histological types has little data to determine if it is effective. For example in the BC2001 trial 97.8% had TCC and sub-group analyses were not presented for SCC or adenocarcinoma which were also permitted. We would propose, at least, caution	We have amended recommendation 1.5.3 to clarify that it only relates to urothelial bladder cancer.

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						and specialist MDT opinion in utilising chemoradiotherapy in pure SCC or adenocarcinoma. Other histological subtypes should not receive it and require specialist MDT review.	
SH	Action On Bladder Cancer (ABC) Charity	20	NICE	21	1.4.5	The level of evidence for adjuvant chemotherapy is significantly less strong than for neoadjuvant chemotherapy. The latter should be the expected normal approach therefore. This recommendation needs to have a strong and unambiguous statement that the standard approach to peri-operative chemotherapy should be to offer it in the neoadjuvant setting.	We agree that the evidence for neoadjuvant chemotherapy is stronger than that for adjuvant chemotherapy. Therefore neoadjuvant chemotherapy should be the standard of care - as reflected by the term 'offer' in recommendation 1.5.2. Please see page 6 of the NICE version for further information on the wording of NICE recommendations. Recommendation 1.5.7 is directed to those people who have had cystectomy for NMIBC and were found to have unsuspected muscle invasion or lymph node spread or people who at the time of surgery had inadequate renal function to receive cisplatin. The GDG debated the wording of recommendation 1.5.3 and 1.5.7 in the light of your comments, and are content that this wording reflects the evidence.
SH	Action On Bladder Cancer (ABC) Charity	21	NICE	21	1.4.5	As with our point above for neoadjuvant chemotherapy we feel that adjuvant chemotherapy for non-TCC muscle invasive (T2-4a N0) bladder cancer should be avoided. There may be a case for treatment in selected node positive cases or those with positive surgical margins after specialist MDT review and acknowledging the lack of evidence in this setting.	We have amended recommendation 1.5.7 to clarify that it only relates to urothelial bladder cancer.
SH	Action On Bladder	22	NICE	21	1.4.6	Trial data indicates encouraging results from	We disagree. The GDG felt that the benefit of

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	Cancer (ABC) Charity					the use of radiosensitisers with radical radiotherapy eg BCON study. However, this is not yet widely practised and it is considered that there is sufficient evidence to make such a strong recommendation for a change in practice.	radiosensitisation (either chemotherapy or Carbogen/Nicotinamide) was clearly demonstrated by the evidence. There was evidence to support both treatment approaches, but it was unclear as to which was superior and therefore both have been recommended as treatment options.
SH	Action On Bladder Cancer (ABC) Charity	23	NICE	22	1.4.9 1.4.10	Use of upper tract imaging every year for five years/annually should be clarified. We presume with ultrasound but this should be defined. CT urogram may also be indicated to check for synchronous upper tract TCC.	There are a number of imaging modalities that could be used to monitor the upper tract including ultrasound, nuclear medicine and CT. No evidence was found to support the use of one modality over another. In addition, CT is already recommended for monitoring of local and distant recurrence and may be used to image the upper tracts. The choice of modality, which could include CT urogram, would also depend on individual patient factors. Therefore the GDG did not specify a modality in the recommendation.
SH	Action On Bladder Cancer (ABC) Charity	24	NICE	22	1.4.9 1.4.10	Some attempt should be made by the guidance to offer a recommendation as to how long patients should be followed up in secondary care and for how long follow-up should progress in primary care. The importance of this is that the follow-up will have cost implications to primary care	The GDG did not feel there was sufficient evidence to guide recommendations on the duration of a follow-up protocol.
SH	Action On Bladder Cancer (ABC) Charity	25	NICE	23	1.5.2	This section suggests cisplatin based chemotherapy should only be given to those with a GFR over 60 mL/min. Oncologists in the UK would commonly give cisplatin with lower GFR levels than this (certainly down to 50 in selected cases). There is no consensus on an appropriate cut point The key focus of this point should be that patients should be offered a cisplatin based combination regimen if they are fit enough to	The GFR level of 60ml/min was taken from the studies in the evidence used to inform this recommendation. Recommendations in NICE guidelines do not substitute for good clinical decision making. However, to acknowledge your point we have added an additional qualifier to this recommendation to allow some flexibility.

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						receive it.	
SH	Action On Bladder Cancer (ABC) Charity	26	NICE	23	1.5.3	We would recommend removing the list of criteria given for use of carboplatin/gemcitabine. In its place we would propose suggesting this is an appropriate treatment to offer when patients are felt to be unsuitable for cisplatin based chemotherapy based on a holistic assessment by a specialist oncologist that should include consideration of renal function, performance status and co-morbidities.	NICE guidelines are not intended to replace clinical judgement. Evidence was available that showed a potential beneficial effect to people with these specific criteria. Hence the GDG included them in their recommendation. The harms may outweigh the benefits in certain people (for example, those with a higher WHO performance status) but this should be established as part of the holistic needs assessment.
SH	Action On Bladder Cancer (ABC) Charity	27	NICE	25	1.5.7 and 1.5.8	The ABC members felt that the chemo. regimens are far too prescriptive and do not reflect the data, expert clinical opinion or routine practice in the UK. No regimen has shown a survival advantage in a randomised clinical trial in the second line setting and cross trial comparisons of the available data, which are of very variable quality and with wide variations in patient type, is fundamentally flawed.	The evidence base for second line chemotherapy has been extensively reviewed by the GDG. Recommendation 1.7.6 recommends the use of those schedules with the strongest available evidence. However the quality of this evidence is reflected by the use of the term 'consider' in the recommendation. Please see page 6 of the NICE version for further information on the wording of NICE recommendations. The evidence on single agent paclitaxel was too weak to support making a recommendation. However in light of feedback received from stakeholders the GDG have deleted the recommendation on single-agent chemotherapy for second line.
SH	Action On Bladder Cancer (ABC) Charity	28	NICE	26	1.5.15	There is limited evidence for the efficacy of embolisation for intractable bleeding. Some case series indicate sporadic benefit. In general we would suggest that radiotherapy is preferred as a first line approach. Embolisation, chemotherapy, surgery or BSC	We agree that the evidence base for the treatment of intractable bleeding is weak and insufficient to recommend one treatment over another. This is why we have used the word 'consider' in recommendation 1.7.15 and made recommendation 1.7.16.

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						should all be considered in selected cases as a subsequent intervention. Such cases require specialist MDT review to facilitate an individualised approach to patient care.	We included recommendation 1.7.14 that the cause of intractable bleeding should be evaluated with the local urology team as the GDG were concerned that not all patients with intractable bleeding are currently discussed with a urology team or fully evaluated.
SH	Action On Bladder Cancer (ABC) Charity	29	NICE	27	1.5.17	We suggest and support involvement of both the urology and oncology teams.	We believe that the responsibility for the evaluation should lie with the local urology team. However they may call on oncology or palliative care to provide best supportive care (as detailed in recommendation 1.7.18).
SH	Action On Bladder Cancer (ABC) Charity	30	FULL &NICE	0General	0General	Throughout both documents we would like to see strong recommendations in each clinical setting that all patients should be offered access to a clinical trial if available as a standard approach to discussing options for management.	We are not able to make this recommendation as the guideline did not look at a review question on this issue. However we have added text to the background in chapter 2 of the full guideline to stress the importance of offering people the opportunity to participate in clinical trials and research. Unfortunately we are not able to include the same text in the NICE version because this only contains the recommendations and does not include background text.
SH	Action On Bladder Cancer (ABC) Charity	31	FULL &NICE	0General	0General	The draft guidelines mention involvement or referral to a 'bladder cancer specialist' and a bladder cancer specialist multidisciplinary team. It would be helpful to have this clarified throughout. Does it mean simply discussion at an MDT or should they actually fall under the care of a specialist bladder cancer urologist or oncologist? ABC take the view that this should be the recommendation and proposed standard of care.	We have carefully considered, for each recommendation, the appropriate level of MDT discussion or referral according to the risk of recurrence, progression or death. We have standardised the wording of the recommendations to reflect this. Several of our recommendations focus on when people should be referred from their local urology MDT to their specialist urology MDT. However, most people with bladder cancer will not have muscle invasive bladder

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							cancer or high-risk non-muscle invasive bladder cancer and therefore will be most appropriately managed by their local MDT.
SH	Action On Bladder Cancer (ABC) Charity	32	FULL &NICE	0General	0General	Although the document refers to 'bladder cancer' many of the measures are specific to transitional cell carcinoma of the bladder. ABC would encourage the addition of a section specifically addressing the issues surrounding the management of squamous cell cancer, adenocarcinoma and small cell cancer.	The scope of the guideline included people with urothelial carcinoma, adenocarcinoma, squamous-cell carcinoma and small-cell carcinoma. The evidence searches looked for evidence relating to all of these types of bladder cancer but there was insufficient evidence to enable recommendations to be made for the management of adenocarcinoma, squamous-cell carcinoma and small-cell carcinoma. We have added text to the NICE introduction to clarify this. We have also amended recommendation 1.5.1 to specifically mention these rarer types of bladder cancer, to ensure they are reviewed by the specialist urology MDT. This should help to ensure they are managed appropriately.
SH	Action On Bladder Cancer (ABC) Charity	33	FULL &NICE	0General	0General	The ABC group are concerned that no mention has been given to the device assisted therapy. Given the evidence available on regimens such as the Di Stasi regimen (Lancet Oncol. 2011 Sep;12(9):871-9) we are surprised that these have not been covered in more detail and recommendations offered.	The priority for the GDG in assessing the evidence was to evaluate whether any intravesical treatment was effective in reducing risk of recurrence and progression. When forming the clinical question the GDG did not prioritise the comparison of modes of delivery of intravesical treatment. Consequently the evidence on device assisted therapy has not been appraised and we are not able to make any recommendations on this specific matter.
SH	Action On Bladder Cancer (ABC) Charity	34	FULL &NICE	0General	0General	The ABC group feel that the difference in outcome based on gender is of significant concern and should represent a high priority research question.	This important point was highlighted by the needs assessment. However we did not have a clinical question to look at the reasons for this and so the evidence has not been

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							examined. Consequently we are not able to make recommendations for research in this area.
SH	Alliance Pharmaceuticals	1	NICE FULL	14 189	1.2.7, 1.3.3 – 1.3.4, 1.3.7 23	Our comments are as follows; the draft guidance differs from the British Association of Urological Surgeons (BAUS) and the European Association of Urology (EAU) in terms of the recommendation for adjuvant intravesical chemotherapy or Bacille Calmette-Guérin (BCG) for patients with **intermediate-risk** non-muscle invasive bladder cancer (NMIBC). However, in terms of treatment recommendations for patients with high-risk NMIBC the NICE draft guidelines are consistent with those developed by EAU and BAUS. BAUS The BAUS guideline on bladder cancer recommends the following for intermediate-risk NMIBC: "Consider further intravesical chemotherapy (maximum 1 year) or BCG + maintenance (1–3 years)". In addition the guideline refers to the superior efficacy of BCG over mitomycin C (MMC) which is not adequately covered in the draft NICE guideline. EAU Current EAU guidelines recommend "either a maximum of 1 year of intravesical chemotherapy or a minimum of 1 year of intravesical BCG". NICE It is not clear what the draft NICE guidance is	The process for developing NICE guidelines is different to that used by BAUS and EAU. Consequently, recommendations made may be different. The evidence used in this guideline has been appraised according to NICE process and methodology. For people with intermediate risk NMIBC (recommendation 1.3.3) we recommend a course of mitomycin. If recurrence occurs

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						recommending and seems to recommend MMC over BCG: "Offer people with newly diagnosed intermediate-risk NMIBC a course of at least 6 doses of MMC. If NMIBC returns after this course refer to bladder cancer specialist multi-disciplinary team. Offer induction and maintenance BCG to people having treatment with BCG". This is not consistent with either BAUS or EAU guidance as detailed above. If the intention is to recommend MMC over BCG then we would like to highlight the inconsistency compared to the BAUS and EAU guidelines, and would request that the GDG review this section and all of the data used to support the BAUS and EAU recommendations.	after this the disease is then re-classified as high-risk NMIBC for which the options of BCG or cystectomy are recommended (recommendation 1.3.6). Recommendation 1.3.7 refers to how BCG is used rather than for whom. Following review of the evidence and discussion of the benefits and risks of different treatments, the GDG agreed it was appropriate to give mitomycin to the intermediate risk group because there is uncertainty over the extent of how much better BGC is over mitomycin C, but there is consistent evidence that BCG has significantly more side effects. We have added text to the Linking Evidence to Recommendations section to clarify this.
SH	Aspire Pharma Ltd	1	zEVIDENCE REVIEW	447 847	24- Table 2 - table	iAluRil (intravesical sodium hyaluronate [800mg/50ml] and sodium chondroitin sulphate[1g/50ml], available as a pre-filled syringe) should be considered as treatment for the irritative urinary symptoms caused by radiation and/ or BCG therapy. Please see point three for a further discussion of this point.	Sodium hyaluronate + sodium chondroitin sulphate was not investigated in this clinical question. Consequently the evidence on it has not been appraised and cannot be included in the evidence review. The evidence search conducted on hyaluronic acid and its use in managing BCG or radiation induced toxicity, identified only 1 case series of very low quality. On the basis of this low quality evidence, no recommendations have been made for intravesical treatment of these side effects.
SH	Aspire Pharma Ltd	2	FULL	229	5	Absence of sodium hyaluronate + sodium chondroitin sulphate as a possible treatment option. Please see point three for a further discussion of this point.	When forming the clinical question the GDG did not prioritise inclusion of sodium hyaluronate + sodium chondroitin sulphate as an intervention. Consequently the evidence on this has not been appraised and we are

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							not able to make any recommendations on its use.
SH	Aspire Pharma Ltd	3	zEVIDENCE REVIEW	846	4 (within the table)	*'New treatments such as intravesical sodium hyaluronate (Cystistat®) and Elmiron are emerging which claim to alleviate Irritative urinary symptoms and improve bladder capacity. The manufacturers suggest either instilling cystistat into the bladder following each BCG treatment to prevent long term side effects of BCG, as treatment of irritative urinary symptoms following BCG or radiotherapy. Although having been used effectively for some time for the treatment of recurrent bacterial cystitis and interstitial cystitis, as yet there is a lack of research to demonstrate their effectiveness for side effects of radiotherapy or intravesical BCG therapies'* Intravesical sodium hyaluronate + sodium chondroitin sulphate (iAluRil) has been shown to be effective for the treatment of recurrent bacterial cystitis and interstitial cystitis.[1,2,3] There is also evidence to support the use of iAluRil in the treatment of cystitis and nocturia caused by BCG treatment.[4-8] In a study by Creta et al (2012), the effect of iAluRil was assessed in patients who had cystitis as a result of treatment with BCG. The initial study was in 15 patients and showed a significant improvement in mean VAS (Visual analogue scale) pain, VAS urgency and number of voids/ 24 hours after the initial 8 week treatment and at 6 month follow-up.[4]	Sodium hyaluronate + sodium chondroitin sulphate was not investigated in this clinical question. Consequently the evidence on it has not been appraised and cannot be included in the evidence review. The evidence search conducted on hyaluronic acid and its use in managing BCG or radiation induced toxicity, identified only 1 case series of very low quality. On the basis of this low quality evidence, no recommendations have been made for intravesical treatment of these side effects.

