



**EUROPEAN COMMISSION**  
JOINT RESEARCH CENTRE

Directorate F - Health, Consumers & Reference Materials (Ispra)  
**Health in Society**

## **European Commission Initiative on Breast Cancer (ECIBC): European guidelines on breast cancer screening and diagnosis**

QUESTION	
<b>Should clip-marking vs. no clip-marking after needle core biopsy (NCB)/vacuum assisted needle core biopsy (VANCB) be used for surgical therapy planning in patients with breast cancer lesions?</b>	
<b>POPULATION:</b>	Women with breast cancer lesions who would undergo surgery, either conservative or mastectomy [Breast cancer lesions: palpable lesions possible candidate to neoadjuvant therapy, and non-palpable lesions. The surgery for palpable lesions is planned after receiving neoadjuvant therapy.]
<b>INTERVENTION:</b>	Clip-marking
<b>COMPARISON:</b>	No clip-marking after needle core biopsy (NCB)/vacuum assisted needle core biopsy (VANCB)
<b>MAIN OUTCOMES:</b>	Overall survival; final margin status; local breast recurrences; adverse events like bleeding, infection, hematoma or pain.
<b>SETTING:</b>	European Union
<b>PERSPECTIVE:</b>	National health authority
<b>BACKGROUND:</b>	<p>In order to reduce the number of deaths due to breast cancer, many countries have implemented screening programs for early detection of breast cancer in asymptomatic women. Therefore, the majority of the suspicious lesions detected by screening mammography are small non-palpable lesions, i.e. mass lesions or calcifications. If the lesion remains suspicious after imaging assessment, a biopsy has to be performed for clarification of the diagnosis and treatment planning, particularly to differentiate between benign and malignant lesions and decide if surgical removal is needed.</p> <p>The detection of non-palpable lesions intraoperatively is difficult and usually directed by wire marking of the lesion before surgery. However, sometimes the whole aberration is removed through needle biopsy, especially if VANCB is used. In case of breast cancer lesions, this could lead to a wider surgical excision of the quadrant where the lesion was located to assure that it is completely removed. This explains why it is helpful to mark these lesions or the lesion bed (when entirely removed) by a marker (clip) which can be applied during the initial biopsy procedure or in a second step.</p> <p>A clip is a very small device (2-3 mm), usually made of hypoallergenic materials, that is visible in different imaging modalities (e.g. ultrasound, mammography, MRI) and anchored in the tissue either during the initial biopsy or in a second intervention. These clips are MRI compatible, easily visible in mammography and MRI, and some of them with ultrasound, too.</p> <p>Clip-marking is done in order to prove the correct location of the biopsy and to guide the surgeon for the excision. It is useful also for the follow up of imaging suspicious lesions with benign histology. A mammography is performed after the placement of the clip to see its relation to the lesion.</p> <p>Before surgery, these clips are usually located by wire marking. In case of clip displacement, the lesion itself could be wire-marked instead of the clip. Exact positioning of the clips within or right next to the lesion helps to reduce the size of tissue that should be surgically removed. Sometimes even several clips need to be placed at the margins of a lesion to show the total extent or the disease and to help the surgical approach. After removal of the tissue, a specimen radiography should be done to assure that the clip is included, indicating that the removed</p>

	<p>tissue includes the area of interest.</p> <p>Modern treatment of breast cancer is adapted to tumour biology, size and stages. In palpable lesions, neoadjuvant therapy is sometimes used for downsizing the tumour to increase the operability. In some cases, mastectomy and/or axillary clearance could be avoided if the neoadjuvant therapy shows significant tumour response that leads to down staging of the tumour. In large locally advanced breast cancer, neoadjuvant chemotherapy can enable operability of initially inoperable tumours (Kümmel S, 2014).</p> <p>Tumours may vanish completely in imaging under neoadjuvant chemotherapy (radiological complete response), but sometimes residual tumour cells remain and have to be removed by surgery. Clip-marking in these cases is important in order to define the area of breast tissue which has to be removed. It can be placed during biopsy or in a second step before the start of chemotherapy or during the first cycles when the tumour is still visible.</p> <p>The clip is also useful, especially for huge tumour specimens or mastectomies, in directing the pathologist to the tumour site to facilitate thorough sampling of tumour bed where tumour may not be visible macroscopically. If the lesion or pathologic area is widespread, more than one clip is sometimes used to define the extent of the disease, or to show in which areas of an extended lesion biopsies have been taken.</p> <p>Disadvantages could be an incorrect placement of the clip either through wrong positioning or through movement of the clip in the tissue (13-20%). In addition, if performed in a second step, the risk of bleeding and infection could occur in very few cases.</p>
<b>CONFLICT OF INTEREST:</b>	<p>Management of Conflicts of Interest (Col): ColS for all Guidelines Development Group (GDG) members were assessed and managed by the Joint Research Centre (JRC) following an established procedure in line with European Commission rules. GDG member participation in the development of the recommendations was restricted, according to Col disclosure. Consequently, for this particular question, the following GDG members were recused from voting: Axel Gräwingholt, Peter Rabe and Kenneth Young; Miranda Langendam, as external expert, was also not allowed to vote, according to the ECIBC rules of procedure.</p>

