How accurate is translaryngeal ultrasound when compared to flexible nasal endoscopy in viewing vocal cord mobility in children?

by

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RMYDIV001

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DECLARATION

I, Dr Divya Pallavi Ramyead, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree at this or any other university.

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Signature: Signed by candidate .....

Date: 17.09.2023

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Authors contributions

Divya Pallavi Ramyead: Data collection, Data capture, Conceptualisation of technique, Formal analysis, Manuscript write up

Fiona Kabagenyi: Protocol write up, Review and editing

Sandhia Padayachee: Conceptualisation, Protocol write up, Review and editing

Jessica McGuire: Protocol editing

Shazia Peer: Conceptualisation, Protocol write up, Ethics approval, Supervision, Manuscript review and editing

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LIST OF ABBREVIATIONS

FFL Flexible fibreoptic laryngoscopy

TVC True vocal cord

TLUS Transcutaneous laryngeal ultrasonography

TITLE: How accurate is translaryngeal ultrasound when compared to flexible nasal endoscopy in viewing vocal cord mobility in children?

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Abstract

Objectives

Flexible fibreoptic laryngoscopy (FFL) is currently the gold standard for assessment of true vocal cord (TVC) mobility but is invasive and not without risk. The COVID-19 pandemic has led to growing interest in assessment tools that avoid aerosol generation and risk for transmission of disease. Transcutaneous laryngeal ultrasonography (TLUS) is a potentially useful and non-invasive alternative diagnostic tool for assessing true vocal cord (TVC) mobility.

The aim of this study was to determine the accuracy of an application based TLUS as a screening tool for assessing mobility of the true vocal cords (TVC), and to assess the feasibility of its use by an otolaryngologist not formally trained in ultrasonography.

Methods

This was a prospective cohort study conducted after approval by UCT Human Research Ethics committee (HREC 202/2021). Forty children attending the ear, nose, and throat (ENT) clinic at Red Cross War Memorial Children's Hospital (RCWMCH) for an upper airway assessment with FFL were recruited. Exclusion criteria were children on oxygen; with airway instability; and with behavioural disorders. The first author (DR), an ENT registrar without prior knowledge of ultrasonography, was trained by a consultant radiologist to use the Lumify® handheld ultrasound probe and application tool to assess the larynx and true vocal cord mobility. Combined TLUS and FFLs, short, looped, and anonymised videos were formulated. Two qualified ENT specialists (neither trained in ultrasonography) consented to evaluate videos for true vocal cord mobility.

Results

In total, 135 videos were obtained from 40 participants. Ages ranged from 10 days to 9 years, with equal gender representation. On FFL, 92.5% (n=37/40) had normal TVC mobility and 7.5% (n=3/40) had unilateral TVC palsy. The overall accuracy of TLUS evaluation was 95.5% (sensitivity of 100%, specificity of 60%). Although the proportion of cases where normal mobility was correctly identified was 93.3% (n=120/135), the proportion of cases in which abnormal mobility (unilateral vocal cord mobility) was present and correctly identified was 100% (n=135/135). The reliability of TLUS when compared to FFL showed a p value <0.001 and a 100% agreement between ENT specialists evaluating the shared videos.

Conclusions

Our study shows TLUS to be a reliable method of assessing TVC mobility. It is also portable, non-invasive and easy-to-use, making it a potentially useful screening tool especially in resource-limited settings, where FFL might not readily be available. Furthermore, it has potential benefit as a screening tool for TVC assessment for practitioners other than radiologists, e.g., otolaryngologists, who have a good understanding of laryngeal anatomy. However, more studies are needed to fully elucidate use of diagnostic and therapeutic ultrasound in children with airway conditions.

