National Institute for Health and Care Excellence

IP839/2 Focal therapy using high-intensity focused ultrasound for localised prostate cancer

IPAC date: 12th January 2023

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1	Consultee 1 Prostate Cancer UK	1.5	Prostate Cancer UK would be keen to understand more about the use of real-world data within its recommendations and guidance. Specifically in this instance why the current HEAT registry and the subsequent propensity matched scoring analysis (Reddy et al 2022) based on this registry are insufficient for a full recommendation by the committee. We would appreciate more clarity on whether it is in fact the uncertainty from propensity matched scoring which makes it difficult to estimate effectiveness, or is it that the underlying data within the registry that results in the uncertainty? For example, insufficient patient numbers, insufficient follow up, differences in HIFU procedure etc. With these questions in mind we would appreciate a more in depth clarification around the acceptable requirements and limits of the recommended registry data. Specifically, we would like clarity on NICE's requirements for propensity matched scoring for HIFU regarding:	Thank you for your comment. The committee considered the HEAT registry (Reddy et al 2022) alongside other evidence included in the overview in their deliberations. The committee would like to see more data on long term follow up and need for subsequent interventions. The committee felt the evidence of efficacy was limited predominantly due to the duration of follow up. The Reddy et al. 2022 study had a median FU of 32 months for most of the population with only a subset of patients been followed up for 5 years. There was also a significant re-intervention rate. Also, registry data was stated first in section 1.5 to emphasise its importance in further research, *"Further research could include registry data or randomised trials. It should include details of patient selection, including size and*

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			• Years of follow up • Number of patients • Number of events (progression and or mortality) • Standardization of prognostic factors between comparison arms	*classification of tumour, technique used and long-term outcomes including quality of life."*
2	Consultee 2	Outcome measures	The oncological, functional and quality of life related outcomes proposed in the prostate cancer core outcomes set (COS) are intended to be collected in routine audit of institutions implementing/using HIFU - an intervention which the COS covers. This is very encouraging as it indicates that the outcomes regraded to be most important by key stakeholders will be collected. It would be helpful for raising awareness of the existence of a prostate cancer COS if the study team could communicate their awareness of this and demonstrate that they are collecting the COS - and to justify if there are any core outcomes they do not indent to collect, and lastly to justify any deviations from the recommended definitions and tools. The COS referred to were developed for effectiveness trials and extended to observational studies, audits and routine data collection - references below. Original COS for effectiveness trials: MacLennan, S., Williamson, P. R., Bekema, H., Campbell, M., Ramsay, C., N'Dow, J., MacLennan, S., Vale, L., Dahm, P., Mottet, N., Lam, T., & COMPACTERS Study Group (2017). A core outcome set for localised prostate cancer	Thank you for your comment. 'Improvement in quality of life' is one of the key efficacy outcomes and the committee supports the use of COS as part of the quality-of-life assessment.

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			effectiveness trials. BJU international, 120(5B), E64–E79. https://doi.org/10.1111/bju.13854 Updated version, with extension to audits and routine data and recommended definitions: Beyer, K., Moris, L., Lardas, M., Omar, M. I., Healey, J., Tripathee, S., Gandaglia, G., Venderbos, L., Vradi, E., van den Broeck, T., Willemse, P. P., Antunes-Lopes, T., Pacheco-Figueiredo, L., Monagas, S., Esperto, F., Flaherty, S., Devecseri, Z., Lam, T., Williamson, P. R., Heer, R., … PIONEER Consortium (2022). Updating and Integrating Core Outcome Sets for Localised, Locally Advanced, Metastatic, and Nonmetastatic Castration-resistant Prostate Cancer: An Update from the PIONEER Consortium. European urology, 81(5), 503–514. https://doi.org/10.1016/j.eururo.2022.01.042 Recommended PROMs: Ratti, M. M., Gandaglia, G., Alleva, E., Leardini, L., Sisca, E. S., Derevianko, A., Furnari, F., Mazzoleni Ferracini, S., Beyer, K., Moss, C., Pellegrino, F., Sorce, G., Barletta, F., Scuderi, S., Omar, M. I., MacLennan, S., Williamson, P. R., Zong, J., MacLennan, S. J., Mottet, N., … PIONEER Consortium (2022). Standardising the Assessment of Patient-reported Outcome Measures in Localised Prostate Cancer. A Systematic Review. European urology oncology, 5(2), 153–163. https://doi.org/10.1016/j.euo.2021.10.004	