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						In a follow up study by Imperatore, Creta et al (2014), the effect of iAluRil was assessed after 8 weeks, 6 months and 1 year in 20 patients. Significant improvements ($p<0.05$) in mean VAS pain, urgency and number of voids/ 24 hours were seen at 8 weeks, 6 and 12 months. In particular mean VAS pain decreased from an initial score of 7.2 to 4.2 after 8 weeks treatment, which was maintained at 1 year follow-up.[5] A pilot study in 15 patients by Li Marzi et al compared treatment with BCG therapy only and treatment with BCG plus iAluRil. There was a significant improvement in VAS pain and International Prostate Symptom Score (IPSS) when iAluRil was co-administered with BCG therapy. The authors concluded that these results were comparable to other publications for hyaluronic acid only (cystistat)[6] Seretta et al investigated the correlation between the expressions of Fibronectin (FN), Epidermal Growth Factor-Receptor (EGF-R) and Heparin-binding Epidermal Growth Factor-like (HB-EGF) in 55 patients undergoing prophylactic treatment of mitamycin, epirubicin or BCG and local bladder toxicity. They found that the FN gene was overexpressed in the presence of local toxicity and reduced with administration of hyaluronic acid and chondroitin sulfate solution with simultaneous symptomatic relief.[7] A pilot study investigated the effect of iAluRil on 23 patients who had been treated with radiotherapy for prostate cancer and were	

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						suffering with bladder pain syndrome (BPS) and nocturia. Mean scores for symptom and bother for nocturia significantly decreased after a course of iAluRil.[8] We believe that iAluRil should be included underneath the evidence for hyaluronic acid as a possible treatment option, with the evidence as discussed above included, to show that Sodium hyaluronate + sodium chondroitin (iAluRil) should be considered as a treatment for urinary tract infection (UTI), recurrent UTI and nocturia caused by the radiation and/or BCG therapy for bladder cancer. **References** 1. Cervigni M, Natale F, Nasta L et al. A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis. Int. Urogynecol J. 19, 943-947 (2008). 2. Damiano R, Quarto G, Bava I et al. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. Eur. Urol. 59(4), 645-651 (2011). 3. Torella M, Schettino MT, Salvatore S et al. Intravesical therapy in recurrent cystitis: a multi-center experience. J. Infect. Chemother. 19(5), 920-925 (2013). 4. Creta M, Di Meo S, Buonopane R,	

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						Imperatore V. Intravesical instillation of hyaluronic acid and chondroitin sulphate for *Bacillius Calmette-Guerin* induced chemical cystitis. 85th Italian Society of Urology (SIU) Congress, Venice, Italy, 21-24 October 2012. (www.siu.it/contents/view/223 - 2nd link) 5. Imperatore V, Creta M, Di Meo S et al. Intravesical instillation of sodium hyaluronate-chondroitin sulfate in patients with Bacillus Calmette-Guerin-induced chemical cystitis unresponsive to conventional therapies: Preliminary experience with 1 year follow-up. Eur Urol Suppl 13; e466 (2014) 6. Li Marzi. V, Del Popolo G., Maurelli V et al. Intravesical administration of hyaluronic acid plus chondroitin sulphate to reduce local bacillus calmette Guerin (BCG) toxicity: A randomized prospective pilot study. ICS 2013, 26-30 August 2013 Barcelona, Spain 7. Seretta V, Alomnge V, Carita G et al. Fibronectin (FN), epidermal growth factor-receptor (EGF-R) and heparin-binding epidermal growth factor-like (HB-EGF) urinary expressions and topical toxicity of adjuvant intravesical therapy for non-muscle invasive bladder cancer (NMI-BC) Eur Urol Suppl;13;e409 (2014) 8. Giannessi C., Villari D., Saleh O. et al. Nocturia related to post radiation bladder pain can be improved by hyaluronic acid chondroitin sulfate	

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						(ialuril). Eur Urol Suppl. 13;e592 (2014)	
SH	Association for Palliative Medicine of Great Britain & Ireland	1	FULL	0General	0General	We welcome the recognition of need for specialist palliative care in these patients	Thank you
SH	Association for Palliative Medicine of Great Britain & Ireland	2	NICE FULL	 69	1.6.4 7	We agree that the patient's primary health care team should be informed in a timely fashion of the diagnosis of incurable bladder cancer. Most palliative care is delivered by primary health care teams. Not all patients with incurable bladder cancer will need referral to specialist palliative care services. Referral should be needs-based rather than diagnosis- or prognosis-based. Specialist palliative care services work with patients with complex needs when the usual medical team is struggling. Perhaps patients should be alerted to the existence of specialist palliative care teams in case their symptoms become complex, but it would be unworkable and unnecessary for all patients with incurable bladder cancer to be seen by specialist palliative care teams (and, if this were offered to patients with bladder cancer it would have to be offered to all patients with cancer). "Access to the specialist palliative care team" means ensuring that there is a local service available for patients rather than referring all patients to the service. It needs to be ensured that all areas have a properly commissioned service that is able to respond as needed.	Thank you. We agree and have clarified in the recommendation that the referral should happen when needed. We recognise the specialist skills that specialist palliative care services have, that are not found in usual medical/surgical teams. This is why we consider it is important to discuss their role with people with incurable bladder cancer. We agree that not all people with incurable bladder cancer will need the services of the specialist palliative care team. We agree, but this is a service implementation issue and cannot be dealt with in the guideline.

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						We agree that patient consent should be acquired before making a palliative care referral.	Thank you.
SH	Association for Palliative Medicine of Great Britain & Ireland	3	FULL	318	16 &17	It is possible for patients to be simultaneously receiving disease modifying treatment (such as chemotherapy) and seeing a specialist palliative care team. As said before, referral should be done on the basis of need rather than by diagnosis or stage in a patient's illness. This section reads as though specialist palliative care and chemo / radiotherapy are mutually exclusive when they often happen simultaneously.	Thank you. We have added text to the start of chapter 6 of the full guideline to stress the importance of specialist palliative care.
SH	Association for Palliative Medicine of Great Britain & Ireland	4	FULL	379	2	Perhaps some mention should be made in this section to consideration of specialist palliative care teams / symptomatic treatment other than chemo / radiotherapy	Thank you. We have added text to the start of chapter 6 of the full guideline to stress the importance of specialist palliative care. Section 6.2 focuses on managing symptoms which are specific to locally advanced and metastatic bladder cancer. Section 2.3 covers more general issues related to palliative care.
SH	Association for Palliative Medicine of Great Britain & Ireland	5	NICE FULL	27 407	1.5.17 – 1.5.18 7	When discussing pelvic pain, there is no mention of trying oral analgesics for the pain. This would be a simple and often appropriate way to manage such pain	We agree. Oral analgesics are covered in recommendation 1.7.18 under the provision of 'best supportive care'.
SH	Association for Palliative Medicine of Great Britain & Ireland	6	FULL	482	0General	We note that no specialist palliative care doctor or nurse was on the GDG. We do not know if a request went out for this, but feel it should be ensured, if possible, there is palliative care representation on GDGs concerned with potentially advanced disease	The importance of input from specialist palliative care in developing this guideline was identified at the scoping stage. Specialist palliative care was therefore included in the list of GDG specialties advertised for on the NICE website. Unfortunately no applications were received and despite extensive searches via the professional networks of

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							other GDG members, we were unable to recruit a specialist. We were however fortunate that one of the clinical nurse specialist members of the GDG had considerable palliative care experience. In addition we had input from a palliative care consultant, who attended one GDG meeting as an expert adviser on the palliative care-related topics. We feel that palliative care input would have been invaluable for other topics too, had we been able to recruit.
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	1	NICE	12	1.1.4	There is no mention of information and support for people with bladder cancer at the end of active treatment. This is specifically in relation to support services such as that provided by Allied Health Professionals in terms of rehabilitation.	Whilst we agree that rehabilitation services are important, unfortunately this was not an area that was prioritised by the guideline. Consequently the evidence on this has not been investigated and we are not able to make any recommendations on this issue.
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	2	NICE	0General	0General	There is a general lack of mention of referral to appropriate rehabilitation services.	Whilst we agree that rehabilitation services are important, unfortunately this was not an area that was prioritised during the scoping process. Consequently the evidence on this has not been reviewed and we are not able to make any recommendations on this issue.
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	3	NICE	16	1.3.6	Where there is mention on impact on quality of life it might be appropriate to use the terminology "side effects that impact on"	We believe that the impact on quality of life is broader than just side effects resulting from treatment, so have not made this change.
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	4	NICE	11	1.1.4	As above	We have included physical activity in recommendation 1.1.5
SH	Association of Chartered	5	NICE	12	1.1.7	Please can we include Allied Health Professionals as well as just psychological	We feel that allied health professionals would be included in the term "specialist healthcare

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	Physiotherapists in Oncology and Palliative Care					support as many issues that result in psychological issues can be helped by their services too.	professionals".
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	6	NICE	11 12	0General	There is no mention of support to enable people to be physically active according to the NICE guidelines on Physical activity demonstrated to reduce the incidence of reoccurrence and death. Or no mention of the importance of highlighting this to people.	We have included physical activity in recommendation 1.1.5
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	7	NICE	17	1.3.14 1.3.15	To include appropriate allied health professional specialist service (rehab) to manage some of the side effects	These recommendations are specifically about toxic side effects from BCG and radiotherapy. We have not reviewed the evidence for the role of rehabilitation services in the management of toxicity and therefore are not able to make any recommendations on this issue.
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	8	NICE	26	1.6.4	Should include specialist palliative rehabilitation professionals within the team.	Rehabilitation professionals are an important component of specialist palliative care services (as detailed in Improving supportive and palliative care for adults with cancer, 2004) and therefore we do not feel that they need to be specified here.
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	9	NICE	31	0General	Should include physical activity guidelines	This guidance is not specific to cancer and therefore we do not think it is appropriate to include.
SH	British Association of Urological Surgeons	1	NICE	0General	0General	Overall sensible and well evidenced guidance. Many of the recommendations have been advocated by clinicians specialising in the management of bladder cancer, and are widely practised at specialist centres. This guidance will hopefully encourage wider utilisation of good practice for these patients.	Thank you
SH	British Association of	2	NICE	11		The WHO performance status table does not include WHO PS 0	This table has been removed from the guideline.

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	Urological Surgeons						
SH	British Association of Urological Surgeons	3	NICE	13	1.2.3	The enthusiasm for PDD, NBI, urinary biomarkers and cytology will be welcomed by many clinicians. The economic and clinical efficacy of these tests are still undergoing evaluation eg the forthcoming PHOTO trial.	Thank you.
SH	British Association of Urological Surgeons	4	NICE	14	1.2.6	Consider using a bladder map to record location, size and number of tumours as this can help with further management eg pathological evaluation, re-resection and follow up	We would consider recording of intraoperative observations to be a routine part of good clinical practice, and therefore have not made a recommendation on this.
SH	British Association of Urological Surgeons	5	NICE	14	1.2.8	Consider further TURBT at 6 weeks if HIGH RISK disease, incomplete resection or imaging and pathological evaluation do not correlate. (unnecessary to perform re-resection for low risk disease). Recommendation 1.3.5 does emphasise high risk cases only – should ensure consistency in the guidance.	This comment relates to 3 recommendations (1.2.4 Obtain detrusor muscle during TURBT; 1.2.8 Consider further TURBT within 6 weeks if the first specimen does not include detrusor muscle; 1.3.5 If the first TURBT shows high-risk non-muscle-invasive bladder cancer, offer another TURBT as soon as possible and no later than 6 weeks after the first resection). The aim of these recommendations is to promote a high quality TURBT at the first procedure, to ensure high-quality staging, by repeating the procedure if there is no detrusor muscle, and to ensure high-quality management of people with high-risk disease. The wording of recommendation 1.2.8 allows the MDT to decide if the repeat TURBT to obtain detrusor muscle is appropriate for the individual patient with low or intermediate risk. Whereas recommendation 1.3.5 requires that the TURBT be repeated if high-

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							risk disease is found.
SH	British Association of Urological Surgeons	6	NICE	14	1.2.12	PET CT is not widely utilised for bladder cancer cases. The problem with this recommendation is that it places a high resource demand on centres. Is there robust evidence to support the utility of PET in bladder cancer and in particular correlation with pathological node status. Guy's study in BJUI autumn 2014 suggested PET for trouble shooting only. We would suggest that this should be strongly supported as a research priority but not necessarily encouraged as standard practice.	The use of the word 'consider' in recommendation 1.2.12 reflects the strength of the evidence (please see page 6 of the NICE version for further information on the wording of NICE recommendations). The GDG did not think that the use of PET-CT was a priority area for research. Finding resources to enable this recommendation to be carried out will be a matter for local implementation.
SH	British Association of Urological Surgeons	7	NICE	15	1.3.1	Allocation of a risk category is useful. However, routine use of risk prediction tools eg EORTC calculator is not widespread. The calculator is based on quite old data and some more recent studies question its current validity.	Thank you. We are aware of the limitations of risk prediction tools but feel that they should be used as part of the decision making process to improve risk categorisation.
SH	British Association of Urological Surgeons	8	NICE	16	1.3.6	Support recommendation that urologist who performs BCG and cystectomy should discuss management. Would suggest going further and recommending that all high risk disease be discussed at MDT and treatment be managed by urologist with special interest. Thus 1.3.8 – the patient would already be under the care of the specialist MDT.	Involvement with the specialist urology MDT for people with high-risk disease is part of the Improving Outcomes in Urology guidance and associated peer review measures. We have therefore not specified this in the recommendations as it would be expected to happen.
SH	British Association of Urological Surgeons	9	NICE	19	1.3.18	Interesting recommendation regarding discharge of low risk cases at 12 months. This will reduce the burden of follow up cystoscopy to patients and the health service and for this reason will be welcome. However, it is a bold change in practice that is not currently in any national or international guidance. In general,	The potential benefits of the recommendation for patients with low risk disease result from the reduced burden of cystoscopic follow-up. The GDG balanced this against the potential for harm resulting from a possible small increase in the late detection of disease recurrence and that patients may experience