Keywords
Translaryngeal ultrasound, flexible fibre-optic laryngoscopy, non-aerosol generating procedure, non-invasive, vocal cord mobility, paediatric airway, vocal cord paresis, vocal cord palsy

1. Introduction

Awake flexible fibre-optic laryngoscopy (FFL) is currently the gold standard for assessing true vocal cord mobility and upper airway structures. However, FFL is invasive and is an aerosol generating procedure [1]. The risk of laryngospasm is increased in patients with laryngeal obstruction, cardiac and respiratory co-morbidities making the assessment of such patients particularly difficult. Furthermore, general anaesthesia may be required to facilitate the procedure which may result in haemodynamic and respiratory compromise [2]. The challenges in paediatric patients include lack of patient cooperation, difficulty in obtaining a sustained view, poor view of the true vocal cords due to larger supraglottic structures and obstruction from secretions.

The COVID-19 pandemic, together with an increase in airborne diseases, has presented otorhinolaryngologists worldwide with unprecedented challenges regarding the safety of aerosol generating diagnostic procedures. There has subsequently been growing interest in safe and effective alternatives.

Translaryngeal Ultrasonography (TLUS) is a potential alternative to FFL to assess mobility of the true vocal cords and is currently being used as an initial screening tool in many centres internationally. It has been shown to be reliable for assessing vocal fold mobility and structural abnormalities of the airway [3]. It is used in Intensive Care Units (ICU) and for perioperative assessment in patients undergoing cardiac, thyroid or head and neck surgery procedures that carry potential risk of injury to the recurrent laryngeal nerve, the nerve responsible for abduction of the true vocal cords, and that if injured can cause significant airway symptoms [4]. TLUS is also non-invasive, radiation-free, and easy to use.

Although frequently performed by radiologists, studies have shown that it is a feasible modality even when performed by clinicians not trained in ultrasonography, yielding similarly accurate results [5]. In addition, the emergence of increasingly compact and

cost-effective ultrasonographic machines, and translatable technology onto portable devices like tablets, has resulted in greater interest in the role of "point of care clinician-performed TLUS", and in our context, airway specialists in the outpatient clinic, and in peri-operative and ICU settings.

The aim of this study was to evaluate the accuracy of application-based TLUS as a screening tool for true vocal cord mobility in children in a resource-limited setting. In doing so, to determine the feasibility of its use by an ENT specialist, with no formal training in ultrasound, but who was coached by a qualified radiologist in basic technique and interpretation.

2.Research Methods and Study Design

2.1 Study design and setting

A prospective cohort study was carried out at Red Cross War Memorial Children's Hospital (RCWMCH) in two phases from1 February to 30 April 2022.

2.2 Study participants, inclusion, and exclusion criteria

In Phase A of the study, 40 children attending the ENT surgery outpatient's department (OPD) at RCWMCH were recruited. Children aged 13 years or younger who attended the ENT OPD for an upper airway assessment, and subsequently had a diagnostic FFL for various indications (upper airway obstruction, dysphonia, or dysphagia) were included. Children requiring oxygen, with any airway instability, and/or children with behavioural disorders were excluded.

In Phase B, two qualified ENT specialists with more than 2 years of clinical experience evaluated TVC mobility from 10 second looped videos of the 2 modalities, namely FFL and TLUS.

2.3 Study procedure

PHASE A

Following consent, participants underwent TLUS, performed by the first author (DR), an ENT registrar, DR had no prior training or skills in ultrasonography. Laryngeal anatomy, technique and key points of reference were practiced with an experienced radiologist, who demonstrated and then assessed DR's performance. Following this, and prior to commencement of the study, investigator DR performed a minimum of ten

TLUS studies under supervision on children with normal airway anatomy and function. Positioning of the patient, placement of the ultrasound probe, identification of landmarks and assessment of vocal cord mobility were standardized during this informal training.

A Lumify® application-based portable ultrasound system (Philips Ultrasound, Inc, Bothell, Washington) was used to perform TLUS. The system comprises of a handheld transducer (Lumify® ultrasound probe, an L12-4 linear array transducer with 12-4MHz bandwidth) that connects directly to a tablet or mobile phone. The application is free for download from Apple/Android® (Figure 1). A Samsung® Galaxy Tablet S3 (Samsung Group, Ridgefield Park, New Jersey) was used in the study.