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3	Consultee 3	Procedure description	We need to state here that prostate cancer is well known to be multifocal and focal therapy is intended to only ablate one area considered the "index" lesion. Unlike radical whole gland therapy it does not treat other areas outside this index area.	Thank you for your comment. This procedure is for localised prostate cancer as stated in the title. Also, Section 2.3 describes the intention for this procedure is to treat localised lesion.
4	Consultee 3	1.1	Absolute agree with this statement- there is so far no direct comparative data on efficacy for meaningful cancer outcomes - focal therapy and HIFU should remain under the audit/research/governance umbrella Modern prognostic estimation and treatment benefit models would suggest that men in the disease range FT sits in may not often benefit greatly from any intervention. Thus to truly establish FT place, this needs head to head studies in cancers known to have lethality risks with the standard of care	Thank you for your comment.
5	Consultee 3	1.1	I think its important to state upfront that clinicians and hospitals are not obliged to offer HIFU FT routinely to patients based on these updated recommendations.	Thank you for your comment. The meaning of 'special arrangements' is described here: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/interventional-procedures-guidance/recommendations This information can be found via the link in section 1.1.
6	Consultee 3	1.2	Shared decision making should include options for non-treatment as well as radical whole gland therapy.	Thank you for your comment. Section 1.2 has been changed to:

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			This is important as many men offered FT have disease which can often safely be managed by surveillance. Suggest include a statement to use NICE NG131 recommendations on options available for each CPG risk criteria when talking about shared decision making and in the MDT discussion Outcomes here are safety and complications? not cancer control outcomes?	*"Give people (and their families and carers as appropriate) clear written information to support shared decision making, including NICE's information for the public,* ***and use NG131 recommendations on treatment options for information and decision support."*** Section 3.2 specifies the key efficacy outcomes to be: recurrence-free survival, metastasis-free survival, improvement in quality of life, and need for subsequent intervention and overall survival.
7	Consultee 3	2.1	Prostate cancer does not cause the prostate to enlarge- this is not based on fact. It also very rarely or never is the cause of urination problems - https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-022-02453-7 suggest delete the rest and keep "localised prostate cancer...	Thank you for your comment. To be consistent with NICE guideline, section 2.1 has been changed to *"****Prostate cancer can cause some lower urinary tract symptoms (LUTS) such as frequency, urgency, hesitancy, terminal dribbling, and overactive bladder.*** *Localised prostate cancer is confined to the prostate and has not spread to nearby tissues or to other parts of the body."*
8	Consultee 3	2.2	Reference the specific treatment and management options recommendations from NG131 by risk group- this then makes this document in line with other NICE guidance	Thank you for your comment. NG131 has been referenced in section 2.2: *"****NICE's guideline on prostate cancer (NG131) describes its diagnosis and management…****"*
9	Consultee 3	2.2	As before specify that treatment is given to the index or the tumour area though to be most prominent , it does not treat other areas of the prostate that may also harbour smaller tumours - it	Thank you for your comment. The scope of this procedure is for localised prostate cancer. Also, section 2.2 stated that