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						not many patients will come to harm if it is adopted. However, it is likely that some recurrent disease will be larger volume/multifocal, more difficult to resect if we wait for haematuria before offering cystoscopy. More rarely patients can develop grade progression from low to high risk.	anxiety after discharge from follow-up. The GDG considered that reducing the burden of follow-up strongly outweighs the possible increase in late detection of recurrence.
SH	British Association of Urological Surgeons	10	NICE	20	1.4.3	For muscle invasive TCC this is reasonable advice. However, chemoradiotherapy for other histological types eg SCC is not very effective.	We have amended recommendation 1.5.3 to clarify that it only relates to urothelial bladder cancer.
SH	British Association of Urological Surgeons	11	NICE	21	1.4.5	Evidence for adjuvant chemotherapy is weaker than that for neoadjuvant. However, is there evidence that this will be less beneficial to those who were eligible for neoadjuvant treatment, why restrict recommendation for this group?	We agree that the evidence for neoadjuvant chemotherapy is stronger than that for adjuvant chemotherapy. Therefore neoadjuvant chemotherapy should be the standard of care (as reflected by the term 'offer' in recommendation 1.5.2. Please see page 6 of the NICE version for further information on the wording of NICE recommendations. Recommendation 1.5.7 is directed to those people who have had cystectomy for NMIBC and were found to have unsuspected muscle invasion or lymph node spread or people who at the time of surgery had inadequate renal function to receive cisplatin. The GDG debated the wording of recommendation 1.5.3 and 1.5.7 in the light of your comments, and are content that this wording reflects the evidence.
SH	British Association of Urological	12	NICE	21	1.4.6	Trial data indicates encouraging results from the use of radiosensitisers with radical radiotherapy eg BCON study. However, this is	We disagree. The GDG felt that benefit of radiosensitisation (either chemotherapy or Carbogen/Nicotinamide) was clearly

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	Surgeons					not yet widely practised and I am not sure if there is sufficient evidence to make such a strong recommendation for a change in practice with logistical implications.	demonstrated by the evidence. There was evidence to support both treatment approaches, but it was unclear as to which was superior and therefore both have been recommended as treatment options.
SH	British Association of Urological Surgeons	13	NICE	22	1.4.9 & 1.4.10	upper tract imaging every year for five years/annually. Presumable ultrasound but this should be defined. CT urogram may be indicated to check for synchronous upper tract TCC	There are a number of imaging modalities that could be used to monitor the upper tract including ultrasound, nuclear medicine and CT. No evidence was found to support the use of one modality over another. In addition, CT is already recommended for monitoring of local and distant recurrence and may be used to image the upper tracts. The choice of modality, which could include CT urogram, would also depend on individual patient factors. Therefore the GDG did not specify a modality in the recommendation.
SH	British Association of Urological Surgeons	14	NICE	26	1.5.15	Very limited evidence for efficacy of embolization for intractable bleeding, some case series indicate sporadic benefit. In general would suggest role of embolization less valuable than radiotherapy for this symptom. Suggest radiotherapy preferred over embolization as first line.	We agree that the evidence base for the treatment of intractable bleeding is weak and insufficient to recommend one treatment over another. This is why we have used the word 'consider' in recommendation 1.7.15.
SH	British Association of Urological Surgeons	15	NICE	27	1.5.17	Suggest involve local urology and oncology team as two of the treatments under consideration are administered by oncologists.	We believe that the responsibility for the evaluation should lie with the local urology team. However they may call on oncology or palliative care to provide best supportive care (as detailed in recommendation 1.7.18).
SH	British Association of Urological Surgeons	16	NICE	14 189	1.2.7, 1.3.3 – 1.3.4, 1.3.7 23	The NICE guidance seems to be recommending MMC over BCG for intermediate risk disease: "Offer people with newly diagnosed intermediate-risk NMIBC a course of at least 6 doses of MMC. If NMIBC returns after this course refer to bladder cancer	The process for developing NICE guidelines is different to that used by BAUS and EAU. Consequently, recommendations made may be different. For people with intermediate risk NMIBC

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			FULL			specialist multi-disciplinary team." This is not consistent with either BAUS or EAU guidance which are both evidence based. We would ask that this be reviewed in the light this inconsistency and in particular the EORTC paper in the European Journal of Urology by Sylvester, Brausi et al (trial 30911) indicating the superiority of BCG over intra-vesical chemotherapy for Intermediate risk disease in terms of both recurrence rates and survival	(recommendation 1.3.3) we recommend a course of mitomycin. If recurrence occurs after this the disease is then re-classified as high-risk NMIBC for which the options of BCG or cystectomy are recommended (recommendation 1.3.6). Recommendation 1.3.7 refers to how BCG is used rather than for whom. The paper you cite was included in the evidence appraisal conducted for this clinical question, in addition to other relevant evidence. Following review of all this evidence and discussion of the benefits and risks of different treatments, the GDG agreed it was appropriate to give mitomycin to the intermediate risk group because there is uncertainty over the extent of how much better BGC is over mitomycin C, but there is consistent evidence that BCG has significantly more side effects. We have added text to the Linking Evidence to Recommendations section to clarify this.
SH	British Uro-oncology Group (BUG)	1	NICE	4	1	Inclusion of squamous cell , adenocarcinoma , small cell carcinomas These are inappropriate to be managed with the treatment strategies mentioned. They have differing chemotherapy regimens, there is a difference in appropriate use of surgery and radiation schedules used for each of these dominant tumour types. It is thus factually incorrect to include these tumour types and the document should be reworded to say that it does not cover these	The scope of the guideline included people with urothelial carcinoma, adenocarcinoma, squamous-cell carcinoma and small-cell carcinoma. The evidence searches looked for evidence relating to all of these types of bladder cancer but there was insufficient evidence to enable recommendations to be made for the management of adenocarcinoma, squamous-cell carcinoma and small-cell carcinoma. We have added text to the NICE introduction to clarify this. We have also amended

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						dominant tumour types	recommendation 1.5.1 to specifically mention these rarer types of bladder cancer, to ensure they are reviewed by the specialist urology MDT. This should help to ensure they are managed appropriately.
SH	British Uro-oncology Group (BUG)	2	NICE	20	1.4.2 1 (under "Managing muscle-invasive bladder cancer") And 1.4.2 on page 20	The sentence should probably be re-worded to state "There is a strong preference for using neoadjuvant chemotherapy with a cisplatin combination regimen before.." for all patients eligible for neoadjuvant treatment, in order to reflect that this should be the standard of care. "Offer.." We understand that this implies a "strong recommendation". However, we propose strengthening this statement in the recommendations as not all commissioners may interpret this "offer " as intended.	Offer is the strongest recommendation we can make. Please see page 6 of the NICE version for further information on the wording of NICE recommendations. We would hope that commissioners would read this information in order to understand what the recommendations mean.
SH	British Uro-oncology Group (BUG)	3	NICE	13 & 14	1.2.2 & 1.2.124 (under Diagnosing and staging bladder cancer: 1.2.2 & 1.2.12)	"Consider CT or MRI staging before.." The MRI and CT imaging modalities should be used for the staging of suspected muscle invasive bladder tumours, where this will influence treatment decisions as per BUG's MDT bladder guidance recommendations, published in 2013 and EAU recommendations published in 2012. There is some evidence to show that MRI is superior to CT in evaluating the T stage of suspected muscle invasive bladder cancer and that should be clarified in the Guideline. In addition, according to EAU guidelines: *MRI is the preferred modality if the patient is evaluated for radical treatment. CT due to its higher specificity may be equivalent to MRI regarding local staging.* In addition, both techniques are unable to	Thank you for this information. Due to the lack of high quality evidence, the GDG could not recommend one type of imaging (CT or MRI) over the other. This was documented in the Linking Evidence to Recommendations section in the full version of the guideline.

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						detect microscopic invasion of perivesical fat (T3a) and can therefore, be only used to detect T3b disease or higher [BUG MDT & EAU guidance] BUG feels strongly that CT thorax should be mandated for patients undergoing radical treatment, palliative chemotherapy or palliative radiotherapy. A bone scan should be performed for patients with bone pain or with a raised alkaline phosphatase. Finally use of FDG PET-CT (1.2.12) is not routine clinical practice in staging advanced disease or has enough evidence-base; therefore this recommendation should be re-worded to state that functional Imaging can be used at the discretion of the Bladder Cancer	This is covered by recommendation 1.2.11. The use of the word 'consider' reflects the strength of the evidence (please see page 6 of the NICE version for further information on the wording of NICE recommendations). No recommendation was made on detecting bone metastases because there was insufficient high quality evidence on techniques looking primarily at bone metastases, and because the GDG felt that the other recommendations made for CT and MRI would likely pick up those people with bone metastases in any event. This was documented in the Linking Evidence to Recommendations section in the full version of the guideline. We would expect that in patients with symptoms appropriate imaging will be performed, which may include a bone scan. The use of the word 'consider' in recommendation 1.2.12 reflects the strength of the evidence (please see page 6 of the NICE version for further information on the wording of NICE recommendations). The wording of the recommendation also clarifies that PET-CT would be considered for people where radical treatment is being contemplated and there are indeterminate findings on CT or MRI. Implicit in this recommendation is that the decision to use

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						MDT in cases where it has the potential to change management plans. Recent UK data on 233 consecutive patients with high risk NMIBC or MIBC being considered for cystectomy showed minor improvement in sensitivity compared with CT alone(54% versus 41%) with similar specificities(97% versus 98%). (Goodfellow et al BJUI 2014:114;389-395). PET CT is not routine practice and would represent significant resource implications. This will raise a clinical dilemma in some patients with equivocal lymph nodes on PET CT but not on MRI/CT. Also, note that the full Guideline pp 110 line 34 states "*18F-FDG-PET/CT can be used for pelvic lymph node staging but is not widely available because of strict NHS commissioning rules on its use in bladder cancer."* This statement is not provided in the shorter NICE Guideline and is thus misleading. Please note that the MARBLE study (Newcastle) will look at how well FLT PET-CT scans are (vs CT scans) at showing how the cancer is responding to treatment early on. Ongoing European trial of FDG PET pre cystectomy will augment current knowledge but currently there is not enough evidence for use of FDG PET-CT to warrant stating "consider.." in the Guideline. PET should be added as an area for research priority.	PET-CT would be made by the specialist urology MDT. Finding resources to enable this recommendation to be carried out will be a matter for local implementation. This text is background information and is not a recommendation, but we have removed this statement from the text. Thank you for this information. The GDG did not think that the use of PET-CT was a priority area for research. This is an expert review rather than a primary

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						We would also wish to refer to omitted references in the full evidence version as detailed below Barentsz JO, Witjes JA. Magnetic resonance imaging of urinary bladder cancer. Curr Opin Urol 1998; 8: 95−103. BUG, BAUS & ABC. Multi-disciplinary Team (MDT). Guidance for Managing Bladder Cancer. 2nd Edition (January 2013) MARBLE study. http://www.cancerresearchuk.org/about-cancer/trials/a-study-looking-type-mri-scan-assess-how-well-bladder-cancer-treatment-working-early-on-marble Last accessed September 2014 Stenzl A, Witjes JA, Comperat E, et al. Guidelines on bladder cancer. Muscle-invasive and metastatic. Arnhem: European Association of Urology, 2012. Tekes A, Kamel I, Imam K, et al. Dynamic MRI of bladder cancer: evaluation of staging accuracy. AJR Am J Roentgenol 2005; 184: 121−127. Zhang J, Gerst S, Lefkowitz RA, Bach A.	study and was therefore not included. However we have included the Barentsz 1996 MRI study (see page 174 of the evidence review). This is a guideline and would not be included as evidence in its own right. However it would have been checked for relevant included primary studies. This is an ongoing trial which will finish recruitment in 2016. As such we were not able to include it in our evidence review. This is a guideline and would not be included as evidence in its own right. However it would have been checked for relevant included primary studies. This study was included (see evidence review page 166). This is another expert review rather than a primary study and was therefore not included.

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						Imaging of bladder cancer. Radiol Clin North Am 2007; 45: 183−205.	
SH	British Uro-oncology Group (BUG)	4	NICE	23	1.5.2 (under "First line chemotherapy" 1.5.2)	Locally advanced or metastatic chemotherapy: The Guideline here stipulates to offer cisplatin-based chemotherapy regimens to people with locally advanced or metastatic bladder cancer who are otherwise physically fit and have adequate renal function (GFR higher than 60 ml/min).This is firstly inconsistent as section 1.4.2 (neoadjuvant chemotherapy with cisplatin containing regimens) stipulates adequate renal function We feel that the Guideline here is being too prescriptive in stipulating that renal function of patients receiving chemotherapy should be "GFR higher than 60 ml/min". Whilst GFR of 60mls/min is that mandated in clinical trials, in real world practice platinum based chemotherapy can be safely delivered for GFR of > 50 mls/min. BUG would advise that GFR > 60 should be replaced with "adequate renal function" BUG, BAUS & ABC. Multi-disciplinary Team (MDT). Guidance for Managing Bladder Cancer. 2nd Edition (January 2013)	The GFR level of 60ml/min was taken from the studies in the evidence review used to inform this recommendation. Recommendations in NICE guidelines do not substitute for good clinical decision making. However, to acknowledge your point we have added an additional qualifier to this recommendation to allow some flexibility.
SH	British Uro-oncology Group (BUG)	5	NICE	21	1.4.5 3 (under "Adjuvant chemotherapy for muscle-invasive	In this section the adjuvant regimen seems to have given equal weight to neoadjuvant regimen. However, there are currently no strong data to support the use of adjuvant chemotherapy. BUG is concerned that such wording will increase the usage of adjuvant chemotherapy and will reinforce the often surgically held non-evidence-based opinion that this is an option to the gold standard evidenced-based neoadjuvant chemotherapy.	We agree that the evidence for neoadjuvant chemotherapy is stronger than that for adjuvant chemotherapy. Therefore neoadjuvant chemotherapy should be the standard of care (as reflected by the term 'offer' in recommendation 1.5.2. Please see page 6 of the NICE version for further information on the wording of NICE recommendations.