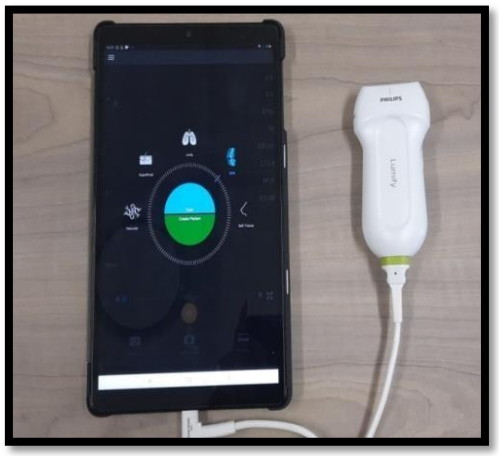

Figure 1: Handheld transducer attached to portable device displaying ultrasound application.

2.4 TLUS technique

Participants were placed in supine position; a small shoulder roll was used for optimum laryngeal position. The neck was exposed from chin to manubrium and skin gently wiped clean. Using contact jelly, the linear probe was then placed in the midline over the anterior larynx in a transverse position over the anterior aspect of the thyroid cartilage.

In the case of difficult visibility, a lateral approach was attempted, with the probe placed transversely on the right, and then left side of thyroid cartilage.

The mobility of the true vocal cords was recorded passively during quiet respiration to avoid arytenoid movement caused by more forceful movement, and where possible, actively with the child vocalising the letter ‘e’. The diagnostic criterion for vocal fold

paralysis used was asymmetric abduction and adduction movements of the true vocal folds during phonation [6]. Where possible the child was asked to temporarily stop breathing to allow the operator to appreciate adduction of the vocal folds to the midline. True vocal cord paresis was seen as decreased movement of true vocal folds while paralysis was seen as no movement. The vestibular folds ("false vocal folds") lie above and slightly lateral to the true vocal folds. They are not involved in phonation. They are composed of echoic fat and are seen as thick, hyperechoic bands in the shape of an inverted letter "v" on ultrasound. On the other hand, true vocal folds are composed of muscle and are much thinner and more hypoechoic on TLUS [7,9,18].

The most described sonographic landmarks are the arytenoids (ART), true vocal folds (TVF) and false vocal folds (FVF) [7,8] as seen in the study images (Figures 2 & 3).

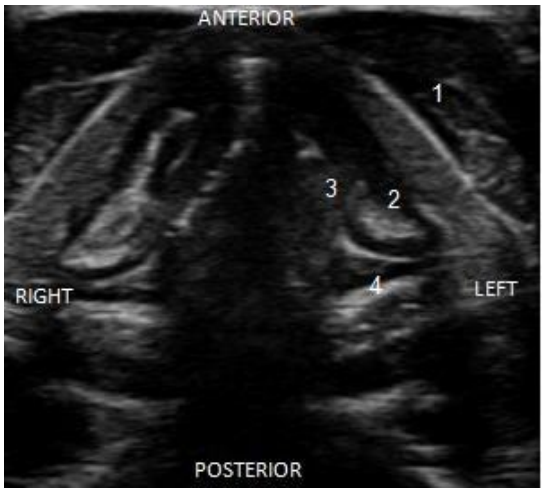

Figure 2: TLUS of vocal cords in abduction where the following anatomical structures are visualised and numbered.
(1) Thyroid cartilage,
(2) Left false vocal cord,
(3) Left true vocal cord and
(4) Arytenoid cartilage

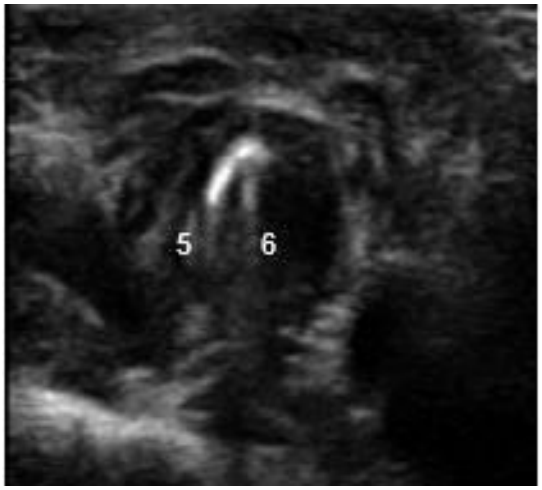

Figure 3: TLUS of left vocal cord palsy with right vocal cord in abduction where the following anatomical structures are visualised and numbered.
(5) Right true vocal cord
(6) Left true vocal cord (fixed in midline)