## ASSESSMENT

<b>Problem</b> Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>The majority of the suspicious lesions detected by screening mammography are small non-palpable lesions, i.e. mass lesions or micro-calcifications.</p> <p>After a biopsy is performed, the lesion or calcifications are mostly removed, especially if VANCb is used. In addition, tumours may vanish completely in imaging under neoadjuvant chemotherapy (radiological complete response),</p> <p>This explains why it is helpful to mark these lesions or the lesion bed (when entirely removed) by a marker (clip) applied during the initial biopsy procedure or in a second step. Main objective of marking is to assure that the area where the lesion was located is completely removed.</p> <p>The clip is also useful, in the follow up of imaging in suspicious lesions with benign histology, as they can be easily identified, and helping the pathologist for identification of areas of interest.</p>	<p>The GDG prioritised this question for the ECIBC.</p>

	Clip-marking may increase costs and time of the diagnostic-intervention procedure and may have some minor complications like bleeding and pain.					
Desirable Effects						
How substantial are the desirable anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS	
<div>○ Trivial</div> <div>○ Small</div> <div>○ Moderate</div> <div>● Large</div> <div>○ Varies</div> <div>○ Don't know</div>	Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
					Risk with no clip-marking after NCB/VANCB	Risk difference with clipmarking
	Number of patients with Close/Positive margins <sup>a</sup>	373 (1 observational study) <sup>1</sup>	⊕○○○○ VERY LOW <sup>b,c,d</sup>	RR 0.72 (0.41 to 1.25)	Study population	
					154 per 1.000	43 fewer per 1.000 (91 fewer to 38 more)
	Local breast recurrence (overall) follow up: median 49 months	373 (1 observational study) <sup>1</sup>	⊕○○○○ VERY LOW <sup>b,d,e</sup>	RR 0.17 (0.04 to 0.70) <sup>f</sup>	Study population	
					83 per 1.000	69 fewer per 1.000 (80 fewer to 25 fewer)
	Risk of recurrence assessed with: Cox hazard multivariate model follow up: median 49 months <sup>f</sup>	373 (1 observational study) <sup>1</sup>	⊕○○○○ VERY LOW <sup>b,c</sup>	HR 0.27 (0.06 to 1.16)	Study population	
				83 per 1.000	60 fewer per 1.000 (78 fewer to 13 more)	
	Mortality <sup>g</sup>	373	⊕○○○○	RR 0.22	Study population	
<div>The ESMO Clinical Practice Guideline for diagnosis, treatment and follow up considers that marking the tumour bed with clips in a standardised way facilitates accurate planning of the radiation boost field, if it is indicated (1).</div> <div>In absence of biopsy clips, clear margins were reported only in 31–62% of women after mammographically guided wire localization (2), (3), (4), but this number increased to 90% in the presence of biopsy clips (5).</div> <div>The evidence included shows 43 fewer cancers with positive margins and 69 fewer local recurrences(6) in the clip-marking group. The GDG had less confidence in the mortality reduction estimated that was 120 fewer per 1,000 women, due to incongruence with the magnitude of effects for positive margins and local recurrences.</div> <div>The GDG notes that it is important to have safe surgical margins to prevent recurrence and that the use of clips may allow smaller surgical resection of a tumour after neo-adjuvant chemotherapy. In addition, the absence of a clip may result in the need of additional boundary biopsies or mastectomy.</div> <div>The presence of a clip may also facilitate identification of the original tumour bed by the pathologist.</div> <div>The GDG agreed by consensus that the desirable effects are large.</div>						

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The presence of a clip may also facilitate identification of the original tumour bed by the pathologist.