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					or lymph-node-positive bladder cancer" 1.4.5)	Consider revising the wording to state that adjuvant chemotherapy is non-evidence-based option for patients with high risk features(locally advanced or Node positive) who were not suitable for neoadjuvant chemotherapy,but are appropriate on basis of adequate renal function, adequate and timely post-operative recovery (adjuvant chemotherapy only appropriate to be considered within 90 days of cystectomy) and performance status , although it does not replace neoadjuvant chemotherapy as the standard of care. This statement should therefore be reviewed. In addition, in the full version of the NICE Guideline pp 270 (quality of evidence), the evidence stated is qualified as low to moderate quality, while it has been generated using 15 studies only 3 of which actually have moderate quality evidence. The others are low or very low quality studies. The full version also states here "*The evidence was limited by the outdated regimens that were used in the trials and there have since been improvements in radical therapy*." Moreover, the full Guideline clearly states on pp 271 that "*The GDG felt strongly that the focus should be on neoadjuvant chemotherapy and that adjuvant chemotherapy is not a suitable alternative*" and this statement is not reflected in the NICE guideline at all. Furthermore, the statements in the NICE and full version of the Guideline do not concur. In the full version (pp 265 line 11) it is stated "*In these people (who had radical cystectomy*	Recommendation 1.5.7 is directed to those people who have had cystectomy for NMIBC and were found to have unsuspected muscle invasion or lymph node spread (i.e. upstaged). These people were not eligible for neoadjuvant pre-radical cystectomy. The GDG debated the wording of recommendation 1.5.3 and 1.5.7 in the light of your comments, and are content that this wording reflects the evidence.

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						without neoadjuvant chemotherapy) it is considered when the pathology findings from the radical cystectomy show invasion into the deep layers of muscle or beyond, involvement of lymph nodes, lymphovascular invasion or variant pathology"; followed by "*There is uncertainty about which patients should be offered adjuvant chemotherapy and which regimens are most effective."* Whereas the NICE Guideline version of the document recommends considering adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive bladder cancer who were not eligible for neoadjuvant chemotherapy. This version does not state that the consideration in the full Guideline version was limited to high risk patients. We believe that it should be clarified in the NICE Guideline version that there is insufficient evidence for adjuvant chemotherapy and the use of it should be confined to patients at high risk of relapse. For selected patients, this discussion with a specialist uro-oncologist should stress the lack of data in support of adjuvant chemotherapy and that is not the standard evidence-based treatment but may be considered on a case by case basis. To summarise, this section of the NICE Guideline on adjuvant chemotherapy may lead to consultants falsely believing that adjuvant chemotherapy is almost "as good as" neoadjuvant chemotherapy and can be given to patients instead of neoadjuvant chemotherapy. This needs to be clarified in the	

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						NICE Guideline, acknowledging the low quality of evidence for adjuvant chemotherapy. The Guideline needs to be clear on the fact that neoadjuvant is standard of care and the evidence for adjuvant treatment is not a replacement for neoadjuvant chemotherapy. BUG, BAUS & ABC. Multi-disciplinary Team (MDT). Guidance for Managing Bladder Cancer. 2nd Edition (January 2013) Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis of individual patient data. Eur Urol 2005; 48: 189−201.	
SH	British Uro-oncology Group (BUG)	6	NICE	23	1.5.3 (under "First-line chemotherapy)	Carboplatin and gemcitabine – this list is inappropriate and as already stated would discriminate against a significant number of patients with GFR between 50 and 60 mls/min in whom cisplatin based chemotherapy can safely be delivered. This demonstrates a lack of familiarity with management of these patients in "real life "practice. The phrase (GFR lower than 60 ml/min) should be removed and the entire list should be replaced with a paragraph stating that gemcitabine and carboplatin combination is appropriate to offer when patients are felt to be unsuitable for cisplatin based chemotherapy based on a full and holistic assessment by a specialist uro-oncologist of GFR/performance	NICE guidelines are not intended to replace clinical judgement. Evidence was available that showed a potential beneficial effect to people with these specific criteria. Hence the GDG included them in their recommendation. The harms may outweigh the benefits in certain people (for example, those with a higher WHO performance status) but this should be established as part of the holistic needs assessment. We have added an additional qualifier about the GFR level to this recommendation to allow some flexibility. We have also amended the recommendation to clarify that it was intended for people who cannot have cisplatin-based chemotherapy.

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						status and comorbidities.	
SH	British Uro-oncology Group (BUG)	7	NICE	23	1.5.2 ("First-line chemotherapy")	All three regimens for first line chemotherapy have been given equal weight in this recommendation. . BUG and the NCRN Bladder Cancer CSG have conducted two audits of contemporary use of regimes in advanced bladder cancer over a seven year period. Accelerated MVAC is used in four UK centres only with > 85% UK clinicians using gemcitabine and cisplatin. Cisplatin plus gemcitabine with paclitaxel is **not** routinely used in clinical practice. Equal weighting is given to regimes not commonly in use and validated by single studies in the case of triplet therapy (Gemcitabine/cisplatin/paclitaxel) It may be prudent here to replace the three regimens with a sentence recommending cisplatin based regimens and then, if needed, the three specific regimens can be named as examples of cisplatin based chemotherapy recommended in this setting. The stated level of GFR >60mls/min for cisplatin based therapy does not reflect standard UK practice by specialist bladder cancer uro-oncologists and should be replaced by "adequate renal function"	In developing the guideline the GDG wished to support the use of evidence-based regimens. That a schedule is not commonly used is not a reason to not recommend it. However, in recognition of feedback received from stakeholders we have amended the recommendations to remove the triplet chemotherapy and focus on the 2 more commonly used schedules. The GFR level of 60ml/min was taken from the studies in the evidence review used to inform this recommendation. Recommendations in NICE guidelines do not substitute for good clinical decision making. However, to acknowledge your point we have added an additional qualifier to this recommendation to allow some flexibility. Due to the removal of the recommendation on triplet chemotherapy, this text is now

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						In FULL Page 341 it is stated "the GDG considered the implementation of these recommendations (for gemcitabine/cislatin/paclitaxel combination or accelerated MVAC) would not cause a significant change in current practice- this is incorrect and BUG strongly refutes this. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005; 23: 4601−4608. BUG, BAUS & ABC. Multi-disciplinary Team (MDT). Guidance for Managing Bladder Cancer. 2nd Edition (January 2013)	correct.
SH	British Uro-oncology Group (BUG)	8	NICE	24	1.5.8 under "Second line chemotherapy" – 1.5.5 to 1.5.8)	Here the Guideline recommends use of gemcitabine plus cisplatin or accelerated (high-dose) methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) with G-CSF. However, the BUG MDT guidance demonstrated that there are no standard treatment regimens in this setting, but patients who have responded for 6 months to first-line treatment may be re-challenged with that regimen.(Edeline J et al, 2012) Furthermore, in the full version of the NICE Guideline the evidence review shows very low quality evidence for the treatments reviewed (single or multi agent chemotherapy (pp 342-344)	The evidence base for second line chemotherapy has been extensively reviewed by the GDG. Recommendation 1.7.6 recommends the use of those schedules with the strongest available evidence. However the quality of this evidence is reflected by the use of the term 'consider' in the recommendation. Please see page 6 of the NICE version for further information on the wording of NICE recommendations.

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						The full version also states on pp 342 *"Management options for people who progress on or relapse after first line treatment are controversial."* In the NICE version – it should be acknowledged that the evidence for the recommended regimen is low. The stated regimens are both too prescriptive and are not in widespread use within the UK. No regimen has shown a survival advantage in the second line setting. In addition, some clinical data support the use of paclitaxel, which has not been mentioned in the NICE Guideline. Single agent paclitaxel is less likely to cause toxicity compared with the double agents recommended by NICE. In addition, the evidence quality for paclitaxel (very low) is the same as for the treatments recommended by NICE in the second line setting so there is no clear rationale for not mentioning paclitaxel in this setting. In this section in the full version, it is stated that clinical experience has not been considered yet in other areas of the full version where good quality data is lacking, clinical experience has been accepted. eg FULL Page 65 " the GDG drew upon their clinical knowledge to form recommendations in absence of any direct high quality evidence" This should be a consistent approach but has been ignored in second line chemotherapy by the GDG. (It states on Page378 of FULL	The NICE version only contains the recommendations made in the guideline. It does not include any evidence. The evidence on single agent paclitaxel was too weak to support making a recommendation. However in light of feedback received from stakeholders the GDG have deleted the recommendation on single-agent chemotherapy for second line. The guideline does not make any recommendations for triplet chemotherapy for second line. Recommendation 1.7.7 (consultation version) covered the use of carboplatin in combination with paclitaxel and gemcitabine in combination with paclitaxel.

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						version*: " no recommendations were based solely on clinical experience"* and "*the lack of any high quality evidence meant that only weak recommendation could be made in relation to specific chemotherapy regimens*" It is thus illogical to recommend gemcitabine/carboplatin/paclitaxel over any other regime as this is more likely to have additional toxicity. In the arena of second line chemotherapy, clinical experience is paramount and two UK surveys have demonstrated that single agent paclitaxel is the agent most commonly in use in the second line setting and has been adopted as the standard arm in the current NIHR portfolio study-PLUTO based on contemporary expert opinion. The British Uro Oncology Group feel strongly that this section does not reflect current UK practice and that clinician experience and opinion has been overlooked with triplet therapy of gemcitabine/carboplatin/paclitaxel being recommended outwith expert practice and evidence. Single agent paclitaxel should be included in the list of possible regimens. BUG, BAUS & ABC. Multi-disciplinary Team (MDT). Guidance for Managing Bladder Cancer. 2nd Edition (January 2013) Vaughn DJ, Broome CM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol 2002; 20: 937−940.	

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SH	British Uro-oncology Group (BUG)	9	NICE	24	1.5.5 under "Second line chemotherapy" – 1.5.5)	We suggest to add "Discuss low quality of evidence base for second line chemotherapy options with patients emphasising that there is no standard treatment in this setting".	We consider that this would be encompassed by the recommendation to 'discuss the advantages and disadvantages of treatment.
SH	British Uro-oncology Group (BUG)	10	NICE	24	1.5.5 under "Second line chemotherapy" – 1.5.5)	We suggest to add a comment here regarding patients with initial good chemotherapy response: • There are no standard treatment regimens in this setting, but patients who have responded for 6 months to first-line treatment may be re-challenged with that regimen. (Edeline et al 2012) In addition, it may be worth adding a comment regarding targeted therapies: Ongoing studies are evaluating targeted therapies for metastatic disease. BUG, BAUS & ABC. Multi-disciplinary Team (MDT). Guidance for Managing Bladder Cancer. 2nd Edition (January 2013)	We think that this issue is already covered by recommendation 1.7.6. The evidence on targeted therapies was reviewed but this did not show any evidence of benefit. Consequently no recommendations were made.
SH	British Uro-oncology Group (BUG)	11	NICE	21	1.4.6 1 (Under "Radical radiotherapy" 1.4.6)	•For section 1.4.6 (Radical radiotherapy) – Consider re-wording to say "biologically equivalent dose" rather than stipulating the radiation dose .	In the absence of evidence for the most effective regimen of radiotherapy, the GDG were aware of two dominant regimens used in practice. These are the examples that have been mentioned in the recommendation because the GDG felt that some guidance would be helpful.

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						•On the same section as above the full Guideline states "Although many UK centres now treat potentially curative patients with radical radiotherapy and a radiosensitiser, there are a group of patients who are not fit or able to tolerate radiosensitisation. These patients are treated with radical radiotherapy alone as their definitive treatment. There are differences of opinion about the volume of tissue to be treated, the radical radiotherapy regimens to be used and the use of radiosensitisers." However, in short NICE Guideline stipulates use of radiosensitiser so that should be re-worded as per the full Guideline.	Thank you for your comment about patients who are not fit/able to tolerate radiosensitisation. Recommendations in NICE guidelines do not substitute for good clinical decision making. So we would expect oncologists to only give radiotherapy in patients who are not fit/able to tolerate radiosensitisation.
SH	British Uro-oncology Group (BUG)	12	NICE FULL	20 8	1.4.3 10 (under key points for implementation)	There is an anomaly in the Key Points: Page 8 final bullet point - there is repeated reference to: *chemoradiotherapy* .....whilst the actual NICE Guideline recommends either *chemoradiation or radiotherapy with carbogen and nicotinamide*. We suggest that the wording be amended to reflect and chemoradiotherapy is replaced by another term or terms to include the use of radiosensitisers as an alternative.	We have amended this text to 'radiotherapy with a radiosensitizer'.
SH	British Uro-oncology Group (BUG)	13	FULL	101	20-35	'DOR' is not defined, and it is not in the document's glossary. Please add the definition.	We have spelt out 'DOR' the first time it is used in the text. We have also added a definition to the glossary.
SH	British Uro-oncology Group (BUG)	14	NICE	22	1.4.9 and 1.4.10	These are very prescriptive follow up recommendations and there is not enough evidence for them. The EAU guidelines follow up recommendations depend on patient	We disagree that the recommendations are very prescriptive and consider that they are worded to allow some flexibility. They use the term 'consider' to reflect the strength of the

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						characteristics and risk of progression. Currently follow up varies across the various centres in the UK, and we understand that the NICE Guideline is aiming to standardise this across the UK. However, some flexibility is important and the recommendations have to be re-worded to reflect individualisation based on patient characteristics and prognostics factors. Babjuk M, Oosterlinck W, Sylvester R, et al. Guidelines on non muscle-invasive bladder cancer (TaT1 and CIS). Arnhem: European Association of Urology, 2011. BUG, BAUS & ABC. Multi-disciplinary Team (MDT). Guidance for Managing Bladder Cancer. 2nd Edition (January 2013)	evidence that underpins them. Please see page 6 of the NICE version for further information on the wording of NICE recommendations.
SH	British Uro-oncology Group (BUG)	15	NICE	0General	0General	Although research priorities are outlined in detail, the option of entry into a clinical trial is not in any of the treatment algorithms, or diagnostic pathways. Consider having a blanket statement throughout management options stating "Consider entering patient into clinical trials if available"	We are not able to make this recommendation as the guideline did not look at a review question on this issue. However we have added text to the background in chapter 2 of the full guideline to stress the importance of offering people the opportunity to participate in clinical trials and research. Unfortunately we are not able to include the same text in the NICE version because this only contains the recommendations and does not include background text.
SH	British Uro-oncology Group (BUG)	16	NICE	11		WHO performance status 0 is omitted	This table has been removed from the guideline.
SH	British Uro-oncology Group (BUG)	17	NICE	13	1.2.3	The use of PPD, narrow band imaging and urinary biomarkers is to be welcomed. The economic and clinical efficacy of these	Thank you.