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			also cannot treat tumors that MRI scans cannot see	decisions on treatment are based on imaging, tumour staging, risk assessment, and prostate-specific antigen levels.
10	Consultee 3	3.2	what about cancer specific survival ? overall survival is a factor of other co-morbidity and like all procedures men selected for FT are usually fitter than men who go onto non surgical procedures like radiotherapy- is OS therefore a good reflection of FT efficacy? esp as the disease range suitable for FT is limited	Thank you for your comment. 'Overall survival' has been placed at the end of the key efficacy outcomes in section 3.2, *"The professional experts and the committee considered the key efficacy outcomes to be: recurrence-free survival, metastasis-free survival, improvement in quality of life, and need for subsequent intervention* ***and overall survival****."*
11	Consultee 4 Patient	General	It may interest you to refer to my attached book Heart-rending and Horrendous, which deals with the consequences of my unhappy experience with HIFU. I would prefer to bring this book to your attention prior to publication of your report than afterwards.	Thank you for your comment. The committee welcomes hearing from patients who have had this procedure and considered your experience and views in their deliberations.
12	Consultee 5 Representative of company	1.1	Our client's position is that the evidence demonstrates that: • Special arrangements are no longer necessary for either safety or efficacy reasons; the guidance should allow for normal or "standard" arrangements to apply • The increased requirements associated with special arrangements are obstructing access to HIFU therapy for many patients who could benefit from it	Thank you for your comment. The committee considered that more evidence is needed on the efficacy of the procedure before it recommends that it can be used with standard arrangements. As outlined in the definition of Special arrangements, the emphasis is on the need for informed consent and for clinicians using these procedures to collect data, either by audit or

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			• Treatment providers in many locations are failing to achieve the cost benefits that would accrue from offering HIFU therapy to appropriate patients.	research. The requirement for local or national audit, especially for interventional procedures that are not considered the standard of care and there is remaining uncertainty around their safety and efficacy, is considered best practice in most surgical specialities in the NHS, especially in oncology and it shouldn't hinder the use of the procedure. Moreover, according to the definition of Special arrangements, there is no direct implication whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
13	Consultee 5 Representative of company	1.1	Special arrangements are recommended for use when there are "significant uncertainties in the evidence on efficacy or safety, or an inadequate quantity of evidence". This was undoubtedly the position in 2005 and 2008 when NICE first published guidance on the use of focal therapy using HIFU for localised prostate cancer. It is not the case now. There is now also a considerable volume of evidence which confirms efficacy, including 20 studies which demonstrate positive oncological outcome. The consultation document sets out that NICE had conducted a "rapid review of the published literature, including 3 systematic reviews, 2 registry analyses, 1 propensity score weighted study, 1 retrospective case series, and 1 retrospective cohort study". We have noted the evidence presented in the summary of key	Thank you for your comment. The guidance [IPG118] published by NICE in 2005 and 2008 refers to 2 different procedures – whole and partial prostate HIFU. The committee considers the quality and quantity of published peer-reviewed evidence on safety and efficacy when it drafts the recommendations. For this procedure, the committee considered that more evidence was needed on patient selection and long-term outcomes, including quality of life, before it recommends that it can be used with standard arrangements. It is not just about the volume of the evidence but the quality, Especially the point

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			evidence section (pages 18 to 45) in the interventional procedures overview, and the additional studies listed in the appendix to the overview. Furthermore, in consultation submissions from our client and from professional experts, IPAC will have seen reference to numerous studies and data sources. IPAC members will no doubt have considered carefully the results of those studies, particularly via the summary of key evidence in the interventional procedures overview, but for ease we set out some selected conclusions: "Focal HIFU for PCa is a feasible therapeutic strategy with acceptable survival and oncological results and a reduction in the 5 year retreatment rates over the last decade" [Armando Stabile; BJU Int; 2019] "In patients with non-metastatic low- intermediate prostate cancer, oncological outcomes over 8 years were similar between focal therapy and radical prostatectomy" [Taimur T. Shah; Prostate Cancer and Prostatic Diseases: December 2020] "Focal HIFU in carefully selected patients with clinically significant prostate cancer, with six and three of ten patients having respectively intermediate and high risk cancer, has good cancer control in the medium term" [Deepika Reddy; EAU; 2022] "Metastasis free, cancer specific and overall survival at 5 year was 98%, 100% and 99% respectively. Among patients who returned validated questionnaires 98% achieved	from the Overview that: there was limited comparative evidence in the literature. Or the point that there was limited long term follow-up from only a subset of patients.