The GDG agreed by consensus that the desirable effects are large.

	(1 observational study) <sup>1</sup>	VERY LOW <sup>b,d,e</sup>	(0.09 to 0.56)	154 per 1.000	<b>120 fewer per 1.000</b> (140 fewer to 68 fewer)
Adverse events	0 (0 studies)	-	-	The study did not report this outcome.	

1. Oh JL, Nguyen G, Whitman GJ, Hunt KK, Yu TK, Woodward WA, et al.. Placement of radiopaque clips for tumor localization in patients undergoing neoadjuvant chemotherapy and breast conservation therapy.. Cancer; 2007.
  - a. This is an operational definition of "final margin status". The status "close" means that the post-surgical specimen had less than 2 mm. of free cancer cells margin. Twelve (8.3%) and four (2.7%) women had close or positive margins respectively in the clip group whereas 23 (10.1%) and 12 (5.3%) of women had close and positive margins respectively in the group without clip.
  - b. Since Oh 2007 included women with palpable lesions, for women with non-palpable lesions the confidence should be downrated due to indirectness.
  - c. The margins of confidence intervals are wide, so there is not enough certainty about the real impact of the intervention.
  - d. There is a serious risk of bias due to confounding factors; women without clip had a more advanced nodal disease (24.5%) than women with clip (13%). The neoadjuvant chemotherapy was not the same for everyone, only 53% received an additional taxane cycle. The reasons for not deployment of a clip in the control group were not clear. There were missing data regarding lymphovascular invasion status, it was unknown in 13% of the total population, it represented 18% of women with clip and 9% in women without a clip.
  - e. The number of events was small. This fact may affect the robustness of estimations.
  - f. This outcome is a supplementary measure for local breast recurrence. None of the 57 women with residual disease (RD) with a clip inserted presented local recurrence; compared with 11 of the 113 (9.7%) women with RD but without clip placement RR 0.09 (95%CI, 0.01-1.42). In women with pathological complete response (pCR) or near pCR there were no differences in local recurrences between clip and no-clip groups ( 2.47% and 6.48% respectively, RR 0.38 (95% CI 0.08- 1.8). Other three factors were independently associated with an increased hazard for local recurrence: T3-T4 clinical tumor size versus clinical stage 1-2 HR 2.66 (95% CI 1.03-6.86), Close or positive margins versus negative margins HR 3.37 (95% CI 1.13-10.07) and Modified Black Nuclear grade (MBNG) 3 versus MBNG 1 or 2 HR 3.86 (95% CI 1.13-13.22).
  - g. Mortality rate was selected instead of overall survival, due incomplete data reporting.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>● Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
					Risk with no clip-marking after NCB/VANCB	Risk difference with clipmarking
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	Mortality <sup>g</sup>	373 (1 observational study) <sup>1</sup>	⊕○○○ VERY LOW <sup>b,d,e</sup>	RR 0.22 (0.09 to 0.56)	Study population	
					154 per 1.000	<b>120 fewer per 1.000</b> (140 fewer to 68 fewer)
						<p>The GDG discussed the fact that certain clips may perform better than others with less migration from the original insertion site. Some studies assessing different types of clips found variation in the pathological success of surgery with clear margins from 60% to 89% [7].</p> <p>The GDG judged that the evaluation different types of clips and their performance is outside of the scope this recommendation.</p> <p>The GDG noted that some women may be concerned about having a clip in the breast and this may have impact on psychological wellbeing.</p> <p>The GDG also notes that the materials (titanium and teflon coating) used in most clips are known to be safe from their use in other devices such as prostheses.</p> <p>The GDG noted that if the clip-marking is performed as a second intervention it requires recall and additional appointment for the women and may cause side effects like bleeding, infection and hematoma.</p> <p>The GDG judged that the undesirable anticipated effects are trivial.</p>