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						diagnostic procedures is under evaluation in upcoming NIHR portfolio studies and is not yet fully established.	
SH	British Uro-oncology Group (BUG)	18	NICE	0General	0General	Throughout the document there is reference to "bladder cancer specialist" and clarification is sought . Does this mean MDT discussion only or should there be care provided only by specialist bladder cancer urologist/non surgical oncologist?	We have carefully considered, for each recommendation, the appropriate level of MDT discussion or referral according to the risk of recurrence, progression or death. We have standardised the wording of the recommendations to reflect this, and to ensure that we are clear when discussion with the specialist MDT is appropriate or when the person's care should be transferred.
SH	British Uro-oncology Group (BUG)	19	NICE	18	1.3.10 Cystectomy	There is no mention of type of surgical technique; suitability for neobladder, management of bladder neck/prostate prior to neobladder and this is a missed opportunity. There is no mention of counselling after cystectomy for both erectile dysfunction and sexual dysfunction in both men and women. There is no clarification on the extent of lymph node dissection.	NICE guidelines focus on areas of uncertainty and variation in clinical practice. Consequently the issues you have raised were not prioritised for inclusion in the guideline. Recommendation 1.3.6 covers discussion of issues around impact on quality of life, body image and sexual and urinary function related to treatment. In addition recommendations 1.1.4 refers to holistic needs assessment which should be carried out after first treatment; and recommendation 1.1.5 covers discussing the impact of treatment on sexual health and body image. Recommendation 1.1.7 offers people opportunities to discuss care with healthcare professionals including those who can provide psychological support.
SH	British Uro-oncology Group (BUG)	20	NICE	19	1.3.20 Low risk NMIBC	Discharge of low risk cases at 12 months appears outwith current national/international guidance. This will reduce the burden of follow up to the	The potential benefits of the recommendation for patients with low risk disease result from the reduced burden of cystoscopic follow-up. The GDG balanced this against the potential

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						health service but is unlikely to be welcomed by patients if the benefit cannot be demonstrated. The clinical concern must be that some recurrent disease will be greater volume/multifocal if haematuria is required before offering cystoscopy.	for harm resulting from a possible small increase in the late detection of disease recurrence and that patients may experience anxiety after discharge from follow-up. The GDG considered that reducing the burden of follow-up (which is associated with anxiety and discomfort of cystoscopy) in this low-risk group strongly outweighs the possible increase in late detection of recurrence. Reduced frequency follow-up was shown to be the most cost-effective strategy in low risk patients. It was substantially cheaper and the strategy was found to be cost-effective. Moreover, significant opportunity costs were identified specifically the opportunity to focus scarce cystoscopy resource on people at higher risk who have the greatest benefit.
SH	British Uro-oncology Group (BUG)	21	NICE	18	1.3.15 Side effects of treatment	It seems illogical to include radiation side effects in this section after the preceding sections outline management of NMIBC and cystectomy. This should be removed and added to a section later in the document separately eg in 1.4.7	We have amended the recommendations to separate out BCG from post radiotherapy toxicity and moved the radiation recommendations to the appropriate section.
SH	British Uro-oncology Group (BUG)	22	FULL	9	Research Recs	BUG welcomes the guidance for research but would suggest that within each section it should be stated that " a clinical trial should be considered if available"	We have added text to chapter 2 of the full version of the guideline to stress the importance of offering people the opportunity to participate in clinical trials and research.
SH	British Uro-oncology Group (BUG)	23	FULL	0General	0General	BUG has noted that the clinicians were not permitted to comment on data directly relating to their own area of expertise e.g. comment on systemic chemotherapy was not allowed by medical oncology. This seems a hugely missed opportunity and	Clinicians were actively encouraged to contribute to discussions about patients and tumour related factors using their clinical knowledge and experience. They were also encouraged to contribute actively to discussion of the evidence and formulation of

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						also a knowledge of patient and tumour related factors that directly influence management is overlooked.	recommendations, except for those specific instances where they had undertaken work which would be considered a conflict of interest as defined by NICE's policy.
SH	British Uro-oncology Group (BUG)	24	NICE	13	1.2	We would like to add the issue of what is essentially a diagnostic procedure being used as a treatment in terms of TURBT. This has major impact on the bladder cancer pathway as is then designated "1st treatment" and subsequent definitive treatment is therefore delayed. This does not appear to have been addressed in either the full version or the abbreviated version and is probably the biggest single thing wrong with the pathway today. A study carried out to assess the patient pathway for bladder cancer in detail to understand delays and improve the patient experience identified unacceptable delays between the initial TURBT to definitive therapy. Furthermore, strategies adopted to reduce these were effective. The study found that the initial diagnostic pathway works well but superficial bladder cancer and MIBC are then managed very differently and warrant two separate pathways (see abstract attached with this document). We welcome the recognition that two pathways are effectively required for muscle invasive and non-muscle invasive disease, and that experienced cystoscopists are suggested regarding using newer techniques like white light TURBT with the consideration of pre TURBT CT – an experienced cystoscopist can recognise a muscle invasive tumour and if	We acknowledge this concern. However the recommendations made are clear on when TURBT should be used. There are also clear recommendations on referral for patients with high-risk non-muscle-invasive and muscle invasive bladder cancer, which we hope will change practice. Thank you.

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						staging is booked at that time including thoracic imaging, then again this would reduce delays in the pathway.  MIBC pathway abstract.docx	
SH	British Uro-oncology Group (BUG)	25	NICE	N/A	N/A	Additional comments: Mandating a consultation for every radical bladder patient with both a clinical oncologist and urologist is to be encouraged but has resource implications.	We agree. This will be a matter for implementation of the guideline. In addition, the urology cancer service guidance also supports this approach.
SH	Combat Medical Ltd	1	NICE	17	1.3.8	If Induction BCG fails guidance refers the person's care to a bladder cancer specialist multi-disciplinary team who assess options see 1.3.9 which include possible radical cystectomy or further intravesical therapy based on clinical experience. Why is there no mention of chemo-hyperthermia as an option to maximise the efficacy of the chemotherapy when the EAU guidelines suggest it as a possible treatment option in BCG failure? (EAU Guidelines 8.4.3- p.27-"installations of gemcitabine or MMC in combination with hyperthermia appear to be good options in these patients")	The priority for the GDG in assessing the evidence was to evaluate whether any intravesical treatment was effective in reducing risk of recurrence and progression. When forming the clinical question the GDG did not prioritise the comparison of modes of delivery of intravesical treatment. Consequently the evidence on chemo-hyperthermia has not been appraised and we are not able to make any recommendations on this specific matter.
SH	Combat Medical Ltd	2	NICE	17	1.3.9	As above the specialist multidisciplinary team should assess suitability of treatment	Thank you – we agree.
SH	Combat Medical Ltd	3	FULL/ NICE	0General	0General	No mention of alternative options in the case of BCG shortage- which seems to be an issue at present and numerous times over the last two years.	The guideline investigated the place of BCG in the management of bladder cancer. Whilst we share your concerns about BCG shortage, it is beyond the remit if the guideline to consider solutions to this

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							potential problem.
SH	Combat Medical Ltd	4	NICE FULL	17 226 /General	1.3.8 – 1.3.9 7	The GDG considered that no specific intravesical therapies could be recommended due to the low quality and general lack of evidence.(P226) Research is recommended by the GDG to establish the efficacy of novel intravesical therapy (P226/ P228) as it is noted on P.143- line40/41 that optimization of the drug's concentration in the bladder may provide better results. This research recommendation would obviously include chemo-hyperthermia. P.228 Also notes that at present there is a recognition that there is a group of patients who fail BCG- i.e can't tolerate it or get a recurrence following a BCG treatment that have NO effective standard treatment at present. As a stakeholder with a chemo-hyperthermia device we would like to point out that we are undertaking a prospective, randomised, multicentre clinical trial in 494 NMIBC intermediate risk patients, 191 patients in the UK, 303 in Spain. Results of which are expected in 2017. The larger HIVEC study follows on from a pilot HIVEC trial (published 2014) which reported that the COMBAT BRS system achieved target bladder temperatures, a favourable side effect profile and at a median 29 months follow up provided preliminary evidence of treatment efficacy with a 3year cumulative incidence of recurrence of 15%. Further information on request. At the point when we have all the evidence from HIVEC I and II trials what is the procedure for changing guidelines if the evidence warrants it?	Thank you for this information. The research recommendation refers to 'novel intravesical therapies' which could encompass your technology. NICE has a process for considering the surveillance of guidelines which is available on the NICE web site. This may be used when your trial reports.
SH	Fight Bladder	1	NICE	3	Para 6	Unless there is a medical reason for this age	Children (under 18) with bladder cancer

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	Cancer (patient led charity)				under "This guideline covers adults (18 years and older.."	restriction we do not believe that one should exist.	would be managed differently to adults with bladder cancer and by different teams. Consequently they were excluded from the scope of the guideline.
SH	Fight Bladder Cancer (patient led charity)	2	NICE	6	Para 2 under "For all recommendations …"	We believe that word "expect" is not strong enough. It is **essential** that these discussions take place with the patient.	This is standard text developed by NICE and we are not able to change it.
SH	Fight Bladder Cancer (patient led charity)	3	NICE	6	Para 4	We believe that the word "offer" could be seen to be a "gentle" recommendation rather than the intended "strong" recommendation when, in certain comments, a stronger phrase should be used. See later comments.	This is standard text developed by NICE and we are not able to change it.
SH	Fight Bladder Cancer (patient led charity)	4	NICE	11	1.1.2	Need to add that the role of the CNS is explained to the patient as in 1.1.3	We feel that this is adequately covered in 1.1.3.
SH	Fight Bladder Cancer (patient led charity)	5	NICE	12	1.1.4	Need to add initial bullet point "when bladder cancer is suspected and initial investigations are being carried out" The concerns of patients, their partners, families or carers don't just start at the confirmed diagnosis.	The list of bullets in recommendation 1.1.4 is not intended to be exhaustive - it illustrates examples of some of the key points. Consequently we do not think it is necessary to make this change.
SH	Fight Bladder Cancer (patient led charity)	6	NICE	12	1.1.5	Provision of information and support for patients is dependent on the knowledge of the medical team. An agreed database of sources need to be included in the guidelines and be updated on a regular basis to ensure that best	Producing such a database to facilitate the provision of information and support to patients is outside the remit of this guideline. However, the Information For the Public will signpost the relevant organisations that could

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						support and guidance is given.	provide this.
SH	Fight Bladder Cancer (patient led charity)	7	NICE	13	1.1.7	Last bullet point should include reference to the Bladder Buddy Service provided by Fight Bladder Cancer on a national basis.	NICE guidelines are not able to link to services provided by external sources. However, the Information For the Public will signpost the relevant organisations that could provide this.
SH	Fight Bladder Cancer (patient led charity)	8	NICE	13	1.1.9	Add that advice should be sought from patient advocacy groups such as Fight Bladder Cancer	NICE guidelines are not able to link to services provided by external sources. However, the Information For the Public will signpost the relevant organisations that could provide this. In addition, we have emphasised the importance of involving people with bladder cancer in our recommendations.
SH	Fight Bladder Cancer (patient led charity)	9	NICE	13	1.2.2	The guidance should be specific about a preference between whether CT or MRI is best used.	Due to the lack of high quality evidence, the GDG could not recommend one type of imaging (CT or MRI) over the other. This was documented in the Linking Evidence to Recommendations section in the full version of the guideline.
SH	Fight Bladder Cancer (patient led charity)	10	NICE	13	1.2.3	This para must make clear that cytology or urinary biomarker is additional to the essential TURBT.	We feel that the recommendation is clear that cytology or urinary biomarkers are additional to TURBT
SH	Fight Bladder Cancer (patient led charity)	11	NICE	14	1.2.8	Second TURBT should be expected standard procedure. Reason should be explained to the patient.	We would consider that this should be part of good clinical practice and does not need to be specified in the guideline.
SH	Fight Bladder Cancer (patient led charity)	12	NICE	14	1.2.9	The guidance should be specific about a preference between whether CT or MRI is best used.	Due to the lack of high quality evidence, the GDG could not recommend one type of imaging (CT or MRI) over the other. This was documented in the Linking Evidence to Recommendations section in the full version of the guideline.
SH	Fight Bladder Cancer (patient led charity)	13	NICE	16	1.3.6	Patient should be advised to talk to other patients about the quality of life effects of the two different pathways via patient advocacy	This is already covered by recommendation 1.1.7.