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			complete pad free urinary continence and none required more than 1 pad. Limitations include the lack of long term follow up. Focal therapy for select patients with clinical significant nonmetastatic prostate cancer is effective in the medium term and has a low probability of side effects" [Stephanie Guillaumier; EAU; 2016] "Short term results of focal high intensity focused ultrasound indicate safety, excellent potency and continence preservation, and adequate short-term prostate cancer control. Radical treatment was avoided in 91% of men at 2 years. Men with bilateral prostate cancer at diagnosis have increased risk for Grade Group 2 or greater recurrence. To our knowledge, this is the initial and largest United States series of focal high intensity focused ultrasound as primary treatment for prostate cancer" [Andre Luis Abreu; JU-20-167; July 2020] Our client accepts that there is reference to the need for further study, and/ or long-term follow-up (although one such reference is from 2016 since when further studies have been conducted). We deal with that issue below. Otherwise, whilst these are selected conclusions, our client's position is that they are a fair representation of conclusions from all studies. The supporting data are set out in detail in the summary of key evidence in the interventional procedures overview.	
14	Consultee 5	1.1	NICE procedure suggests that the recommendation for special arrangements is also made where "the procedure is considered to be	Thank you for your comment.

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	Representative of company		emerging practice in the NHS". That clearly does not apply in these circumstances; in responses to the consultation question on how innovative/ novel HIFU treatment is considered to be, all professional experts (without exception) stated that "Established practice and no longer new" best describes the HIFU procedure. Experts describe having used HIFU for many years (the longest since 2005; another for over 15 years; two for more than 10 years), and there is reference to use of the procedure multiple times each month. Most significantly, it is clear from the professional experts' comments that HIFU treatment fills an important gap between active surveillance, which can represent under-treatment of, e.g., medium risk non-metastatic prostate cancer, and radical prostatectomy, which can represent over-treatment, and which carries high (and for many men, unacceptable) risks of side-effects.	A recommendation for 'Special arrangements' means that there are uncertainties about whether a procedure is safe and effective. In this case, the committee considered that more evidence was needed on patient selection and long-term outcomes, including quality of life. A special arrangements recommendation places emphasis on the need for informed consent. This includes both the patient (or carer) and senior medical staff, such as the clinical governance lead in their trust. Clinicians using these procedures should collect data, either by audit or research. Please note that the NG131 does not consider HIFU as standard practice. Other recent international guidelines such as the 2022 German S3 Evidence-Based Guidelines on Focal Therapy in Localized Prostate Cancer: The First Evidence-Based Guidelines on Focal Therapy or the 2018 European Association of Urology published Focal Therapy in Primary Localised Prostate Cancer: The European Association of Urology Position also do not consider HIFU as the standard of care. The experts also noted that there is variability on the level of acceptance for this procedure across the NHS. This is also reflected in the consultation comments the committee received. Few experts also noted in their responses that the efficacy of the procedure, especially in the long-term, is still unknown. Although the experts pointed out that some NHS centres have been performing the procedure for a number of years

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				they also pointed out that there is still controversy in 2 main areas, the effect that HIFU may have: -on overtreating patients with low risk cancer, who might otherwise be managed with active surveillance until and unless their disease progresses and radical treatment is indicated. -on undertreating men with higher risk disease, who should otherwise have radical treatment
15	Consultee 5 Representative of company	1.1	The case for standard arrangements to apply For a procedure to be recommended for use with standard arrangements for clinical governance, consent and audit, NICE procedure requires that the evidence should be adequate in the following respects: • It should be valid, relevant and of good quality • It should be available in sufficient quantities for the committee to make a positive decision • It should be sufficiently consistent in nature • It should show benefits within an appropriate time of the procedure (short- or long- term efficacy) • It should be shown that the frequency and severity of adverse effects of the procedure are similar to, or less than, those of any comparable and established procedures. Our client submits that the evidence presented to IPAC on the efficacy of focal therapy using HIFU for localised prostate cancer meets, or more than meets, those criteria.	Thank you for your comment. The committee considered that more evidence was needed on patient selection and long-term outcomes, including quality of life, before it recommends that it can be used with standard arrangements.
16	Consultee 5	1.1	Our client is aware that IPAC's role in finalising guidance is to consider only safety and efficacy.	Thank you for your comment.

