PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomised controlled trial comparing surgical intervention rates between two protocols for the management of asymptomatic adnexal tumours in postmenopausal women: A study protocol
AUTHORS	Nunes, Natalie ; Foo, Xulin; Widschwendter, Martin; Jurkovic, Davor

VERSION 1 - REVIEW

REVIEWER	N J Raine-Fenning MRCOG MBChB PhD Reader in Reproductive Medicine and Surgery Division of Obstetrics & Gynaecology, School of Clinical Sciences, University of Nottingham Director of Research / Senior Consultant Nottingham University Research & Treatment Unit in Reproduction (NURTURE)
REVIEW RETURNED	19-Sep-2012

GENERAL COMMENTS	This is an excellent idea for a trial. The protocol is well written and describes the concept, aims and methods clearly. I fully support what the team are trying to achieve and wish them all the best with this. I have a few minor questions: OUTCOME / AIMS I understand that the trial is designed to look at intervention rates and that it is powered to do this. I do wonder if this is the right primary outcome. Surely the better trial would be a larger one to look at the secondary outcomes and how effective these two methods are? Intervention rates are important of course but not as important as a missed diagnosis of cancer. Again one could debate this especially if the lead time to diagnosis is considered but I would be interested to hear what the patients have to say about this. Have the group done any PPI/E? They should. Clearly one Unit could not deliver this and a multicentre study would be needed so if this trial does go ahead as planned I would describe it as a pilot study to assess recruitment etc and ensure all such data are collected to allow the subsequent larger multicentre RCT. I would interested to hear what the team think about this and what their intentions are. I am also a little unsure as to the follow-up period. 12 months seems extremely short especially as the intervention rates must be compared against the diagnosis of cancer which could come after the 12 month period. In a way this study only looks at 12 month intervention rates. Is this clinically valid? The team also need to clarify what will happen at the end of the study especially to women who still require follow up.

	STUDY DESIGN There is no mention of blinding. This must be addressed. Will the surgeons know if the patient has been triaged based on IOTA or RMI and are they all happy to do this? Has a clinician survey been undertaken or, given the single unit design, all potential surgeons involved in the design? The sample size has been estimated based on a 50% reduction in intervention without any increase in a delayed cancer diagnosis. This has been described as 'significant'. I would like to know how these figures were arrived at and whether the team feel 50% is realistic. I know the IOTA rules and team behind them well and it may be that they could advise on this. DJ is part of this so may be able to answer directly. IOTA are very specific about the fact their rules have been developed by 'experts'. They are currently looking at the interobserver variability of the simple rules when used by less experienced centres and sonographers. Who will do these scans and will the sonographers be comparable when broken down by RMI and IOTA? It is essential they are and that there is no bias between the two groups. Are the sonographers (and by this I refer to all healthcare practitioners scanning) equally experienced? The IOTA simple rules are a new concept and whilst the name suggests they are easy to apply there is a learning curve and the team must ensure everyone is au fait with colour scores, measurement of papillations etc. RMI clearly divides women into the 3 groups outlined in the protocol. IOTA simple rules do not however. The team have created their own version of low, intermediate and high risk from them. The concept seems fair and the oncology team seem happy to accept this but this is a deviation from the 'rules'. As far as I can remember the IOTA rules are only applicable to 70% of patients. Should the 30% requiring a second opinion be randomised? The intention to treat design is correct of course but this does add another element and level of complexity into the decision making process. OTHER The IOTA simple rules are referred to by the RCOG Guideline on 'pre-menopausal' women NOT 'post-menopausal' women. This study is about the latter group. I think this reflects the timeline and expect the RCOG to update the latter guideline (last reviewed in 2003). IOTA rules clearly apply to both groups and we are all surprised the post-menopausal guideline was not modified when the pre-menopausal one written (2011). I do think a comment re this is required however as these are two very different groups of patients. I felt that the introduction to the Abstract did not clearly show this is a trial of RMI vs IOTA.