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						groups alongside the detailed and specific medical advice. Fear of the unknown can influence patient choice.	
SH	Fight Bladder Cancer (patient led charity)	14	NICE	17	1.3.7	Patient needs to be advised on the detail of the induction and maintenance BCG treatment. Currently patients who have less than 3 years of treatment can, unless informed by their medical team, believe that they are not getting the full recommended treatment.	We agree – we would expect that this would form part of good clinical practice and shared and informed decision making. However we do not feel that this needs to be specified in the recommendation.
SH	Fight Bladder Cancer (patient led charity)	15	NICE	18	1.3.11	Patient should be advised to talk to other patients about the quality of life effects of the different pathways via patient advocacy groups alongside the detailed and specific medical advice. Fear of the unknown can influence patient choice.	Recommendation 1.1.7 already covers this.
SH	Fight Bladder Cancer (patient led charity)	16	NICE	18	1.3.12	Para should be added that people who choose a continent urinary diversion should be offered practical advice on exercises and techniques to aid continence control post surgery.	When forming the clinical question the GDG did not prioritise the inclusion of continence control post surgery. Consequently the evidence on this has not appraised and we are not able to make any recommendations on this. However, the GDG would expect that there would be a discussion of post operative continence under recommendation 1.3.6.
SH	Fight Bladder Cancer (patient led charity)	17	NICE	19	1.3.16	Patients to be advised to contact their medical team if haematuria or other symptoms occur	We would expect that this would form part of good clinical practice and do not feel it needs to be specified in a recommendation.
SH	Fight Bladder Cancer (patient led charity)	18	NICE	19	1.3.20	We are very concerned about this recommendation to discharge to primary care after such a short period. We would suggest that the care and management remains with the specialist urological teams for a full three years.	Recommendation 1.4.5 relates to people with low risk disease who will be under the care of local urology MDTs rather than specialist urology MDTs. The evidence reviewed (clinical and cost effectiveness) does not support follow up for 3 years. The GDG were also particularly mindful of the opportunity recommendation 1.4.5 provides to focus

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						Also, on discharge to primary care it is essential that the primary care team and the patient is given best advice on what symptoms would suggest that a referral back to the urology team would be recommended.	scarce cystoscopy resource on people at higher risk who have the greatest benefit. On discharge, patients will be given a care plan specifying factors that would warrant referral back to secondary care, as part of the Department of Health's National Survivorship Initiative. This is generic to all cancer patients and we do not feel it needs to be specified in the recommendation.
SH	Fight Bladder Cancer (patient led charity)	19	NICE	19	1.3.23	On discharge to primary care it is essential that the primary care team and the patient is given best advice on what symptoms would suggest that a referral back to the urology team would be recommended	On discharge, patients will be given a care plan specifying factors that would warrant referral back to secondary care, as part of the Department of Health's National Survivorship Initiative. This is generic to all cancer patients and we do not feel it needs to be specified in the recommendation.
SH	Fight Bladder Cancer (patient led charity)	20	NICE	20	1.4.3	Quality of Life issues should be discussed with the patient relating to both options during treatment, recovery and in the longer term. The patient should be encouraged to contact patient advocacy groups in order to understand the patient experience.	There are several existing recommendations relating to discussion of quality of life issues and treatment options (1.1.4, 1.1.5, 1.1.7 and 1.5.3 itself). Recommendation 1.1.5 covers finding information on support groups and recommendation 1.1.7 covers having discussion with other people with bladder cancer.
SH	Fight Bladder Cancer (patient led charity)	21	NICE	22	1.4.9	Follow up protocol should be for a minimum of 5 years post RC. Pros and Cons on continuation of follow up protocol longer than 5 years post surgery should be discussed with the patient. If discharged to primary care it is essential that the primary care team and the patient is given best advice on what symptoms would suggest that a referral back to the urology team would be recommended	The GDG did not feel there was sufficient evidence to guide recommendations on the duration of a follow-up protocol following cystectomy. If discharged, patients will be given a care plan specifying factors that would warrant referral back to secondary care, as part of the Department of Health's National Survivorship Initiative. This is generic to all cancer

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							patients.
SH	Fight Bladder Cancer (patient led charity)	22	NICE	22	1.4.10	Follow up protocol should be for a minimum of 5 years post radical radiotherapy. Pros and Cons on continuation of follow up protocol longer than 5 years post surgery should be discussed with the patient. If discharged to primary care it is essential that the primary care team and the patient is given best advice on what symptoms would suggest that a referral back to the urology team would be recommended	The GDG did not feel there was sufficient evidence to guide recommendations on the duration of a follow-up protocol. If discharged, patients will be given a care plan specifying factors that would warrant referral back to secondary care, as part of the Department of Health's National Survivorship Initiative. This is generic to all cancer patients.
SH	Fight Bladder Cancer (patient led charity)	23	NICE	28	Research recommendations	Patient Satisfaction: Patient advocacy groups such as Fight Bladder Cancer should be consulted in the scoping of any study on patient satisfaction. BCG or Primary Cystectomy: It is essential that Quality of Life Issues are researched alongside clinical effectiveness between BCG and Radical Treatment. High Risk NMIBC follow up: Substitution of non invasive testing should only be recommended if the research evidence shows that they are "as good" as cystoscopies. Other research recommendations: From a patient perspective the following are areas where research is urgently needed: 1. BCG treatment is a treatment that has	The guideline has identified areas for research and prioritised them in line with NICE processes. However it is beyond the remit of this guideline to specify the methodology of any such research. We agree and have specified this in the research recommendations We agree and wait to see what the results of the research are. The GDG did not feel that these were priority areas for research.

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						many quality of life issues and, alongside what are poor long term results for many, has frequent supply issues that result in delay in treatment that can adversely effect prognosis. Treatment selection research for the use of BCG for non invasive bladder cancer is required to ensure that patients have BCG treatment that is likely to be effective. Alternative new treatments are needed for patients where BCG is found to be ineffective. 2. Research is required to demonstrate what is the best effective treatment plan for BCG. When is one year of treatment the correct advice or should it always be 1 year induction then 2 years of maintenance? 3. The SPARE trial was intended to look at the outcome evidence between radical surgery and chemoradiation. The current lack of guidance to patients on this key issue causes great anxiety for patients who are left to make a choice without the essential facts for an informed choice. 4. There is an urgent need for a Quality of Life study on the choices for RC patients between neo bladders and stoma diversion. The scoping of such a study must involve patient advocacy groups like Fight Bladder Cancer and have involvement from a CNS perspective, stoma nurses and continence specialists.	

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SH	Fight Bladder Cancer (patient led charity)	24	NICE	0General	All	There is no mention of the Patient Decision Aids that should be intrinsic to the patient choices along the different treatment pathways. These must be updated and linked to these guidelines.	NICE guidelines are not able to link to information created by external sources. Unfortunately it is beyond the remit of this guideline to recommend that these Patient Decision Aids are updated.
SH	Ipsen Limited	1	FULL	78	26	Incorrect/misleading data: The overall recurrence rate in the meta-analysis by Burger et al, 2013 was 34.5% in the PDD group versus 45.4% in the WLC group and not vice versa.	We have made this correction.
SH	Ipsen Limited	2	FULL	79(?) 97	6 to 9	Though there is no direct comparison between NBI and PDD the evidence of the available data has to be reflected in the recommendation. Relating to the recurrence rate, the PDD recommendation is based on 7 randomized clinical trials, including 1478 patients treated with PDD and 1545 patients treated with WLC. On the other hand, the NBI recommendation is based on a single trial including 76 patients treated with PDD and 72 with WLC. We suggest that this different power of the available clinical data has to be mentioned in the recommendations.	Whilst there was less evidence available on NBI, this evidence was assessed by GRADE as moderate quality, as was the evidence on PDD. Due to the lack of evidence comparing PDD with NBI the GDG were not able to determine which was the most effective. They therefore recommended them both as options. This is documented in the Linking Evidence to Recommendations section in the full guideline.
SH	Ipsen Limited	3	NICE	3	5	Main risk factors (age, smoking, occupational exposure to carcinogens and mutagens) could be highlighted to provide a complete introduction to the disease.	We have added text to the introduction of the NICE version on this.
SH	Ipsen Limited	4	FULL	185	1	Additional cost-effectiveness data: HAL-BLC as an adjunct to WLC was shown to be a dominant strategy over WLC alone when used at initial TURB for patients diagnosed with NMIBC in England and Wales. Improved patient outcomes and cost-savings are expected to offset investment in HAL (hexaminolevulinate) and HAL-related	This paper was identified in the search of the economic literature conducted for the guideline. However, as the paper was available as an abstract only, it was not possible to fully appraise the methodology and thus it was not included in the evidence review.

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						technology. Marteau F. Cost-effectiveness of the optical imaging agent hexaminolevulinate for patients with non-muscle invasive bladder cancer. In: ISPOR 16th Annual European Congress; 2013; Dublin; 2013.	
SH	NHS Choices, Digital Assessment Service	1	FULL &NICE	0General	0General	We welcome the guidance and have no comments on its content.	Thank you
SH	Nottingham University Hospitals NHS trust	1	NICE	10	n/a	NICE guidelines should not inadvertently promote unproven therapies and should not hinder research.	We agree.
SH	Nottingham University Hospitals NHS trust	2	NICE	20	1.4.2 1.4.3	The recommendations 1.4.2 and 1.4.3 taken together imply that neo adjuvant chemotherapy followed by synchronous chemoradiotherapy is standard of care. This is unproven and potentially puts patients at risk of harm from an intensive treatment regimen. There is level A evidence for using 5FU+ Mitomycin combination concurrently with bladder radiotherapy. There is level A evidence for using CMV chemotherapy before surgery or radiotherapy. (ref 1-3). But there is no level A evidence for using chemotherapy before radiotherapy followed by more chemotherapy given concurrently with radiotherapy. I am concerned the NICE guideline is inadvertently promoting an unproven therapy.	The GDG disagree. In the BC2001 study, pre-planned subgroup analysis demonstrated a consistent benefit of chemoradiation irrespective of whether or not the patient received prior neoadjuvant chemotherapy. The GDG therefore consider there is clear evidence to support the sequential use of neoadjuvant chemotherapy followed by chemoradiotherapy. All 3 of the studies you cite were included in the evidence review for this guideline. Only James et al (2012) is referenced directly as the other two trials were included within systematic reviews.

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						This recommendation would not only puts patients at risk of serious harm, but would also seriously impede the need to test such an intensive schedule in a clinical trial References . 1. James ND, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med. 2012 Apr 19;366(16):1477-88 2. Grossman et al. Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer. N Engl J Med 2003; 349:859-866 3.Griffiths et al. International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial. JCO Jun 1, 2011:2135-2137.	
SH	Royal College of General Practitioners	1	FULL	0General	0general	I welcome the opportunity to comment on this comprehensive document. These are strengthened by the direct involvement of 2 people with bladder cancer in the guideline development. It would have been useful to include carer representation.	Patient members of the group contributed their own experiences, and that of their carers to the work of the GDG. Co-incidentally, two members of the GDG had been a carer of a patient with bladder cancer from diagnosis to end of life care.
SH	Royal College of General Practitioners	2	NICE FULL	 7	1.3.20 45-47	" Discharge to primary care people who have had low-risk non-muscle-invasive 46 bladder cancer and who have no recurrence of the bladder cancer within 12 months.". This will need clear surveillance instructions to the person with bladder cancer, their carer and	On discharge, patients will be given a care plan specifying factors that would warrant referral back to secondary care, as part of the Department of Health's National Survivorship Initiative. This is generic to all cancer patients and we do not feel it needs to be specified in

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						their GP. It would useful to maintain a register such as the cervical cytology system to help ensure follow up. Unless a condition is covered by QOF primary care clinical IT systems are poor at ensuring follow up and requires considerable administrative work in primary care and will compete with other unfunded surveillance work and potentially restrict access for other patients with acute illness.	the recommendation. We are not suggesting a call and re-call system as for cervical cancer.
SH	Royal College of General Practitioners	3	NICE FULL	8	1.3.22 1-2	"What are the causative and contributory factors underlying the persistently very low levels of reported patient satisfaction for bladder cancer?" is a key research question recommendation which I support. I think it is also worth looking at surveillance systems in areas where there is success. It would useful to do qualitative research. I suspect that socio economic factors, distance to clinics and continuity of care may be significant factors.	Thank you for this information.
SH	Royal College of Nursing	1	FULL &NICE	0General	0General	This is just to inform you that the feedback I have received from nurses working in this area of health suggests that there are no comments to submit on behalf of the Royal College of Nursing to inform on the consultation of the draft scope of Bladder cancer. Thank you for the opportunity to participate. We look forward to participating at the next stage	Thank you
SH	Royal College of Physicians & Surgeons of Glasgow	1	FULL &NICE	0General	0General	On recommendation, RCPSG asked an expert to review this Guideline. His brief response was that all the recommendations are in line with current literature. He was unable to find any issues.	Thank you

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						If you wish more a more detailed response, please let us know.	
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	1	NICE	11	Table	The WHO performance status table does not include WHO PS 0 or 5 and uses the definition for 0 under 1.	This table has been removed from the guideline.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	2	NICE	13	1.2.3	The enthusiasm for PDD, NBI, urinary biomarkers and cytology will be welcomed by many clinicians. However, the economic and clinical efficacy of these tests are still undergoing evaluation eg within the forthcoming PHOTO trial in the UK, and so the strength of the recommendation should be reconsidered.	Thank you. The wording of the recommendation reflects the strength of the evidence (please see page 6 of the NICE version for further information on the wording of NICE recommendations).
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	3	NICE	14	1.2.6	We feel that the guidelines could suggest clinicians to consider use of a bladder map to record location, size and number of tumours as this can help with a number of aspects of further management eg pathological evaluation, re-resection and follow up.	We would consider recording of intraoperative observations to be a routine part of good clinical practice, and therefore have not made a recommendation on this.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	4	NICE	14 and 16	1.2.8 and 1.3.5	Consideration of further TURBT at 6 weeks should be clarified to apply for those patients with HIGH RISK disease, incomplete resection or imaging and pathological evaluation that do not correlate. It would generally be considered unnecessary to perform re-resection for low risk disease. Recommendation 1.3.5 does emphasise high risk cases only – the guidelines should ensure consistency between these two points.	This comment relates to 3 recommendations (1.2.4 Obtain detrusor muscle during TURBT; 1.2.8 Consider further TURBT within 6 weeks if the first specimen does not include detrusor muscle; 1.3.5 If the first TURBT shows high-risk non-muscle-invasive bladder cancer, offer another TURBT as soon as possible and no later than 6 weeks after the first resection). The aim of these recommendations is to promote a high quality TURBT at the first procedure, to ensure high-quality staging, by repeating the procedure if there is no detrusor muscle, and to ensure

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							high-quality management of people with high-risk disease. The wording of recommendation 1.2.8 allows the MDT to decide if the repeat TURBT to obtain detrusor muscle is appropriate for the individual patient with low or intermediate risk. Whereas recommendation 1.3.5 requires that the TURBT be repeated if high-risk disease is found.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	5	NICE	14	1.2.9 to 1.2.12	In addition to the current recommendations for staging investigations we believe a bone scan is required in all patients with clinical features, including a raised plasma ALP level, consistent with possible bony metastatic involvement that would otherwise be considered for radical therapy, and in any other case where the result would alter management.	No recommendation was made on detecting bone metastases because there was insufficient high quality evidence on techniques looking primarily at bone metastases, and because the GDG felt that the other recommendations made for CT and MRI would likely pick up those people with bone metastases in any event. This was documented in the Linking Evidence to Recommendations section in the full version of the guideline. We would expect that in patients with symptoms, appropriate imaging will be performed, which may include a bone scan.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	6	NICE	14	1.2.11	A CT scan of the thorax is suggested as a test to 'consider'. However, for any patient being considered for radical therapy our experts feel that the recommendation must be made more strongly than this (so change to 'offer'). We believe that the use of radical treatments without this level of certainty that metastatic disease is excluded cannot be justified. We also believe it should be at least 'considered' in all other patients undergoing palliative systemic therapy to allow proper	The use of the word 'consider' reflects the strength of the evidence (please see page 6 of the NICE version for further information on the wording of NICE recommendations). Section 1.2 on diagnosing and staging bladder cancer is not confined to the initial stages of assessment and we would expect

