National Institute for Health and Care Excellence

IP1020/2 Irreversible electroporation for treating prostate cancer

IPAC date: 10th November 2022

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 on behalf of the UK Focal Therapy User Group Professional organisation	**General, 3.1**	"NICE Consultation on Focal IRE/Nanoknife™ Ablation for Prostate Cancer – Response from UK Focal Therapy User Group (a group of urologists conducting focal therapy in clinical care and within research) We're grateful for the opportunity to respond to this timely review of NICE guidance. We would argue the evidence base has advanced significantly since the last review in 2016 and supports a move to a 'special arrangements' provision. We believe the points below specifically support such a move. 1. The state of the focal IRE evidence base at present is broadly equivalent to other prostate treatments that are currently on special arrangements. 2. We would respectfully disagree with conclusion 3.4 given that the larger series reporting oncological outcomes [1,2] included were based on diagnostic workup with multiparametric MRI and modern biopsy techniques as well as the use of PSMA PET CT when indicated.	Thank you for your comment. The main recommendation has been changed from 'research' to 'special arrangements', and a rationale section 'why the committee made these recommendations' has been added. Section 3.4 has been renumbered as section 3.5 and "the published evidence does not reflect this change in practice" has been removed. Section 1.2 has been renumbered as section 1.4. 'preferably' was used and extra wording has been added *"Further research should preferably be randomised controlled trials with an appropriate comparator.* ***Further research could also include analysis of registry data or research databases****..."*

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			3. Pair matched data versus radical surgery shows the improved functional outcomes associated with the more established ablation modalities [3]. 4. Published evidence this year shows equivalent outcomes for radical surgery after IRE to primary prostatectomy [4]. 5. We would argue the safety profile of focal IRE is well established from the data available. The uncertainty over long term oncological outcomes is less meaningful if the consequences of radical treatment for cases failing primary focal treatment are equivalent to those of primary radical treatment. 6. The impediments to recruitment in randomised prostate cancer treatment trials are significant and have resulted in the failure of multiple previous projects. 7. This is likely a function of the very different patient impacts of options ranging from surveillance through focal therapy to the radical options and a problem that will only worsen as public appreciation of these different options increases via scientific, charity and media output. This effect may be seen not only in the failures of historical projects to recruit but in the ongoing challenges facing the currently open comparative trials.	The listed publications from Blazevski (2020), Guenther (2019) and Scheltema (2018) were included in the summary of key evidence. The listed publication (ref. 4) from van Riel (2022) has been added to the appendix.

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			8. A move to special arrangements guidance for IRE would allow for more rapid accrual of higher volume registry data and faster dissemination of the outcome evidence we all seek than is likely from the RCT framework facing the challenges outlined. References: 1. Blazevski A, Scheltema MJ, Yuen B, Masand N, Nguyen TV, Delprado W, Shnier R, Haynes AM, Cusick T, Thompson J, Stricker P. Oncological and Quality-of-life Outcomes Following Focal Irreversible Electroporation as Primary Treatment for Localised Prostate Cancer: A Biopsy-monitored Prospective Cohort. Eur Urol Oncol. 2020 Jun;3(3):283-290. doi: 10.1016/j.euo.2019.04.008. Epub 2019 May 16. PMID: 31103721. 2. Guenther E, Klein N, Zapf S, Weil S, Schlosser C, Rubinsky B, Stehling MK. Prostate cancer treatment with Irreversible Electroporation (IRE): Safety, efficacy and clinical experience in 471 treatments. PLoS One. 2019 Apr 15;14(4):e0215093. doi: 10.1371/journal.pone.0215093. PMID: 30986263; PMCID: PMC6464181 3. Scheltema MJ, Chang JI, Böhm M, van den Bos W, Blazevski A, Gielchinsky I, Kalsbeek AMF, van Leeuwen PJ, Nguyen TV, de Reijke TM, Siriwardana AR, Thompson JE, de la Rosette JJ, Stricker PD. Pair-matched patient-reported quality of life and early oncological control following focal irreversible electroporation versus robot-assisted radical prostatectomy. World J Urol. 2018 Sep;36(9):1383-1389. doi: 10.1007/s00345-018-2281-z. Epub 2018 Mar 28. PMID: 29594551; PMCID: PMC6105143.	