REVIEWER	Peggy Geomini, MD, PhD Gynaecologist

	Maxima Medical Center Veldhoven the Netherlands
REVIEW RETURNED	23-Sep-2012

THE STUDY	The authosrs already notice that the skills of the ezaminator (who's performing the ultrasound) should be skilled in the 'simple rules'". Because it is a single centre study there can be a problem in extarnal validation of the study results. May be you are going to test the skills of the examinator in stead of the performance of "simple rules".
RESULTS & CONCLUSIONS	primary outcome is rate of surgical intreventions; in my opinion this is not the goal of teh study; primary outcome should be improvement of sens/ spec (show that the 'simple rules' better discriminate between benign and malignant adnexal masses compared to 'RMI".

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

"I understand that the trial is designed to look at intervention rates and that it is powered to do this. I do wonder if this is the right primary outcome. Surely the better trial would be a larger one to look at the secondary outcomes and how effective these two methods are? Intervention rates are important of course but not as important as a missed diagnosis of cancer. Again one could debate this especially if the lead time to diagnosis is considered but I would be interested to hear what the patients have to say about this."

• Large studies have already been published showing the diagnostic accuracy of both RMI and Simple Rules. Although the two methods have not been compared in a prospective randomised trial, available data indicate that their ability to discriminate between benign and malignant adnexal lesions is similar. The management models evaluated in this study have been designed to assist clinicians who are treating women diagnosed with adnexal tumours. In order to minimise the risk of missing an ovarian cancer the models have been set to maximise sensitivity of the diagnosis of ovarian cancer at the expense of specificity. This leads to a relatively large number of interventions in women with benign cysts. Recent trials have shown that unnecessary interventions in women with benign adnexal lesions lead to significant morbidity and mortality, which offsets the potential benefits of screening for ovarian cancers1. It is therefore imperative to continue with efforts to develop diagnostic and management algorithms which would minimise the number of interventions in women with benign cysts without delaying detection of ovarian cancer. This has been added to the discussion.

"Have the group done any PPI/E? They should. Clearly one Unit could not deliver this and a multicentre study would be needed so if this trial does go ahead as planned I would describe it as a pilot study to assess recruitment etc and ensure all such data are collected to allow the subsequent larger multicentre RCT. I would be interested to hear what the team think about this and what their intentions are."

• A pilot observational study was done prior to this study. We have a very high throughput of patients and we should be able to complete this study with three years in a single centre. A larger multicentre trial would be certainly something to consider in the future.

"I am also a little unsure as to the follow-up period. 12 months seems extremely short especially as

the intervention rates must be compared against the diagnosis of cancer which could come after the 12 month period. In a way this study only looks at 12 month intervention rates. Is this clinically valid? The team also need to clarify what will happen at the end of the study especially to women who still require follow up."

• The 12-month follow up period is to ensure that, should any cancers misclassified on the initial assessment, the treatment in not excessively delayed. It follows the Guideline published by the Royal College of Obstetricians and Gynaecologists which stipulates that 12 months follow up should be offered to all asymptomatic women with presumed benign cysts. It is very unlikely that a malignant lesion would not increase in size or change in some other way over the 12 months period to alert the examiner of its nature. At the end of the study women will be offered yearly scans for further four years. This has been added to the interventions section.

"There is no mention of blinding. This must be addressed. Will the surgeons know if the patient has been triaged based on IOTA or RMI and are they all happy to do this? Has a clinician survey been undertaken or, given the single unit design, all potential surgeons involved in the design?"

• The study is not blinded as this would not affect the management of women. The protocol was developed in collaboration between clinicians with expertise in gynaecological diagnosis, surgery for benign conditions and gynaecological oncology team. We have already completed the pilot study and there have been no complaints from the clinicians regarding the use of different management algorithms.

"The sample size has been estimated based on a 50% reduction in intervention without any increase in a delayed cancer diagnosis. This has been described as 'significant'. I would like to know how these figures were arrived at and whether the team feel 50% is realistic. I know the IOTA rules and team behind them well and it may be that they could advise on this. DJ is part of this so may be able to answer directly."

• Our pilot study showed a much greater reduction in surgical rates. As some women may still opt for surgery during follow up, we felt a 50% reduction represented a reasonable estimate, which was clinically relevant.

