Study Title: AIM 2: Adequate Selection of Patients for Thyroid Biopsy: Evaluation of a Shared Decision Making Conversation Aid

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Abstract

Thyroid nodules are commonly discovered and their evaluation and diagnosis precede the epidemic of thyroid cancer that is harmful to patients and overwhelms the medical system. We hypothesize that the use of an electronic conversation aid during clinical visits can help patients and clinicians collaborate when deciding between performing a thyroid biopsy or following thyroid nodules with serial ultrasound. As a result, the use of this tool can lead to a more careful selection of patients that should undergo thyroid biopsy.

The proposed research seeks to conduct a pilot clinical trial to evaluate the feasibility of conducting a larger study evaluating the efficacy of this conversation aid in supporting shared decision making, decreasing the number of unnecessary thyroid biopsies and leading to improved patient centered thyroid cancer diagnosis.

Background

We are living in an epidemic of thyroid cancer diagnoses that directly harms patients. The incidence of thyroid cancer in the United States has tripled during the last three decades, with >50, 000 patients diagnosed annually, mostly due to identification of small indolent cancers that would not be harmful if left undiagnosed and untreated. These patients receive risky treatment and suffer emotional and economic burden. For example: 1) the quality of life of patients with thyroid cancer is decreased when compared with patients with worse prognosis, 2) a diagnosis of thyroid cancer is associated with the highest incidence of bankruptcy and 3) the cost of caring for patients with thyroid cancer is expected to rise to $21 billion. This diagnostic and treatment journey leaves most patients with a diagnosis of thyroid cancer that only leads to harm without improving the duration or the quality of their life. This reality of over-diagnosis and over-treatment affects 7 out of 10 women and 5 out of 10 men diagnosed with thyroid cancer in the United States.

This detrimental epidemic is partially attributed to the inadequate selection of patients who would benefit from a thyroid biopsy and thyroid cancer diagnosis. Six out of 10 people have thyroid nodules that can be detected by imaging. The diagnostic cascade that leads to the over-diagnosis of thyroid cancer begins most commonly with the incidental discovery of these nodules. Patient selection for thyroid nodule biopsy and thyroid cancer diagnosis is inadequate and leads to harm. To address this quality gap, recent practice guidelines recommend for careful selection of patients for thyroid biopsy and against biopsy of small thyroid nodules with low risk for thyroid cancer. However, the implementation of these recommendations can be hindered by challenging clinical conversations with patients who are anxious about a potential cancer diagnosis and assume that more investigation is always better. Counseling about complex topics such as thyroid cancer risk and over-diagnosis can be difficult. In fact, most patients after a thyroid biopsy know little about these topics and are not routinely engaged in making the decision to further investigate thyroid nodules.

Shared decision-making (SDM) is a communication process in which patients and clinicians work together to decide the next best step. The use of conversation aids that support SDM helps patients make medical decisions that are consistent with their informed values, be more knowledgeable and

active in the decision-making process and better understand concepts such as risk. In oncology, the use of conversation aids can help overcome barriers for patient-centered care. To support SDM, promote patient centered care and help clinicians identify patients who would benefit from a thyroid nodule biopsy according to guideline recommendations, we have developed an electronic conversation aid for patients diagnosed with a thyroid nodule. This conversation aid includes a summary of the clinical evidence guiding patient selection for thyroid biopsy, the values of each diagnostic alternative (biopsy vs observation) and allows clinicians to incorporate the patients' preferences and situation into the decision-making process. We hypothesize that use of this conversation aid will support SDM, improve patient selection for thyroid biopsy and reduce the unnecessary diagnosis of thyroid cancer.

Specific Aims

AIM 2. Conduct a pilot randomized multicenter trial. Participants (90) will be enrolled at the UF and MC. Patients will be randomized to receive counseling about thyroid biopsy with the conversation aid or routine counseling without it. We hypothesize that conducting a larger efficacy trial and evaluating the effects of using the conversation aid on SDM and rate of unnecessary thyroid biopsies is feasible.