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			4. van Riel LAMJG, Geboers B, Kabaktepe E, Blazevski A, Reesink DJ, Stijns P, Stricker PD, Casanova J, Dominguez-Escrig JL, de Reijke TM, Scheltema MJ, Oddens JR. Outcomes of salvage radical prostatectomy after initial irreversible electroporation treatment for recurrent prostate cancer. BJU Int. 2022 Apr 27. doi: 10.1111/bju.15759. Epub ahead of print. PMID: 35474600."	
2	Consultee 2 Company Angiodynamics	**3.2**	"Given committee considerations 3.2 - ""The professional experts and the committee considered the key efficacy outcomes to be: overall survival, recurrence-free survival, metastasis-free survival, improvement in quality of life, and need for subsequent intervention."" And the overview of evidence shows ranges of 90-97% failure free survival, 99% metastasis free survival, 100% overall survival, an improved quality of life compared with radical prostatectomy. Combined with safety data that's encouraging, we believe the evidence is strongly pointing to a benefit for the patient with small risk (not none). Acknowledging the level of evidence is not level 1 but has come from different centres, it seems prudent to be clear on patient selection and a managed roll out of the procedure rather than research only. A well informed consent procedure should be implemented, highlighting that not all side effects are avoided, and there is still potential for repeat procedures, but it has been shown that some men weigh up this risk and choose focal therapy rather than radical treatment if they can."	Thank you for your comment. The main recommendation has been changed from ‘research’ to ‘special arrangements’, and a rationale section ‘why the committee made these recommendations’ has been added.

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3	Consultee 2 Company Angiodynamics	**General**	RCTs have been shown to be very difficult to enroll in this clinical space. To assure that appropriate data is collected in a consistent manner, UCLH are developing a prospective long term (10 year) international registry for intermediate risk patients. Please reach out to [redacted] to collaborate on the requirements for data suitability.	Thank you for your comment. NICE contacted the named person and received additional information about the registry. Section 3.8 has been added.
4	Consultee 2 Company Angiodynamics	**General**	We believe the condition should be narrowed to intermediate risk, unifocal prostate cancer, and also low risk who refuse active surveillance (this one is similar to German Urological Society - https://www.awmf.org/leitlinien/detail/ll/043-022OL.html). https://www.nature.com/articles/pcan20178	Thank you for your comment. The main recommendation has been changed from 'research' to 'special arrangements', a rationale section 'why the committee made these recommendations' has been added, and section 3.9 has been added. Tay et al. (2017) does not meet inclusion criteria since it does not include any efficacy or safety outcomes for IRE.
5	Consultee 2 Company Angiodynamics	**2.4**	Cardiac synchronisation is not compulsory when treating prostate cancer. ECG Synchronization is the preferred setting for ablations in the abdominal and thoracic cavities.	Thank you for your comment. *'Cardiac synchronisation is used to time delivery of the electrical pulse within the refractory period of the heart cycle, to minimise the risk of arrhythmia'* has been removed from section 2.4.
6	Consultee 2 Company Angiodynamics	**Overview**	Blazevski 2020 paper showed when margins of targeting lesions were increased to 10mm significant in-field disease was only 2 out of 74 (2.7%) whereas their initial experience of 5mm had 8 out of 28 (29%), which averaged out to the 13% significant in field disease for all patients. This will be	Thank you for your comment. The efficacy section of the overview has been amended to clarify the difference in results

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			similar in the van den Bos 2018 data as it is the same site's earlier work	obtained when different margins for targeting lesions were used.
7	Consultee 2 Company Angiodynamics	**General**	Recently published data by Yaxley et al 2022 who were trained by the Australian group had biospy proven in field recurrence at median 24 months of 4 out of 40 patients (7.5%) https://pubmed.ncbi.nlm.nih.gov/35534217/	Thank you for your comment. The listed publication (Yaxley 2022) has been added to the key evidence of the overview.
8	Consultee 2 Company Angiodynamics	**General**	Hifu focal therapy received full guidance with 60 patients in 3 case series at 12 month follow up. Only 20 patients had information on sexual function post procedure. https://www.nice.org.uk/guidance/ipg424/evidence/overview-pdf-438614317 IRE showed similar outcomes with more patients at a longer follow up (Guo et al 2021), and it would be fair to maintain the same standard as Hifu considering IRE can be used in areas of the prostate that hifu cannot treat. (scheltema 2018) We commissioned an independent literature review of IRE and HiFu if the committee would like to have that sent in?	Thank you for your comment and sharing the independent literature review. The main recommendation has been changed from 'research' to 'special arrangements', and a rationale section 'why the committee made these recommendations' has been added. For the independent literature review, all relevant papers that met the inclusion criteria were included in the overview.
9	Consultee 2 Company Angiodynamics	**General**	We believe a strong emphasis on failure free survival is important to the real world value of focal therapy. Preventing or delaying a larger treatment is an important outcome to patients, and a potential cost saving to the NHS. Especially given the nature of waitlists at the moment. If intermediate risk men can have another treatment option that requires less resources and time, while allowing the men to return to work more quickly than a radical treatment, important clinical resources could be more readily available	Thank you for your comment. The main recommendation has been changed from 'research' to 'special arrangements', and a rationale section 'why the committee made these recommendations' has been added.