Following consent, participants underwent TLUS, performed by the first author (DR). The participants had had prior FFL but the investigator was blinded from the diagnoses.

2.5 Video selection and preparation

Once the true vocal cords were adequately visualised, a 10 second video recording was made. All videos were of a suitable clinical quality for viewing the anatomy and mobility of the true vocal cords. Video recordings and related data during each patient TLUS assessment were stored in a password-protected folder on the Samsung® Galaxy Tab S3 (Samsung Group, Ridgefield Park, New Jersey).

A total of 135 TLUS videos and 40 FFL videos were obtained from the 40 participants. All were anonymised, and given a random video study number to prepare for performing phase B of the study i.e., evaluation of the 2 modalities for TVC assessment.

PHASE B

Consent was obtained from both evaluators prior to commencement. Evaluators also oriented to laryngeal anatomy, the position and mobility of the true vocal cords on the ultrasound and videos prior to commencement of their participation in the study. The evaluators were asked to imagine a line drawn from the anterior commissure (apex of where both true vocal cords meet anteriorly), down the centre of the screen to divide the image of the larynx into 2 halves – left and right. They were then asked to report on the true vocal cord mobility of each side. The evaluators were given 60 seconds per video to answer the following questions:

A) Were both true vocal cords mobile?
B) Was a unilateral true vocal cord immobile?
C) If so, which side was immobile (right or left)?
D) Was there a glottic gap in cases of palsy?
E) Evaluators were also asked to comment on other findings.

2.6 Study analysis

Patient demographics included age, gender and any underlying condition were presented descriptively. Categorical variables were presented as number proportions, and percentages. The proportion of “failed assessments”, where the evaluator is unable to clearly visualise the anatomy in each video, was calculated. The proportion of anatomical landmarks identified correctly on TLUS when compared to FFL was

calculated. The proportion of cases in which abnormal mobility, (unilateral true vocal cord paresis) was present and was correctly identified, was also calculated. Fisher's exact test was used to test statistical significance.

2.7 Ethical considerations

Ethical approval was granted by the Human Research Ethics Committee of the of the University of Cape Town (HREC 202/2021).

3. Results

A total of 40 participants aged 10 days to 9 years (median (IQR) = 3yrs) were included in the study and genders were equally represented (Table 1). Normal mobility of the true vocal cords was noted on FFL in 37/40 (92,5%), with the remaining 3 (7.5%) having a unilateral true vocal cord palsy. The overall accuracy, sensitivity, and specificity of TLUS evaluation was 93.3%, 100% and 60% respectively (Table 2). Although the proportion of cases in which normal mobility was correctly identified was 93.3% (n=120/135), the proportion of cases in which abnormal mobility (unilateral true vocal cord mobility) was present and correctly identified was 100% (n=135/135). It was noted that the evaluators detected the correct mobility by 100% on FFL. On the other hand, from TLUS videos, 40% (n= 6/15) of cases with immobile vocal cords were perceived as mobile while 100% of cases with mobile cords (120/120) were correctly identified. The rule of thumb says for a test to be useful; the sensitivity and specificity should be more than 1.5. Our study had a value of 1.6, proving TLUS to be useful. The reliability of TLUS when compared to FFL showed a p value <0.001 and there was 100% agreement between ENT specialists evaluating the shared videos.