The resulting evidence will serve as proof of concept for the use of a SDM conversation aid to improve the care of patients with thyroid cancer and preliminary evidence for larger efficacy trial.

Research Plan

We hypothesize that the use of a conversation aid in patients with thyroid nodules will enhance the collaboration between patients and clinicians, supporting SDM and lead to adequate and careful selection of patients that should undergo thyroid biopsy in accordance with current clinical practice recommendations. If successful, this innovative intervention will help close the gap between practice recommendations and adequate selection of patients for thyroid biopsy.

In this proposal, we plan to use tools from communication and implementation science to update our conversation aid. The updated prototype will be used on a pilot feasibility, Hybrid 1 study design in which we aim to understand the barriers to implementation (following the Consolidated Framework for Implementation Research Construct) at the same time as we assess feasibility and obtain preliminary estimates of efficacy.

The sample size that is provided for each aim is the total recruitment goal for both centers, with the goal of recruiting half of the patients at each site.

AIM2. Conduct a pilot randomized multicenter trial using the updated conversation aid to assess feasibility and obtain preliminary estimates of efficacy for a larger clinical trial.

In order to understand the extent to which a conversation aid will support SDM and allow for a better selection of patients for thyroid biopsy, a large multicenter randomized trial would be required. In order to obtain information about the feasibility of conducting such trial and preliminary information about outcome effects that can serve as scientific premise, we will conduct a pilot feasibility study.

Settings. The Endocrinology, Ear, Nose and Throat (ENT) and Surgery Clinic at the University of Florida, FL and the Division of Endocrinology at MC, MN.

Participants and identification procedures.

1.Patients: Eligible patients would be identified by review of the upcoming clinic schedule of participating clinicians. We will include up to 50 English-speaking adults > 18 years old who present for evaluation of a thyroid nodule and discuss the need for thyroid biopsy. UF students and staff will be included in the study, although not targeted. We will exclude patients with hyperthyroidism, pregnant patients and those in which the nodule of interest has already been biopsied or who have received counseling by a local specialist in the year before their visit.

2.Clinicians: We will enroll clinicians that counsel patients with thyroid nodules from the endocrinology, ENT and surgery divisions at UF and from the endocrinology division at MC.

Intervention/control: We will randomize patients who need to receive counseling regarding the need for thyroid biopsy to clinicians that will use the updated conversation aid (final result of AIM1) in the intervention arm or usual counseling (without the aid) in the control arm.

In the intervention group, clinicians will conduct the encounter per standard care procedures with the addition of having access to the conversation aid for thyroid nodules prototype. The tool will be accessed online or through an available link in the Electronic Medical Record (EMR). The tool summarizes the risk for thyroid cancer, management options, prognosis of thyroid cancer and has been developed to facilitate the conversation between patients and clinicians. (See supplementary material or previously provided link.) Before clinicians use the tool, study personnel will review the conversation aid with participating clinicians and do a demonstration so that they are familiarized with the tool.

The clinician will conduct the encounter per their standard of care. As access to the tool will be available to ensure contamination does not occur the study coordinator will inform the clinician prior to entering the room that the patient is to receive standard care and that the tool is not to be accessed.

Enrollment, randomization and blinding: Eligible patients will be allocated using a random sequence generated by the study statistician at UF. Study coordinators at both sites will approach eligible patients at the time of their visit and invite them to participate. Once the patient is enrolled, the coordinator will obtain their allocation using an online tool, allowing for allocation concealment. Clinicians will be aware of the arm to which the patient has been randomized. Patients will be blinded to the research question, as informed consent documents will only inform them of the goal of testing different communication approaches. Data analysts, statisticians, video reviewers, will not be blinded to group allocation given the pilot nature of this project.

Consent.

1) Patients. Patients would be invited to participate once they have been roomed and are waiting to see their clinician. The informed consent process will take place in a private room. We will obtain written informed consent, consent for video/audio recording and authorization for medical chart review to obtain information related to their medical history and thyroid nodule features. Study participation also includes completion of a post visit survey and a 6 month follow up survey (in person/mail/electronic version).