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			to the men a higher risk who need a more intensive treatment option. This would reduce wait time for those at high risk. We understand that IPAC does not do cost analysis, but given the minimal nature of interventional procedures this would be an important element to consider.	Currently, cost-effectiveness is not part of the remit of the IP Programme.
10	Consultee 2 Company Angiodynamics	**Overview**	Erectile dysfunction - Blazevski 2020 showed 7% of men already potent pre procedure were not able to have erections sufficient for intercourse post IRE procedure.	Thank you for your comment. The efficacy section of the overview has been amended to include this additional information on sexual dysfunction.
11	Consultee 2 Company Angiodynamics	**General**	van den Bos 2015 is a key paper that performed ablate and resect to examine histological findings post IRE. Showing complete ablation of cells within the desired zone. The paper showed previous Hifu ablate and resect did not have full destruction within targeted zone. Highlighting the usefulness of the mechanism of IRE and using needle based "bracketing" to develop the target area. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4841841/	Thank you for your comment. The listed publication from van den Bos (2015) was not included in the summary of evidence because it focuses on electrode configuration and does not include specific data on clinical efficacy or safety of IRE.
12	Consultee 2 Company Angiodynamics	**General**	Another "risk" of focal treatment is what happens if you need follow up radical procedures. van Riel 2022 showed that "salvage" surgery outcomes post IRE are similar to primary treatment outcomes, but with some added difficulty in the procedure so needs to be done by specialist centres https://pubmed.ncbi.nlm.nih.gov/35474600/	Thank you for your comment. The listed publication from van Riel (2022) has been added to the appendix of the overview.
13	Consultee 2 Company	**General**	One comment is that the evidence relies heavily on one single centre study, but Two prospective case series and	Thank you for your comment.

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	Angiodynamics		one retrospective were not included: - Collettini et al 2019 - 30 patients, 1 year follow up https://pubmed.ncbi.nlm.nih.gov/31161973/ - Minana Lopez et al 2022 - 41 patients, 2 year follow up (published after review period) https://pubmed.ncbi.nlm.nih.gov/36073928/ - Yaxley et al 2022 - 40 patients, 2 year follow up https://pubmed.ncbi.nlm.nih.gov/35534217/	The listed publication from Collettini (2019) was included in the appendix of the overview. The listed publications from Lopez (2022) and Yaxley (2022) have been added to the overview.
14	Consultee 2 Company Angiodynamics	**General**	Hifu focal therapy received full guidance with 60 patients in 3 case series at 12 month follow up. Only 20 patients had information on sexual function post procedure. https://www.nice.org.uk/guidance/ipg424/evidence/overview-pdf-438614317 IRE showed similar outcomes with more patients at a longer follow up (Guo et al 2021), and it would be fair to maintain the same standard as Hifu considering IRE can be used in areas of the prostate that hifu cannot treat. (scheltema 2018)	Thank you for your comment. The main recommendation has been changed from 'research' to 'special arrangements', and a rationale section 'why the committee made these recommendations' has been added.
15	Consultee 2 Company Angiodynamics	**General**	Cryotherapy focal therapy received full guidance with 1330 patients, 366 with biopsy follow up. IRE has similar outcome and improved failure free survival (Guo et al 2021)	Thank you for your comment. The main recommendation has been changed from 'research' to 'special arrangements', and a rationale section 'why the committee made these recommendations' has been added.
16	Consultee 3	**General**	I have carefully reviewed all the documentation.	Thank you for your comment.

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	NHS professional Royal Surrey NHS Foundation Trust		It was my intention to submit the following citation for an important publication, currently in press, and would ask you to kindly direct to the evaluation committee as it should be taken into account. Geboers B, Gondoputro W, Thompson JE, . Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging to Detect Residual Prostate Cancer Following Irreversible Electroporation-A Multicenter Validation Study. Eur Urol Focus. 2022 May 13:S2405-4569(22)00106-7. doi: 10.1016/j.euf.2022.04.010. Epub ahead of print. PMID: 35577751.	The listed publication from Geboers (2022) does not meet the inclusion criteria because it focuses on utility of multiparametric MRI and does not include any efficacy or safety outcomes for IRE.

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