	TOTAL PARTICIPANTS (40)
AGE (MONTHS)	
N	40
Median (IQR)	41.1 (13.6-74.3)
Range	1.70-210
GENDER	
Female	20 (50.0%)
Male	20 (50.0%)
UNDERLYING CONDITION	
Upper airway	
Laryngeal	
○ Laryngeal cleft	1 (2.5%)
○ Laryngeal papilloma	2 (5.0%)
○ Laryngomalacia	1 (2.5%)
○ Croup	1 (2.5%)
○ Laryngopharyngeal reflux	1 (2.5%)
Nasal	
○ Adenoid hypertrophy	22 (55.0%)
○ Allergic rhinitis	1 (2.5%)
○ Rhinitis and adenoid hypertrophy	1 (2.5%)
○ Sleep apnoea	1 (2.5%)
Central	
○ Cerebral palsy	1 (2.5%)
○ Traumatic brain injury	1 (2.5%)
○ Myelomeningoencephalocoele	1 (2.5%)
○ Subdural hygroma	1 (2.5%)
Post cardiac operation	5 (12.5%)

Table 1 shows the demographic profile of participants- age, gender, and underlying condition.

EVALUATOR	TLUS	FFL TRUE VOCAL CORD ASSESSMENT						
		Mobile N=120	Immobile N=15	Total N=135	P value Fishers Exact	Sensitivity	Specificity	Accuracy
1								
	Mobile	120	6	126	<0.001	100.0%	60.0%	93.3%
	Immobile	0	9	9				
2								
	Mobile	120	6	126	<0.001	100.0%	60.0%	93.3%
	Immobile	0	9	9				

Table 2 shows results of evaluators' TLUS vocal fold assessment when compared to FFL vocal cord assessment.

4. Discussion

There has been a surge of interest in the use of neck ultrasonography into visualise true vocal cord movement in recent years. In 1987 Raghavendra *et al.* [9] reported that in their cohort of 41 healthy volunteers, TLUS was limited by acoustic shadowing caused by calcification of the laryngeal cartilages. Hu *et al* [10] looked at 229 volunteers with no pathology and found that ultrasonography can "quantitatively measure both the true and false vocal cords with good reliability and reproducibility". A thorough anatomical study of the upper airway was performed by Singh *et al* [11] and showed the ability for TLUS to investigate anatomical variations in the larynx, speech, and swallowing abnormalities, to confirm endotracheal tube placement, as a treatment adjunct in percutaneous tracheostomy and cricothyrotomy, and to predict post-extubation stridor and difficult intubations.

Friedman compared TLUS to FFL in correctly diagnosing vocal cord immobility in infants and children [12]. There are many studies in literature that have since confirmed TLUS as a successful alternative to FFL to evaluate vocal fold mobility in children [7,13,14,16,18].

In our study, the first author underwent ultrasound training with a radiologist and completed 10 suitable ultrasound examinations before starting with study participants. *Wong et al*. evaluated the learning curve of TLUS training in a group of inexperienced

ultrasound assessors and found them to be competent in TLUS after the 7th examination, with little to no change in outcome thereafter [5].

In our study the accuracy was 93.3%, similar to accuracies of >90, and 99-100% reported in studies by Klinge *et al* and Jadcheria *et al* respectively [8,16]. Wang *et al* reported an inter-rater agreement of 96% when comparing TLUS to FFL in children and subsequently found TLUS to be a useful diagnostic tool in vocal fold paralysis [1]. We found an inter-rater agreement of 100% between assessors in our study.

Interestingly, during the TLUS examination, we identified vocal fold movements resulting from the Bernoulli's effect of air through the glottis during respiration. This is not seen with FFL.

Our study, like similar reported studies, has shown feasibility and utility of TLUS to assess true vocal cord mobility by ENT specialist surgeons in a clinic setting. TLUS is non-invasive and is well tolerated by children and their families [6]. In particular, TLUS can be included in practice protocols especially in resource-constrained settings with poor access to expensive flexible fibreoptic laryngoscopy. In addition, the ultrasound device is robust and can be easily transported to outreach facilities far from tertiary hospitals, thereby preventing delays in diagnosing airway conditions in children.