"IOTA are very specific about the fact their rules have been developed by 'experts'. They are currently looking at the interobserver variability of the simple rules when used by less experienced centres and sonographers. Who will do these scans and will the sonographers be comparable when broken down by RMI and IOTA? It is essential they are and that there is no bias between the two groups. Are the sonographers (and by this I refer to all healthcare practitioners scanning) equally experienced? The IOTA simple rules are a new concept and whilst the name suggests they are easy to apply there is a learning curve and the team must ensure everyone is au fait with colour scores, measurement of papillations etc."

• Level 2 ultrasound operators who have been fully trained to analyse adnexal tumours using both the RMI and Simple Rules Protocols will do all the scans. This has been added to the intervention section.

"RMI clearly divides women into the 3 groups outlined in the protocol. IOTA simple rules do not however. The team have created their own version of low, intermediate and high risk from them. The

concept seems fair and the oncology team seem happy to accept this but this is a deviation from the 'rules'.

As far as I can remember the IOTA rules are only applicable to 70% of patients. Should the 30% requiring a second opinion be randomised? The intention to treat design is correct of course but this does add another element and level of complexity into the decision making process."

• When RMI is used as a diagnostic test for ovarian cancer, the test result is reported as positive or negative. The management protocol for postmenopausal cysts, which is based on the use of RMI divides women in three groups: high, intermediate and low risk of cancer. We have utilised the same approach to our novel management protocol based on Simple Rules.
• It is true that "Simple Rules" have been found to only be applicable in 70-75% of tumours in previous studies. These studies; however, have been conducted on populations of women who had already been selected for surgery based on local management protocols. As a result the proportion of cancers and 'difficult' tumours was high. Our population of women is very different as it only includes asymptomatic postmenopausal women with an incidental diagnosis of adnexal tumours. As expected, our pilot study showed that the prevalence of benign lesions in this population of women is much higher and simple rules were applicable to 92% of women.

"The IOTA simple rules are referred to by the RCOG Guideline on 'pre-menopausal' women NOT 'post-menopausal' women. This study is about the latter group. I think this reflects the timeline and expect the RCOG to update the latter guideline (last reviewed in 2003). IOTA rules clearly apply to both groups and we are all surprised the post-menopausal guideline was not modified when the pre-menopausal one written (2011). I do think a comment re this is required however as these are two very different groups of patients."

• The RCOG do indeed refer to the "Simple Rules" in pre-menopausal women. They have not yet revised the guidelines for post-menopausal women and it is not clear what will be the recommendation regarding the use of "Simple Rules".

"I felt that the introduction to the Abstract did not clearly show this is a trial of RMI vs IOTA."

• This trial does not represent a comparison of RMI and IOTA Simple Rules diagnostic model. The trial aims to compare two clinical protocols which utilise these two different diagnostic models to formulate structured approaches for the management of women with adnexal tumours.

Reviewer 2

"The authors already notice that the skills of the examiner (who's performing the ultrasound) should be skilled in the 'simple rules'". Because it is a single centre study there can be a problem in external validation of the study results. May be you are going to test the skills of the examiner instead of the performance of "simple rules"."

• The advantage of a single centre study is the standardization of the assessments but a disadvantage will be the reduced ability to generalise the results. This will be stated when the final results are published. We have amended the interventions section to describe skills of the ultrasound examiners.

“Primary outcome is rate of surgical interventions; in my opinion this is not the goal of the study; primary outcome should be improvement of sens/ spec (show that the 'simple rules' better discriminate between benign and malignant adnexal masses compared to 'RMI".”

• See reply to the Reviewer 1.

Reference

1. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, Reding DJ, Greenlee RT, Yokochi LA, Kessel B, Crawford ED, Church TR,Andriole GL, Weissfeld JL, Fouad MN, Chia D, O'Brien B, Ragard LR, Clapp JD, Rathmell JM, Riley TL, Hartge P, Pinsky PF, Zhu CS, Izmirlian G,Kramer BS, Miller AB, Xu JL, Prorok PC, Gohagan JK, Berg