2) Clinicians. Eligible clinicians are those who counsel patients with thyroid nodules. We will approach eligible clinicians at their convenience to discuss the goals of the study and their potential participation. We will obtain written informed consent and consent for audio/video recording. Study participation also includes completion of a baseline survey and post visit short survey (in person/electronic).

3) Guest. If an eligible patient has a caregiver/guest with them we will seek the consent for participation given that their participation during the medical visit would be recorded. If a guest does not want to participate, the patient would not be included in the study as we don't want to disrupt their visit dynamic. Informed consent and consent for audio/video recording will be obtained.

4) Other. Commonly, clinicians would work with scribes, students, and other ancillary staff. We will obtain consent for audio/video recording during the medical visit.

Measurements and Outcomes. The main outcome of AIM 2 (pilot study) is to determine if conducting a larger study introducing a conversation aid for patients with thyroid nodules is feasible. This pilot study will allow us to test the performance characteristics and capabilities of study designs, measures, procedures, recruitment and operational strategies that can inform the design of a larger study. To achieve this aim we will measure the following outcomes using collected data from recordings of the medical visit, post visit survey during the day of the visit and 6-9 months for patients and at baseline and after each encounter for clinicians, and medical record review). To easy participation, surveys can be completed using printed versions in person/mail or electronic.

1. Feasibility of trial procedures. We will measure the proportion of eligible patients after review of upcoming clinical visits, enrollment and refusal reasons, ability to randomize patients and tolerability by patients and clinicians of the required assessments (time to complete assessments and obtain complete assessment at 6-9 months of follow up). This information will be obtained from adequate documentation and collection of data in pre-designed electronic forms.

2. Feasibility of using the conversation aid in clinical practice (implementation of the intervention in clinical encounters). We will evaluate the recording of clinical encounters to assess fidelity of use of the conversation aid. We will review the recordings of the control group to assess for contamination. Contamination refers to a clinician who, having used the conversation aid with a prior patient, is able to recreate elements of the conversation aid with a subsequent patient allocated to receive usual care. If there is lack of fidelity with the intervention or contamination in the control group, this would require further exploration and possible changes in the study design of a larger trial.

3. Empirical evidence of the study parameters for the outcomes of interest. Preliminary information regarding outcomes in pilot studies is at risk for bias due to imprecision associated with small samples sizes; a future randomized clinical trial would be powered using clinically significant differences. The main goal of this study is to assess the feasibility of assessing the effect of this novel conversation aid to increase the likelihood of completing a subsequent larger efficacy trial. However, obtaining information about study parameters would be helpful.

We will measure these outcomes by direct observation of recorded clinical visits and post-visit questionnaires given to patients and their clinicians.

A. Quality of SDM. The quality of decision-making is multidimensional. To measure the quality of SDM we will measure: 1) Knowledge transfer: assessed using a 13-item questionnaire that would include 10 questions related to the content of the conversation aid and three questions not contained in the conversation aid. We would expect similar performance between the groups in the questions that are not included in the conversation aid. 2) Risk communication: assessed by asking patients to estimate their risk for thyroid cancer, as ___ out of 100 people just like you. 3) Satisfaction of patients and

clinicians with the amount of information shared and recommendation for the use SDM to others, assessed with a single item (Likert format). 4) Patient satisfaction with their decision assessed using the Decisional Conflict Scale (DCS), a 16-item, extensively validated, and commonly used scale.

B. Processes of SDM. We will explore:1) the degree to which clinicians involved patients in the medical decision process, by evaluating the clinical visit recordings using the OPTION score. This is a 12-item scale that is based on review of clinical encounters with each item receiving a score of 0-4. It has been validated and is used extensively in SDM trials.

C. Rate of biopsy and distribution according to guidelines recommendations. We will calculate the overall rate of biopsy at the time of visit and at 6-9 months of follow up based on chart review and patient contact. We will compare the rate of biopsy between groups according to guidelines recommendations (categorized as biopsy recommended, consider biopsy, do not perform). These recommendations are based on the size of the nodule and the risk for thyroid cancer. We will expect more variation in the group where biopsy should be considered; but will also explore the availability of the conversation aid to support conversation where thyroid biopsy should not be performed.