4.1 Strengths and limitations

TLUS assists with challenges faced when assessing patients with communicable diseases such as Tuberculosis and COVID-19 where aerosol generating procedures like FFL are considered high risk [9,15]. Furthermore, TLUS proves to be particularly useful in medically fragile patients or patients with difficult FFL as it does not alter the physiological parameters associated with invasive procedures [19].

However, while it has been shown to be effective in identifying gross true vocal fold mobility, our study did not investigate the laryngeal anatomy or pathology beyond assessing vocal cord mobility Our study was limited by the fact that our cohort comprised 40 participants and only a small proportion had vocal cord paresis. Our study looked solely at vocal cord mobility, which is a limitation.

There are also recognised limitations in the use of TLUS. One of the major drawbacks of TLUS is that it is operator dependent and assessments, such as the objective movement of the true vocal folds, may be subject to inter-user interpretation. In the case of "clinician performed ultrasound", no formal ultrasound training is obtained and there is a learning curve involved for each clinician [5,15]. Fortunately, computer aided diagnostic applications hold promise for the future by making it possible for individuals with basic ultrasound training and a good understanding of the laryngeal anatomy to assess mobility of the true vocal cords. Moreover, some studies have noted difficulty diagnosing mobility of the true vocal cords in children under 12 months of age due to the smaller window of access for the probe and lack of cooperation of younger patients [17]. Finally, a grading system for vocal cord paralysis using TLUS has not been formalised [4].

5. Conclusions

TLUS is a non-invasive and useful alternative screening tool to assess mobility of the true vocal cords. This is the first study in Sub-Saharan Africa to report the use of TLUS in assessing vocal cord mobility in children. Findings from our study correlate similarly with those reported in the literature. While being an adjunctive diagnostic tool, TLUS can potentially reduce the need for, but not replace FFL, in patients requiring assessmentof true vocal cord mobility. The ease and portability of its use, make it an attractive additional tool for otolaryngologists who want to assess vocal cord function. The lack of formal ultrasound training, can be circumvented by working with a qualified radiologist to acquire key diagnostic and technical skills for TLUS assessment. We aim to encourage resource constrained settings to train in using an ultrasound as a screening tool, particularly where FFL is not readily available. This will help identify patients who can then be directed to centres with FFL. More studies, however, are needed to fully define the place of laryngeal ultrasound in the diagnosis and management of children with airway abnormalities.

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APPENDICES

(A) ASSENT FORM

Clinical Research Form (CRF): Assessment

Study No. _____

THE UTILITY OF APPLICATION-BASED TRANSLARYNGEAL ULTRASONOGRAPHY (TLUS) FOR LARYNGEAL ASSESSMENT IN CHILDRENAT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL: A PROSPECTIVE STUDY

ASSENT FORM: (To be used forchildren aged 7 - 13 years of age)

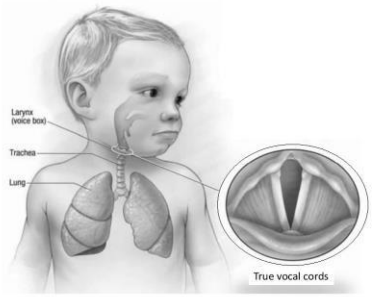
Background

-We breathe and speak through our voice boxthat is found in the neck. This voice box has two bands calledthe vocal cords, which vibrate to formsound. *(see image on right)*

-There are 2 ways a doctor can see these vocal cords and how well they move to produce sound.

1) By using a small camera that passes through the nose. You have probably experienced this already.

2) By using special machine called an ultrasound thatuses a special wand that moves over the front of your neck to the voice box and the vocal cords housed inside. This givesus a black and white picture in real time.



We are asking you to help us find out if this ultrasound method is good enough to look at the voice box, and the movement of the vocal cords that are housed within.

The Procedure:*what we need from you*

-This will only take 20 minutes.

-You will not be alone - your mum or dad will be with you at all times.

-We will ask you to lie on your back. A pillow will be placed under your shoulders.

-A small amount of clear jelly will be applied to your neck andthe small plastic wand also known as a probe,will slide up and down your neck to get a nice picture of your vocal cords.