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						evaluation and a baseline for monitoring response.	re-staging to occur as appropriate. Therefore recommendation 1.2.11 for CT thorax remains appropriate and is supported by recommendation 1.7.4 (radiological monitoring for people having first-line chemotherapy for locally advanced or metastatic bladder cancer).
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	7	NICE	14	1.2.12	PET CT is not widely utilised for bladder cancer although some centres in the UK do so in selected cases. The problem with this recommendation is that it places a high resource demand on centres. We are not aware of robust evidence to support the utility of PET in bladder cancer and in particular correlation with pathological lymph node status. We would suggest that this is an area that should be strongly supported as a research priority (and UK investigators are developing studies to do so) but not necessarily encouraged as standard practice at least without specialist uro-radiologist and MDT approval.	The use of the word 'consider' in recommendation 1.2.12 reflects the strength of the evidence (please see page 6 of the NICE version for further information on the wording of NICE recommendations). The GDG did not think that the use of PET-CT was a priority area for research. Finding resources to enable this recommendation to be carried out will be a matter for implementation. The wording of the recommendation also clarifies that PET-CT would be considered for people where radical treatment is being contemplated and there are indeterminate findings on CT or MRI. Implicit in this recommendation is that the decision to use PET-CT would be made by the specialist urology MDT.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	8	NICE	15	1.3.1	The proposed allocation of a risk category within the details to be recorded is useful. However, routine use of risk prediction tools, eg the EORTC calculator, is not widespread. The calculator is based on quite old data and some more recent studies question its current validity. Although we would support its inclusion these potential limitations might be acknowledged and the need for further	Thank you. We are aware of the limitations of risk prediction tools but feel that they should be used as part of the decision making process to improve risk categorisation. We acknowledge the need for further research in this area but it was not prioritised

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						research in this area might be highlighted.	in this guideline.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	9	NICE	16 and 17 and general	1.3.4 and 1.3.8 and general	Both of these points suggest referral to a bladder cancer specialist multidisciplinary team if a patient relapses after intravesical therapies. Our experts felt that all potentially curative treatment decisions should be made in this context (ie widen this to other aspects within the guidelines that are radical in intent.)	The requirement for all radical treatments to be discussed at the specialist MDT is already covered by the Improving Outcomes in Urological Cancers guidance.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	10	NICE	16 and 17	1.3.6 and 1.3.8	We would support the recommendation that a urologist who performs BCG and cystectomy should discuss management in these circumstances. We would suggest going further however and recommending that all high risk disease be discussed at a specialist MDT and that treatment should be managed by a urologist with special interest. Thus for 1.3.8 the patient would already be under the care of the specialist MDT.	Involvement with the specialist urology MDT for people with high-risk disease is part of the Improving Outcomes in Urology guidance and associated peer review measures. We have therefore not specified this in the recommendations as it would be expected to happen.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	11	NICE	18	1.3.10 to 1.3.12	Our experts felt a number of details needed further comment here: 7. Although practice is fairly consistent in the UK we believe that a description of an acceptable standard operation could be made in men and women undergoing radical cystectomy in terms of its extent. 8. No mention is made of who should or should not be a candidate for neobladder 9. Nothing is said about how to manage the bladder neck or prostate prior to a neobladder 10. No mention is made about the role of urethrectomy	NICE guidelines focus on areas of uncertainty and variation in clinical practice. Consequently the issues you have raised were not prioritised for inclusion in the guideline. However, recommendation 1.3.6 does cover discussion of issues around impact on quality of life, body image and sexual and urinary function related to treatment. In addition recommendations 1.1.4 refers to holistic needs assessment which should be carried out after first treatment; and recommendation 1.1.5 covers discussing the impact of treatment on sexual health and body image. Recommendation 1.1.7 offers people opportunities to discuss care with healthcare

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						11. No mention is made about counselling after cystectomy for ED or sexual dysfunction in both men and women 12. No mention is made regarding lymph node dissection and its extent	professionals including those who can provide psychological support.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	12	NICE	19	1.3.20	The recommendation regarding discharge of low risk cases at 12 months is of interest. This will reduce the burden of follow up cystoscopy to patients and the health service and for this reason would be welcome. However, it is a bold change in practice that is not currently in any national or international guidance. In general, not many patients would be expected to come to harm if it is adopted. However, it is likely that some of the inevitable recurrent disease will be of larger volume or multifocal and potentially more difficult to resect if we wait for haematuria before offering cystoscopy. More rarely patients can develop grade progression from low to high risk. We are interested in this change but would propose that it is a research question currently and that the strength of the recommendation should be altered to 'consider' at most. We would not view the current level of available evidence to be acceptable to proscribe longer or more intensive follow up by specialist MDTs/urologists.	The potential benefits of the recommendation for patients with low risk disease result from the reduced burden of cystoscopic follow-up. The GDG balanced this against the potential for harm resulting from a possible small increase in the late detection of disease recurrence and that patients may experience anxiety after discharge from follow-up. The GDG considered that reducing the burden of follow-up (which is associated with anxiety and discomfort of cystoscopy) in this low-risk group strongly outweighs the possible increase in late detection of recurrence. Reduced frequency follow-up was shown to be the most cost-effective strategy in low risk patients. It was substantially cheaper and the strategy was found to be cost-effective. Moreover, significant opportunity costs were identified specifically the opportunity to focus scarce cystoscopy resource on people at higher risk who have the greatest benefit. Given the evidence to support making this recommendation we do not consider that a research recommendation was warranted.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	13	NICE	20 (and page	1.4.2	Neoadjuvant chemotherapy in non-TCC bladder cancer has virtually no evidence to support its use. The key trials (MRC and SWOG) restricted to TCC (or mixed histology that included TCC for the MRC trial). Non-TCC	We agree. Recommendation 1.5.2 only refers to urothelial bladder cancer.

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				10)		bladder cancer should not receive neoadjuvant chemotherapy therefore which we feel should be made explicit here.	
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	14	NICE	20	1.4.3	For muscle invasive TCC a choice of cystectomy or chemoradiotherapy is appropriate advice. However, chemoradiotherapy for other histological types has little data to determine if it is effective. For example in the BC2001 trial 97.8% had TCC and sub-group analyses were not presented for SCC or adenocarcinoma which was also permitted. We would propose, at least, caution and specialist MDT opinion in utilising chemoradiotherapy in pure SCC or adenocarcinoma. Other histological subtypes should not receive it and require specialist MDT review.	We have amended recommendation 1.5.3 to clarify that it only relates to urothelial bladder cancer.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	15	NICE	21	1.4.5	The level of evidence for adjuvant chemotherapy is significantly less strong than for neoadjuvant chemotherapy. The latter should therefore be the expected normal approach. This recommendation needs to have a strong and unambiguous statement that the standard approach to peri-operative chemotherapy should be to offer it in the neoadjuvant setting. The suggestion in the current draft of a restriction of adjuvant treatment to those who were 'not eligible' for neoadjuvant treatment should be clarified by giving examples of where this might come about. These are essentially those cases that are upstaged after radical cystectomy from <T2 N0 disease to T2-	We agree that the evidence for neoadjuvant chemotherapy is stronger than that for adjuvant chemotherapy. Therefore neoadjuvant chemotherapy should be the standard of care (as reflected by the term 'offer' in recommendation 1.5.2. Please see page 6 of the NICE version for further information on the wording of NICE recommendations. Recommendation 1.5.7 is directed to those people who have had cystectomy for NMIBC and were found to have unsuspected muscle invasion or lymph node spread or people who at the time of surgery had inadequate renal function to receive cisplatin.

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						4 and/or N1 where adjuvant chemotherapy should be routinely offered assuming a patient meets the same criteria as for neoadjuvant chemotherapy of being fit for a cisplatin based regimen and having pure or mixed histology TCC.	The GDG debated the wording of recommendation 1.5.3 and 1.5.7 in the light of your comments, and are content that this wording reflects the evidence.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	16	NICE	21	1.4.5	As with our point above for neoadjuvant chemotherapy we feel that adjuvant chemotherapy for non-TCC muscle invasive (T2-4a N0) bladder cancer should be avoided. There may be a case for treatment in selected lymph node positive cases or those with positive surgical margins after specialist MDT review and acknowledging the lack of evidence in this setting.	We have amended recommendation 1.5.7 to clarify that it only relates to urothelial bladder cancer.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	17	NICE	21	1.4.6	Carbogen/nicotinamide is included as a possible radiosensitiser strategy along with mitomycin/5FU. Use of carbogen/nicotinamide does occur in some centres but does not have widespread availability. There are some logistical differences and there are no direct comparisons between these approaches. We strongly support a recommendation for the use of radiosensitisers but the lack of evidence for the optimal approach might be highlighted and again this might be proposed as an area requiring ongoing research activity.	There was evidence to support both treatment approaches, but it was unclear as to which was superior and therefore both have been recommended as treatment options. The GDG have made a research recommendation on p296 of the full version of the guideline.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	18	NICE	22	1.4.9 1.4.10	Use of upper tract imaging every year for five years/annually should be clarified. We presume this would be with ultrasound but this should be defined. CT urogram may also be indicated to check for synchronous upper tract TCC.	There are a number of imaging modalities that could be used to monitor the upper tract including ultrasound, nuclear medicine and CT. No evidence was found to support the use of one modality over another. In addition, CT is already recommended for monitoring of

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							local and distant recurrence and may be used to image the upper tracts. The choice of modality, which could include CT urogram, would also depend on individual patient factors. Therefore the GDG did not specify a modality in the recommendation.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	19	NICE	23	1.5.2	This section suggests cisplatin based chemotherapy should only be given to those with a GFR over 60 mL/min. However specialist bladder cancer oncologists in the UK would commonly give cisplatin with lower GFR levels than this (certainly down to 50 in appropriately selected cases). There is no consensus on an appropriate GFR cut point and it is wrong to suggest 60 (or any other arbitrary level). Our experts believe that the guideline should instead suggest a requirement for 'adequate renal function' to be confirmed but that the precise cut point should be removed. In addition, we believe that the prescriptive list of chemotherapy regimens here was difficult to understand in the sense that the cisplatin/gemcitabine/paclitaxel regimen is based on a negative study that failed to show superiority for its primary endpoint over cisplatin/gemcitabine. It therefore adds cost with no clear evidence for added benefit. We would therefore suggest that the list is removed. If it remains it should be as 'possible examples'. The key focus of this point should be that patients must be offered a cisplatin based combination regimen if they are fit enough to	The GFR level of 60ml/min was taken from the studies in the evidence used to inform this recommendation. Recommendations in NICE guidelines do not substitute for good clinical decision making. However, to acknowledge your point we have added an additional qualifier to this recommendation to allow some flexibility. In developing the guideline the GDG wished to support the use of evidence-based regimens. That a schedule is not commonly used is not a reason to not recommend it. However, in recognition of feedback received from stakeholders we have amended the recommendations to remove the triplet chemotherapy and focus on the 2 more commonly used schedules.

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						receive it.	
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	20	NICE	23 and 24	1.5.3	Following on from our comments on point 1.5.2, again the cut point for GFR is problematic here and our experts do not feel it reflects widespread UK practice by specialist bladder cancer oncologists. We would suggest removing the list of criteria given for use of carboplatin/gemcitabine. In its place we would propose suggesting that this is an appropriate treatment to offer when patients are felt to be unsuitable for cisplatin based chemotherapy based on a holistic assessment by a specialist oncologist that should include consideration of renal function, performance status and co-morbidities. In addition, our experts are aware that some centres in the UK would offer cisplatin based therapy on a split dose basis in patients unsuitable for conventional cisplatin based regimens based on various data (eg Hussain et al, British Journal of Cancer 2004;91, 844–849). We would suggest adding this as an option in addition to carboplatin/gemcitabine.	We have added an additional qualifier about the GFR level to this recommendation to allow some flexibility. We have also amended the recommendation to clarify that it was intended for people who cannot have cisplatin-based chemotherapy. NICE guidelines are not intended to replace clinical judgement. Evidence was available that showed a potential beneficial effect to people with these specific criteria. Hence the GDG included them in their recommendation. The harms may outweigh the benefits in certain people (for example, those with a higher WHO performance status) but this should be established as part of the holistic needs assessment. The GDG were aware of this paper but the evidence was not strong enough to support a change to the recommendations.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	21	NICE	25	1.5.7 and 1.5.8	Our experts felt strongly that the proposed and proscribed regimens here are far too prescriptive and do not reflect the data, expert clinical opinion or routine practice in the UK. No regimen has shown a survival advantage in	The evidence base for second line chemotherapy has been extensively reviewed by the GDG. Recommendation 1.7.6 recommends the use of those schedules with the strongest

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						a randomised clinical trial in the second line setting. Cross trial comparisons of the available data, which are of highly variable quality and with wide variations in patient type, is fundamentally flawed. Audit data of UK practice has shown that paclitaxel as a single agent is amongst the more commonly used regimens in this setting. The British Uro-Oncology Group support its use in their published guidelines. It was also adopted, based on consensus expert opinion, as the control arm within the Bladder Cancer CSG supported PLUTO trial which is currently running in the UK. As we lack comparative data to show any particular regimen being superior then it has the advantage of being relatively non-toxic. Ideally, we would suggest removing any mention of specific regimens or otherwise providing examples of possible options that might include those in point 1.5.7 but would also need to include paclitaxel to be credible.	available evidence. However the quality of this evidence is reflected by the use of the term 'consider' in the recommendation. Please see page 6 of the NICE version for further information on the wording of NICE recommendations. The evidence on single agent paclitaxel was too weak to support making a recommendation. However in light of feedback received from stakeholders the GDG have deleted the recommendation on single-agent chemotherapy for second line.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	22	NICE	26	1.5.15	There is limited evidence for the efficacy of embolisation for intractable bleeding. Some case series indicate sporadic benefit. In general we would suggest that radiotherapy is preferred as a first line approach. Embolisation, chemotherapy, surgery or BSC should all be considered in selected cases as a subsequent intervention. Such cases require specialist MDT review to facilitate an individualised approach to patient care.	We agree that the evidence base for the treatment of intractable bleeding is weak and insufficient to recommend one treatment over another. This is why we have used the word 'consider' in recommendation 1.7.15 and made recommendation 1.7.16. We included recommendation 1.7.14 that the cause of intractable bleeding should be evaluated with the local urology team as the GDG were concerned that not all patients

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							with intractable bleeding are currently discussed with a urology team or fully evaluated.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	23	NICE	27	1.5.17	We would suggest involvement of both the urology and oncology team as two of the treatments under consideration are administered by oncologists.	We believe that the responsibility for the evaluation should lie with the local urology team. However they may call on oncology or palliative care to provide best supportive care (as detailed in recommendation 1.7.18).
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	24	FULL &NICE	0General	0General	Throughout both documents we would like to see strong recommendations in each clinical setting that all patients should be offered access to a clinical trial if available as a standard approach when discussing options for management.	We are not able to make this recommendation as the guideline did not look at a review question on this issue. However we have added text to the background in chapter 2 of the full guideline to stress the importance of offering people the opportunity to participate in clinical trials and research. Unfortunately we are not able to include the same text in the NICE version because this only contains the recommendations and does not include background text.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	25	FULL &NICE	0General	0General	The draft guidelines mention involvement or referral to a 'bladder cancer specialist' and a bladder cancer specialist multidisciplinary team. It would be helpful to have this clarified throughout. Does it mean simply discussion at an MDT or should they actually fall under the care of a specialist bladder cancer urologist or oncologist? Our experts take the view that patients with bladder cancer should be under the care of a specialist bladder cancer urologist or oncologist, working within a specialist MDT, in virtually all of the guidance presented here. This is the case in many high quality centres. It would be helpful in bringing up standards in other centres to make this a target to aspire to.	We have carefully considered, for each recommendation, the appropriate level of MDT discussion or referral according to the risk of recurrence, progression or death. We have standardised the wording of the recommendations to reflect this and to ensure that we are clear when discussion with the specialist MDT is appropriate or when the person's care should be transferred.