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	Representative of company		We nevertheless include here some further points which we hope it is agreed are relevant to IPAC's decision making, and we therefore request that they are at least noted as part of IPAC's deliberations: HIFU is not currently widely available across the UK, but only in a limited number of expert centres. Anecdotal evidence from professional experts is that some obstacles to availability/ referral arise from a lack of knowledge about, or trust in, the procedure. Our client suggests that this negative perception results, at least in part, from the fact that HIFU remains, after many years and despite a large volume of outcomes data, subject to special arrangements. The requirement to comply with special arrangements represents a disincentive for many clinicians because of time and cost; it also carries with it the implication that the treatment is experimental and therefore presents additional risk for patients. As shown above, that is not an accurate reflection of the evidence, but it means that many men will be unnecessarily deprived of effective, cancer-controlling, treatment (and put at greater risk), or alternatively subjected to radical treatment with the strong likelihood of debilitating side-effects (including, in some instances, adverse psychological outcomes). Some professional experts have called for additional research, including (prospective) randomised controlled trials, and we are aware (as detailed in the interventional procedures overview) that some trials are planned or ongoing. Two experts have pointed out, however, that	The guidance states that further research could include registry data. Cost-effectiveness is not part of the remit of the IP Programme. There are several ongoing randomised controlled trials, which are listed in the overview. The guidance may be updated when relevant new research is published. Please see also our response to comment 12 on the definition of Special arrangements and the impact on commissioning decisions or the requirement for audit data. Existing evidence is only one of the parameters considered by committee not the only one.

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			multiple previous attempts to conduct RCTs have been shown not to be feasible because of failed recruitment. The evidence is that where men are randomized to active surveillance or radical treatment or focal therapy (HIFU), those participating in the trial who are allocated to standard treatment have withdrawn consent and requested treatment with HIFU. This conduct demonstrates the lack of equivalence or comparability of standard treatments to HIFU therapy, as well as giving a strong indication that future attempts at RCTs may not produce the expected evidence. A decision by IPAC to maintain guidance that focal therapy using HIFU for localised prostate cancer should be subject to special arrangements would be inconsistent with the approach taken for other comparable procedures. For example, in 2005, guidance was issued for low dose rate brachytherapy for localised prostate cancer (IPG132). Use of the treatment was recommended subject to normal arrangements for consent, audit and clinical governance, despite evidence on safety and efficacy being available only for the short- to medium- term. The evidence relied on included publications with large patient cohorts, and there were two failed RCTs. Evidence relating to HIFU would appear to face an almost identical scenario: there are several publications with large patient cohorts (the most recent with 1379 patients) and two failed RCTs. It is impossible therefore to understand why a different conclusion has been reached and different requirements imposed.	

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			In the current economic and healthcare climate, it would be wrong to ignore the cost/benefit advantages of HIFU treatment. The professional experts who responded to the consultation attempted to place some figures on the cost aspects of treatment. Our client submits that there are two vitally important cost considerations to take into account: o HIFU therapy is almost always delivered as a day case, with shortened recovery time. This is a significant advantage over standard treatments which require a hospital stay, with attendant resourcing issues; o The reduced likelihood of complications, especially long-term complications, must be associated with reduced long-term costs exposure. Our client is grateful to you and to members of IPAC for considering our client's position as set out in this letter. For all the reasons expressed above, our client submits that IPAC's decision, and the guidance published, should reflect the advances made in focal therapy using HIFU for localised prostate cancer, and, reasonably, should recommend that this treatment can now be made available under normal/ standard arrangements.	

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