-We will askyou to say some words that bring out the movement of the vocal cords, to get the best quality video of your vocal cords moving.

-If at any point, you feel uncomfortable, and no longer want to continue, you can say so, and we will stop. There will be no consequences to this.

What happens with the videos?

We will remove any information that identifies you on the videos, and we will combine them with all the study videos. At a future date, we will then ask 3 ENT surgeons to looks at all the videos taken for the study, to determine if vocal cords are moving or not.

Signing this paper means that you have read and understand what the study is about and that you agree to be a part of this study. Being in the study is up to you and no one will be upset if you don't sign the paper or if you change your mind later. This means that it is voluntary.

There may be some words you don't understand or things that you want me to explain more about because you are interested or worried.

Do you have any other questions? We can explain anything that you don't understand to that you want more explanation for.

Certificate of Assent

I have read this information (or had the information read to me). I have had my questions answered and know that I can ask questions later if I have them. I agree to take part in the research.

Name of child _____Signature of child: _____ OR

Date:_____

thumb print

(B) CONSENT FORM: (For Parents, legal guardians)

Clinical Research Form (CRF): Assessment

Study No. _____

THE UTILITY OF APPLICATION-BASED TRANSLARYNGEAL ULTRASONOGRAPHY (TLUS) FOR LARYNGEAL ASSESSMENT IN CHILDRENAT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL: A PROSPECTIVE STUDY

CONSENT FORM: (For parents, legal guardians)

Background

You are invited to allow your child to take part in this research study which aims to identify if using an ultrasound to look at the larynx, is a good enough method to assess vocal cord mobility.

Traditionally, children with problems of the voice box (larynx) are assessed by putting a camera into their nose, in a procedure called flexible nasendoscopy (FNE). Your child already had this assessment earlier. As you know, it is invasive, and it can cause some discomfort. The ultrasound, however, is not invasive, and it can be repeated many times without causing any discomfort to breathing or swallowing, compared to the FNE. It is also simpler, cheaper and has been proven to be as effective as FNE to diagnose vocal cord movement.

Purpose of study and procedure

To evaluate the use of an application-based ultrasound scan of the larynx to assess the vocal cord movement. If you decide to participate, the procedure will take 20 minutes to complete. These will be uploaded with all the other participants' videos, anonymised, and will then be assessed at a later stage by 3 ENT specialists.

Benefits of participating in this study

No risks are involved in the study.The knowledge gained through this research will be helpful in guiding use of ultrasound for detecting vocal cord movement, assessment policies and practice protocols in resource -constrained settings that face similar challenges in management.

Confidentiality

Your privacy is important. All the information gathered during this study will be kept private. The results of this study will be published or presented at a medical meeting or in a medical journal. However, no information will be included that will make it possible for you to be identified.

Costs for participation

There will be no additional costs for you to take part in this study. You will not be reimbursed for taking part in this study. However, the information gained in the results of this study will help children like your child, in need of vocal cord and airway assessments and the use of ultrasonography in thereof.

Can my child stop being in the study?

You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or if you decide to stop.

Participants Authorisation

Your signature below means that you have received this information, have asked the questions you currently have about the research, and have received acceptable answers.By signing this consent form, you indicate that you are voluntarily choosing for your child to take part in this research study. You will receive a copy of the signed and dated form to keep for future reference.

Name of child (please print):_____Date: _____

Parent/legal guardian signature: _____Witness signature:_____

Contact Information

Investigators:
Dr S Peer &Dr F Kabagenyi
University of Cape Town, Faculty of Health Sciences
Division of Paediatric Otolaryngology,
Department of Paediatric Surgery, 6th Floor,
ICH Building, Red Cross Children's Hospital,Milner Road, 7700.