D. Worry/Distress. Patients that undergo surveillance for the management of low risk thyroid cancer significantly worry. Significant distress/worry in those choosing observation of a thyroid nodule might limit the implementation of conservative management. To understand the baseline and 6-month level of distress/worry, about a thyroid cancer diagnosis we will use the Impact of Event Scale (IES); a tool of 22 items scored from 0-4. We will also use four questions to assess the degree of worry based on previous studies on thyroid cancer patients (Likert score).

E. Barriers/facilitators: We will collect information regarding length of visit and satisfaction with the decision-making process, as well as fidelity to the use of the decision aid. Additional questions might be added based on the results of the in-depth assessment of feedback from patients and clinicians (AIM 1).

F. Information related to setting up the plan of care: we will collect information through video-graphic analysis in terms of discussion of the diagnostic process and next steps in the plan of care.

We will also include a single item health literacy screening, a 4 item modified subjective numeracy scale and a single item health status measure, to further characterize patients.

In summary, patients with be identified from upcoming clinic visits and asked to participate in the study. The study description and informed consent process will be conducted on a private room. If agreeable to participate the patient and caregiver if present, will allow for video recording of their medical visit and review of their medical record to obtain information related to their past medical history and thyroid disease. After their visit, they will complete a 15-20 minute survey at the clinic or given the opportunity to mail the survey back or complete electronically. Efforts would be made to have the patient complete the visit at the day of the visit. Patients would be asked to complete a 6 month survey and given the option to complete this over the phone/mail or electronic.

The study team will contact patients by phone or email at the 6-9 month mark to follow up on the survey and have it completed. We will use phone and email recorded on the medical record and call patients to discuss how they will prefer to complete the survey. This survey could be completed on the phone or by a link that will be send to participants that will include the an online version of the survey (Qualtrics/Redcap). If unable to talk to the patient on the phone, we will send the survey link directly.

We will attempt to contact the patients by phone/email up to three times during a 2 week period, if not response not further attempts will be completed.

Clinicians would be ask to participate at their convenience and a description of the study and the informed consent process will be conducted in a private room. A demonstration on the use of the conversation aid and a baseline survey will be completed before the first patient is enrolled. A short post visit survey will be completed after each visit.

The data from these sources (recordings of the medical visit, post visit survey during the day of the visit and 6-9 months for patients and at baseline and after each encounter for clinicians, and medical record review) will be used to evaluate the outcomes of interest.

Sample size. Our primary interest is precise estimates of feasibility and acceptability, as well as outcome variability that will aid planning a larger efficacy trial. We plan to enroll up to 90 patients. A sample size of 41 patients per group will allow us to be relatively precise in our conclusions of feasibility outcomes. If we observe a 15% attrition rate out of 41 patients in the intervention group, the 95% confidence interval (CI) for that rate would be (4%, 26%). While this number of patients is insufficient for a definitive answer about efficacy, it allows us to ascertain the following differences, assuming equal variances and alpha of 0.05, we will have 80% power to detect the following differences: 1. For risk communication, based on our previous study approximately 45% of patients in the control group should be able to identify their thyroid cancer risk; with a sample of 41 patients per arm, we will be able to detect a 30% difference and 2. If we estimate that there is adequate selection for thyroid biopsy according recommendations in 60% of patients in the control group, with a sample size of 41 patients per arm we will be able to detect a 27% difference.

In terms of feasibility for patients, the Division of Endocrinology at UF, performs more than 500 thyroid biopsies annually. At the Mayo Clinic, nine clinicians perform more than 750 thyroid biopsies annually.

We have the support of the faculty of both divisions; as such enrolling 3-5 patients per clinician (30-75 clinical encounters), during a 8-month period is feasible. (AIM 1). Similarly, enrolling 90 patients during an 18-month period is feasible for the pilot randomized trial (AIM 2).