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SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	26	FULL &NICE	0General	0General	A significant concern to the bladder cancer community in the UK is the designation of TURBT as a 'definitive treatment' in those with muscle invasive disease when it is primarily a diagnostic test in these circumstances. This creates the very unhelpful situation of removing any drive to get to definitive treatment in terms of waiting time initiatives. We would like to see these guidelines attempt to address this.	We acknowledge this concern. However the recommendations made are clear on when TURBT should be used. There are also clear recommendations on referral for patients with high-risk non-muscle-invasive and muscle invasive bladder cancer, which we hope will change practice.
SH	Royal College of Physicians /ACP/ NCRI Bladder Cancer Clinical Studies Group	27	FULL &NICE	0General	0General	The draft guidelines claim to cover adenocarcinoma, squamous cell carcinoma and small cell carcinoma (page 4 of the NICE version) in addition to urothelial carcinoma. The evidence base for care of these less common histologies (if pure) is very limited. Much of the recommendations made here are based on TCC and are not appropriate for extrapolation. Such patients require central specialist MDT review to guide individualised management by specialist bladder cancer urologists and oncologists. We think this needs clarity within the document.	The scope of the guideline included people with urothelial carcinoma, adenocarcinoma, squamous-cell carcinoma and small-cell carcinoma. The evidence searches looked for evidence relating to all of these types of bladder cancer but there was insufficient evidence to enable recommendations to be made for the management of adenocarcinoma, squamous-cell carcinoma and small-cell carcinoma. We have added text to the NICE introduction to clarify this. We have also amended recommendation 1.5.1 to specifically mention these rarer types of bladder cancer, to ensure they are reviewed by the specialist urology MDT. This should help to ensure they are managed appropriately.
SH	South Wales Cancer Network	1	FULL &NICE	0General	0General	We have no comments to make on the final draft.	Thank you
SH	The Royal College of Pathologists	1	NICE FULL	13 7	1.2.2 15	Explain that "Muscle-invasive bladder cancer" throughout the rest of the document (and associated documents) refers to muscularis propria/detrusor muscle-invasive bladder	We are confident that the urology clinical community will understand that 'muscle-invasive bladder cancer' refers to invasion of the muscularis propria.

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						cancer to distinguish this from cancer invading muscularis mucosae only	
SH	The Royal College of Pathologists	2	NICE FULL	15 7	1.3.1 20	Either within the bullet points beginning line 20 or as a separate main bullet point: "Use of the Royal College of Pathologists Dataset on Tumours of the Urinary Collecting System is encouraged for recording of pathological data" [published on RCPath website April 2013] see http://www.rcpath.org/publications-media/publications/datasets/urinary-collecting-system.htm	Specifying how data is collected is outside the scope of this guideline.
SH	The Royal College of Pathologists	3	FULL	26	9	Explain that transitional cell carcinoma (TCC) and urothelial carcinoma are synonymous. [Urothelial carcinoma is the term recommended by the WHO but TCC is in common usage]	We have changed transitional cell carcinoma to 'urothelial carcinoma'.
SH	The Royal College of Pathologists	4	FULL	32	19	Liverpool and Manchester are in the North West, not in the North East	We have amended this text
SH	The Royal College of Pathologists	5	FULL	109	Research points 1 and 2 (in green)	The recommendation for further research into the role of biomarkers (especially FISH, NMP22 and ImmunoCyt) in the diagnosis and follow-up of bladder cancer (in the context of clinical trials) is supported. Incorporation of biomarkers has potential for a reduction in the frequency of cystoscopy, but only if appropriate further evidence becomes available.	Thank you
SH	The Royal College of Pathologists	6	NICE	9	Bottom of page	(referring both to non-muscle invasive and muscle invasive tumours in preceding sections) Use of the Royal College of Pathologists Dataset on Tumours of the Urinary Collecting System is encouraged for recording of pathological data [published on RCPath	Thank you for this information.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						website April 2013] see http://www.rcpath.org/publications-media/publications/datasets/urinary-collecting-system.htm	
SH	The Royal College of Pathologists	7	NICE	13	1.2.1	The recommendation given that clinical use of biomarkers should be considered only in the context of clinical trails is endorsed	Thank you
SH	The Royal College of Pathologists	8	NICE	30 and 31	Section 2.4	The need for further research into predictive markers for response to radiotherapy is supported	Thank you
SH	The Royal College of Pathologists	9	zEVIDENCE REVIEW	6	13	Change "Prostrate" to "Prostate"	We have made this correction
SH	The Royal College of Pathologists	10	zEVIDENCE REVIEW	25	Column headed: "Outcome Measures", para 3, line 1	Change "genitor-urinary" to "genito-urinary"	We have made this correction
SH	The Royal College of Pathologists	11	zEVIDENCE REVIEW	357	Last line in column headed: "Intervention"	Change "Suitabel" to "Suitable"	We have made this correction.
SH	The Royal College of Pathologists	12	FULL &NICE	0General	0General	Congratulations on your excellent work on this huge task!	Thank you

These organisations were approached but did not respond:

Abertawe Bro Morgannwg University Health Board

ADDEPT

Aintree University Hospital NHS Foundation Trust

Alere Ltd

Allergan Ltd UK

Allocate Software PLC

American Medical Systems Inc.

American Medical Systems UK Ltd

Amgen UK

Association of Anaesthetists of Great Britain and Ireland

Association of British Insurers

Astrazeneca UK Ltd

Barnsley Hospital NHS Foundation Trust

Belfast Health and Social Care Trust

Bladder and Bowel Foundation

Boehringer Ingelheim

British Association for Cytopathology

British Dietetic Association

British Medical Association

British Medical Journal

British Medical Ultrasound Society

British National Formulary

British Nuclear Cardiology Society

British Nuclear Medicine Society

British Pain Society

British Psychological Society

British Red Cross

British Society of Interventional Radiology

Caduceus Support Limited

Cambridge University Hospitals NHS Foundation Trust

Camden Carers Centre

Camden Link

Cancer Commissioning Team

Cancer National Specialist Advisory Group

Cancer Phytotherapy Service

Cancer Research UK

Cancer52

Capsulation PPS

Care Not Killing Alliance

Care Quality Commission

Central Manchester and Manchester Children's Hospital NHS Trust

Cepheid Uk Ltd

Chartered Physiotherapists Promoting Continence

Chartered Society of Physiotherapy

Cheshire and Merseyside SCN

Clarity Informatics Ltd

CLIC Sargent

Coloplast Limited

Covidien Ltd.

Croydon Clinical Commissioning Group

Croydon Health Services NHS Trust

Croydon University Hospital

Cumbria Partnership NHS Foundation Trust

CWHHE Collaborative CCGs

Deltex Medical

Department of Health

Department of Health, Social Services and Public Safety - Northern Ireland

East and North Hertfordshire NHS Trust

East Kent Hospitals University NHS Foundation Trust

Economic and Social Research Council

Ethical Medicines Industry Group

False Allegations Support Organisation

Five Boroughs Partnership NHS Trust

GfK Bridgehead

GP update / Red Whale

Greater Manchester, Lancashire and South Cumbria Strategic Clinical Network

Health and Care Professions Council

Health and Social Care Information Centre

Healthcare Improvement Scotland

Healthcare Infection Society

Healthcare Quality Improvement Partnership

Healthwatch East Sussex

Help Adolescents With Cancer

Herts Valleys Clinical Commissioning Group

Hinchingbrooke Healthcare NHS Trust

Hindu Council UK

Hockley Medical Practice

Humber NHS Foundation Trust

Independent Healthcare Advisory Services

Institute of Biomedical Science

Integrity Care Services Ltd.

Intuitive Surgical

Isabel Hospice

Johnson & Johnson Medical Ltd

King's College Hospital NHS Foundation Trust

Lancashire Care NHS Foundation Trust

Leeds Teaching Hospitals NHS Trust

Local Government Association

London Borough of Islington

London Cancer

London cancer alliance

Luton and Dunstable Hospital NHS Trust

MacGregor Healthcare

Macmillan Cancer Support

medical directorate DMS

Medicines and Healthcare products Regulatory Agency

Merck Sharp & Dohme UK Ltd

Mid Cheshire Hospitals NHS Trust

Mid Yorkshire Hospitals NHS Trust

Midlands Centre for Spinal Injuries

Milton Keynes Hospital NHS Foundation Trust

Ministry of Defence (MOD)

Monash Health

National Association of Primary Care

National Cancer Action Team

National Cancer Intelligence Network

National Clinical Guideline Centre

National Collaborating Centre for Cancer

National Collaborating Centre for Mental Health

National Collaborating Centre for Women's and Children's Health

National Council for Palliative Care

National Deaf Children's Society

National Institute for Health Research Health Technology Assessment Programme

National Institute for Health Research

National Patient Safety Agency

NHS Barnsley Clinical Commissioning Group

NHS Coastal West Sussex CCG

NHS Connecting for Health

NHS County Durham and Darlington

NHS Cumbria Clinical Commissioning Group

NHS England

NHS Hardwick CCG

NHS Health at Work

NHS Improvement

NHS Medway Clinical Commissioning Group

NHS Plus

NHS Sheffield

NHS South Cheshire CCG

NHS Wakefield CCG

NHS Warwickshire North CCG

NHS West Cheshire CCG

Nordic Pharma

Norfolk and Suffolk Palliative Care Academy

North Essex Partnership Foundation Trust

North of England Commissioning Support

North West London Hospitals NHS Trust

Northern Health and Social Care Trust

Nottingham City Council

Nova Healthcare

Nursing and Midwifery Council

Oxford Health NHS Foundation Trust

Oxfordshire Clinical Commissioning Group

Parenteral and Enteral Nutrition Group

Partneriaeth Prifysgol Abertawe

Pathfinders Specialist and Complex Care

Pelvic Obstetric and Gynaecological Physiotherapy

Pfizer

Pierre Fabre Ltd

PrescQIPP NHS Programme

Primary Care Pharmacists Association

Primrose Bank Medical Centre

PromoCon

ProStrakan Group

Public Health Agency for Northern Ireland

Public Health England

Queen Elizabeth Hospital King's Lynn NHS Trust

Queen's University Belfast

Randox Laboratories Limited

Rarer Cancers Foundation

Roche Diagnostics

Roche Products

Royal College of Anaesthetists

Royal College of General Practitioners in Wales

Royal College of Midwives

Royal College of Obstetricians and Gynaecologists

Royal College of Paediatrics and Child Health

Royal College of Psychiatrists

Royal College of Radiologists

Royal College of Speech and Language Therapists

Royal College of Surgeons of Edinburgh

Royal College of Surgeons of England

Royal Cornwall Hospital NHS Trust

Royal Derby Hospital

Royal Free London NHS Foundation Trust

Royal Liverpool and Broadgreen University Hospitals NHS Trust

Royal Pharmaceutical Society

Royal Society of Medicine

Royal Surrey County Hospital NHS Trust

Salford Royal NHS Foundation Trust

Sandoz Ltd

Sanofi

Scottish Intercollegiate Guidelines Network

Sheffield Children's Hospital

Sheffield Teaching Hospitals NHS Foundation Trust

Social Care Institute for Excellence

Society and College of Radiographers

South East Coast Cancer Strategic Clinical Network

South Eastern Health and Social Care Trust

South London & Maudsley NHS Trust

South Tees Hospitals NHS Trust

South West Yorkshire Partnership NHS Foundation Trust

Southern Health & Social Care Trust

Southport and Ormskirk Hospital NHS Trust

Spectranetics Corporation

St Mary's Hospital

Staffordshire and Stoke on Trent Partnership NHS Trust

Stockport Clinical Commissioning Group

Tameside Hospital NHS Foundation Trust

Tenovus The Cancer Charity

Teva UK

The African Eye Trust

The Institute of Cancer Research

The Patients Association

The Urology Foundation

UCL Partners

UHS NHS Foundation Trust

UK National Screening Committee

United Lincolnshire Hospitals NHS

University Hospital Birmingham NHS Foundation Trust

University Hospital Southampton NHS Foundation Trust

University Hospitals Birmingham

Urostomy Association

Velindre NHS Trust

Walsall Local Involvement Network

Welsh Government

Welsh Scientific Advisory Committee

West Suffolk Hospital NHS Trust

Western Health and Social Care Trust

Western Sussex Hospitals NHS Trust

Westminster Local Involvement Network

Wigan Borough Clinical Commissioning Group

Wirral University Teaching Hospital NHS Foundation Trust

York Hospitals NHS Foundation Trust

Yorkshire and Humber Strategic Clinical Network