Adverse events	0 (0 studies)	-	-	The study did not report this outcome.
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  - a. This is an operational definition of "final margin status". The status "close" means that the post-surgical specimen had less than 2 mm. of free cancer cells margin. Twelve (8.3%) and four (2.7%) women had close or positive margins respectively in the clip group whereas 23 (10.1%) and 12 (5.3%) of women had close and positive margins respectively in the group without clip.
  - b. Since Oh 2007 included women with palpable lesions, for women with non-palpable lesions the confidence should be downrated due to indirectness.
  - c. The margins of confidence intervals are wide, so there is not enough certainty about the real impact of the intervention.
  - d. There is a serious risk of bias due to confounding factors; women without clip had a more advanced nodal disease (24.5%) than women with clip (13%). The neoadjuvant chemotherapy was not the same for everyone, only 53% received an additional taxane cycle. The reasons for not deployment of a clip in the control group were not clear. There were missing data regarding lymphovascular invasion status, it was unknown in 13% of the total population, it represented 18% of women with clip and 9% in women without a clip.
  - e. The number of events was small. This fact may affect the robustness of estimations.
  - f. This outcome is a supplementary measure for local breast recurrence. None of the 57 women with residual disease (RD) with a clip inserted presented local recurrence; compared with 11 of the 113 (9.7%) women with RD but without clip placement RR 0.09 (95%CI, 0.01-1.42). In women with pathological complete response (pCR) or near pCR there were no differences in local recurrences between clip and no-clip groups (, 2.47% and 6.48% respectively, RR 0.38 (95% CI 0.08- 1.8). Other three factors were independently associated with an increased hazard for local recurrence: T3-T4 clinical tumor size versus clinical stage 1-2 HR 2.66 (95% CI 1.03-6.86), Close or positive margins versus negative margins HR 3.37 (95% CI 1.13-10.07) and Modified Black Nuclear grade (MBNG) 3 versus MBNG 1 or 2 HR 3.86 (95% CI 1.13-13.22).
  - g. Mortality rate was selected instead of overall survival, due incomplete data reporting.

## Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		<p>The GDG noted that downgrading was performed for imprecision and risk of bias. Risk of bias was identified as serious because patients who are healthier or with less advanced disease may have received clip-marking.</p> <p>There is also serious prescription bias that may introduce confounding in the results due to the lack of random allocation of treatment: patients who received the indication for clip-marking may have smaller lesion and therefore have a better prognosis than those who did not receive clip-marking, independently of the intervention.</p> <p>The results identifying benefits in this evidence for palpable lesion was assumed to be of greater magnitude in non-palpable lesions.</p> <p>The GDG judged that the overall certainty of the evidence is very low.</p>

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	No systematic review was conducted.	<p>The GDG agreed by consensus that there is possibly important uncertainty or variability in how people value the main outcomes.</p>



## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		<p>The GDG noted significant concern with potential confounding in the results that are presented (healthier women may be more likely to receive the clips).</p> <p>As there was not agreement within the GDG for the balance of effects, voting among members without Col took place, the results of which were: 1 member voted for 'favours the comparison', 2 members voted for 'does not favour either the intervention or comparison', 13 members voted for 'probably favours the intervention', 3 members voted for 'favours the intervention', 1 member voted for 'don't know', and 1 member abstained.</p>

## Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>● Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>No systematic review was conducted.</p>	<p><b>Cost (estimated from information provided by members of the GDG):</b></p> <p>Bard ultracip (5 clips) EUR 450 (Hospital setting in Germany, 2017).</p> <p>No research evidence was identified for the total resources required for clip-marking. However, one study reporting costs for MicroMark; Biopsy Ethicon Endo-Surgery clip was found. In this study the unitary clip cost was USD 64 estimated from the Medicare perspective in 1997 in the USA (8).</p> <p>The GDG discussed that the clip, on the basis of the data identified, is expensive; however, it considered that few women compared to the number of women examined would require a clip and judged that in general costs are moderate.</p>

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		The GDG judged that the certainty of the evidence of resource requirements is very low.

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	No systematic review was conducted.	<p>The GDG noted that no evidence was identified, however, they noted that re-biopsy and re-surgery must be considered in the context of cost-effectiveness.</p> <p>The GDG discussed that there may be benefits in reducing other interventions such as additional biopsies and surgeries, which would have significant reductions in costs.</p> <p>The GDG noted that due to the costs of clips, it may not be inserted if there are concerns over costs and reimbursement in certain settings.</p>

## Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>○ Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	No systematic review was conducted.	<p>The GDG noted that equity would be impacted by whether the cost of the clip and insertion would be borne by women. If women have to pay for the intervention in certain settings equity may be reduced.</p> <p>The GDG noted that if the costs of the intervention are reimbursed for everyone equity would probably increase.</p> <p>The GDG agreed by consensus that the impact on health equity would therefore vary.</p>

## Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><li><input type="radio"/> No</li><li><input type="radio"/> Probably no</li><li><input checked="" type="radio"/> Probably yes</li><li><input type="radio"/> Yes</li><li><input type="radio"/> Varies</li><li><input type="radio"/> Don't know</li></ul>	No systematic review was conducted.	<p>For women and providers the GDG judged that the intervention would probably be acceptable to implement.</p> <p>For policy-makers and healthcare payers there may be less acceptability due to the costs of the clip and insertion.</p>

## Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"><li><input type="radio"/> No</li><li><input type="radio"/> Probably no</li><li><input checked="" type="radio"/> Probably yes</li><li><input type="radio"/> Yes</li><li><input type="radio"/> Varies</li><li><input type="radio"/> Don't know</li></ul>	No systematic review was conducted.	<p>The GDG judged that the training for this type of intervention is relatively easy and it is widely used in practice at the present time.</p> <p>The GDG agreed by consensus that the intervention is probably feasible to implement.</p>

## SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

## TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
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## CONCLUSIONS

### Recommendation

The ECIBC's Guidelines Development Group suggests using clip-marking after NCB/VANCB for surgical therapy planning in patients with breast cancer lesions (conditional recommendation, very low certainty of the evidence).

### Justification

#### Overall justification

The GDG agreed by consensus to support a conditional recommendation for the intervention.

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable effects were large, including fewer cancers with positive margins and fewer local recurrences with the use of clip-marking after NCB / VANCB for surgical therapy planning.

##### *Undesirable Effects*

The GDG noted differences in the performance of clips from the research evidence. The GDG noted that some women may be concerned about having a clip in the breast. The GDG also notes that the materials used in most clips are known to be safe from their use in other devices.

##### *Certainty of evidence*

The GDG noted that only one study with very low certainty of evidence was reviewed. The GDG had significant concern of risk of allocation bias, as it notes that patients in the intervention group receiving clips may have been healthier or had less advanced disease.

##### *Balance of effects*

The GDG judged that the balance of effects probably favours the intervention.

##### *Resources required*

The GDG judged that the intervention would require moderate costs due to the high costs of the clip, however, the GDG noted that the number of women requiring clips would be small.

##### *Cost effectiveness*

No cost-effectiveness studies were included, however, the GDG noted that cost-effectiveness considerations should include the potential for clips to reduce additional interventions such as additional biopsies or surgeries, which would have significant reductions in costs.

## Subgroup considerations

Palpable lesions possibly candidate for neoadjuvant therapy and non-palpable lesions: the GDG considered both types of lesion and agreed that the evidence did not support distinguishing these subgroups in this recommendation or in any of the ETD considerations. The GDG noted that lesions that are initially palpable may later become non-palpable following neoadjuvant chemotherapy.

## Implementation considerations

1. The GDG noted that effective communication at the time of clip insertion is essential to ensure that women understand the implications on future management.
2. The GDG noted that the timing of clip insertion is critical and whether it is feasible to insert clips during initial biopsies instead of a follow-up procedure may change the harm/benefit ratio because of the additional stress, complications and costs associated with placing the clip in a second time.

## Monitoring and evaluation

The GDG noted that monitoring for whether clips are inserted in the correct position in relation to a lesion is important. The GDG suggests that further assessments are needed for the appropriateness of clip positioning either by radiology follow-up imaging or pathology. The GDG refers this to the QASDG for consideration.

## Research priorities

1. The GDG suggests the need for more and higher quality evidence on the effectiveness of the intervention improved research with higher quality of evidence from observational studies or where clip-marking is not routinely used considering the use of randomized studies for high quality evidence. The GDG notes that improved evidence on the effectiveness is very important. Some members of the GDG suggested that in the context of clinical equipoise randomized trials would provide higher quality evidence.
2. The GDG suggests further research on the local effects of clips and impacts on the psychological wellbeing for women and whether there is an impact of clips on breast cancer progression or recurrence.
3. The GDG suggests improved cost-effectiveness evidence on the use of clip-marking and comparing the economic impact of clip-marking on the need for additional procedures such as biopsies and surgeries. 4. The GDG suggests research on the use of clip-marking for palpable vs non-palpable lesions.

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