The introduction of a conversation aid into clinical practice and the time required for patient enrollment and interview can disrupt clinical flow. KER unit investigators have used the proposed methods for 15 years and we successfully followed these methods during the development of our prototype. Contamination can result from physicians modifying their usual care practice given exposure and use of the conversation aid. Although possible, implementation of SDM in clinical practice has been a challenge suggesting clinicians do not perform these activities without the use of a conversation aid. Moreover, previous studies randomizing at the clinical encounter level have found no evidence of contamination.86 Nonetheless, we will assess for contamination by quantifying the degree of elements of SDM noted in the control group. If contamination is noted, we will consider alternative research designs, e.g., a stepped-wedge approach by which clinicians evaluate patients as usual and start using the conversation aid at randomly selected intervals.

Statistical analysis. The distribution of study variables will be described (using frequencies for categorical variables and measures of central tendency for continuous variables) and compared using relative (relative risk) or absolute (mean differences) measures of association and their 95% CI. For the

primary aims of this study related to the feasibility of conducting a larger RCT, we will calculate the rate of successfully completing each of the identified outcomes and calculate the appropriate 95% CI. For the secondary outcomes, we will follow the intention to treat principle.

We will use standard techniques appropriate for trials, with each outcome compared between study arms using t-tests for continuous outcomes and chi-square tests for dichotomous outcomes. If there are differences in baseline characteristics found by statistical means or found to have clinical relevance between the two study groups, these will be accounted for using regression models which include an indicator for study arm.

Similarly, we anticipate evaluating (as done on previous studies) the potential clustering effect of clinicians evaluating a different number of patients. In addition, we are collecting multiple clinical variables, that can potentially affect outcomes, but in this pilot study will only serve as hypothesis generating.

Data management

Patients approached by study staff that agree to participate will be captured in the remote data capture system (REDCap). Potential eligible patients found to be ineligible or eligible but who decline participation will be captured as well. The reason for ineligibility or reason for decline will be captured along with patients' age, sex, and race/ethnicity.

Data from the medical record will be obtained for all enrolled patients that agree to capture demographic and clinical data.

All video recording will be stored in a secure drive to which only the study personnel will have access.

Clinical information and survey data would be stored into REDCAP and available only to study personnel.

The transcription of recordings required for qualitative analysis will be completed by a third party company. Audio recordings will be send electronically (https://thelai.com/ , Landmark Transcription)

In order to complete study analysis we will receive study information from Mayo including both de-identified and limited data sets. UF data will not be shared with Mayo.

7. Possible Discomforts and Risks:

The participants in the study will not be expose to any significant risks.

This study does not involve any procedures, medications or tests. However, we will be recording the medical encounters during routine care, which might make participants uncomfortable. We will offer the option of audio recording only if preferred and underline with participants that the recording can be stopped at any time.

We will approach patients for enrollment once they are roomed and this could result in a minimal delay in the clinic schedule. To avoid interruption, we will discuss with clinicians before approaching patients during clinic time and if they are running behind, we will not approach the patient. We have completed a study following this approach in our outpatient clinics, and have had no issues related to timing.

In the case of patients enrolled for AIM2, we will randomize patients to receive counseling using a conversation aid that has been develop to facilitate the conversation between patients and clinicians.

We don't anticipate any risk of using this tool, as this is to be used during the visit to support the routine conversation. In addition, they will be asked to complete a survey after their visit and would be contacted for a follow up phone/mail survey 6-9 months after their visit. Similarly, this can result in burden in terms of time. Clinicians in Aim2, would be asked to complete a questionnaire after each visit.

In addition, we will be collecting information from the medical records of patients and recording the medical encounters. These records will only be available to medical personnel and would be stored in a secure network. However, the possibility of data breach would be discussed with participants.

8. Possible Benefits:

The participants of the study would not receive any direct benefit. However, the information obtained from this study will help us refine and test a tool that aims to improve the quality of the conversation between patients and clinicians when discussing the need of thyroid biopsy. This tool will be beneficial for patients diagnosed with thyroid nodules in the future.

9. Conflict of Interest:

None of the investigators has any conflict of interest in regards to patents, owning stock or serving as consultant.

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