Human Research Ethics Committee
Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za

(C) EVALUATOR CONSENT FORM: (For the ENT Specialist)

Clinical Research Form (CRF): Assessment

Study No. _____

Telephone: 021 658 5012

THE UTILITY OF APPLICATION-BASED TRANSLARYNGEAL ULTRASONOGRAPHY (TLUS) FOR LARYNGEAL ASSESSMENT IN CHILDRENAT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL: A PROSPECTIVE STUDY

EVALUATOR CONSENT FORM: (For the ENT Specialist)

Dear Colleague,

You are invited to participate in a research study comparing two techniques for laryngeal assessment, TranslaryngealUltrasonography (TLUS) and Flexible Nasendoscopy (FNE) as an evaluator.

Traditionally, children with problems of the larynx are assessed using a flexible nasendoscopy (FNE). The equipment used is expensive, delicate and takes a lot of resources. However, translaryngeal ultrasound scan of the larynx (TLUS) is simpler, cheaper and has been proven to be as effective as FNE to diagnose vocal cord movement.
This study aims to determine if TLUS is a good enough method to assess vocal cord mobility when compared to FNE.
We have randomly assigned a number from V1-V120 in no particular order, of paired TLUS and FNE videos from 40 participants that have already taken part 1 of this study. No patient information or identifying data regarding the functional status of the vocal folds will be made available.You will be asked to evaluate the vocal cord mobility of all 120 randomly selected paired videos (V1-V120).

Instructions:
You will be asked to imagine a line drawn down the center of the screen from the anterior commissure, that divides the vocal cords into 2 halves. With this in mind, you will be asked to report;
A) if the vocal cords on either side of the drawn line appears to have equal motion, or if the image on one side of the drawn line appears to be moving more or less than the opposite side;
B) If asymmetry is noted, you will be asked to identify which side appears to be moving less.
You will be given 60 seconds to answer these questions and record your answers on an evaluation form.

Utmost confidentiality of your responses and anonymity will be upheld. There are no risks of participating in this study**.** You will not be reimbursed for taking part in this study. This study is voluntary and you can stop at any time.

What happens at the end of the study?
The results of this study will be published in a medical journal or presented at a medical meeting. However, no information will be included that will make it possible for you to be identified. We hope that the knowledge gained through this research will be helpful in guiding the use of ultrasound for detecting vocal cord movement.

Participants Authorisation
Your signature below means that you have received this information, have asked the questions you currently have about the research, and have received acceptable answers.By signing this consent form, you indicate that you are voluntarily choosing to take part in this research study. You will receive a copy of the signed and dated form to keep for future reference.

Name of Evaluator (please print):_____Date: _____

Signature: _____Witness signature: _____

Contact Information

Investigators:Dr S Peer &Dr F Kabagenyi
University of Cape Town, Faculty of Health Sciences
Division of Paediatric Otolaryngology, Department of Paediatric Surgery,
6th Floor, ICH Building, Red Cross Children's Hospital,Milner Road, 7700.
Telephone: 021 658 5012

Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za

(D) Clinical Research Form (CRF): Assessment

Clinical Research Form (CRF): Assessment

Study No. _____

TITLE:THE UTILITY OF APPLICATION-BASED TRANSLARYNGEAL ULTRASONOGRAPHY (TLUS) FOR LARYNGEAL ASSESSMENT IN CHILDRENAT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL: A PROSPECTIVE STUDY

A) PATIENT DETAILS

Sex: …… MRN: ……

Date of birth: ……..

B) FLEXIBLE NASENDOSCOPIC (FNE) FINDINGS

Date of FNE: ……..Adequate video of more than 10 sec: Yes | No

Underlying condition: …… Adequate video for viewing the vocal cords: Yes | No

Indication for FNE: dysphonia | upper airway obstruction| dysphagia | aspiration | other

Objective Findings:

Normal Bilateral Vocal Cord mobility: Yes | No *If yes, skip to TLUS.*

If NO Unilateral Vocal Cord immobility: Yes | No

If YES, LEFT or RIGHT

If palsy: is there a glottic gap? Yes | No

If palsy, is there compensation of the opposite vocal cord? Yes | No

Other findings / comment: ……..

Reported difficulty of scope: No difficulty | Some difficulty | Moderate difficulty | completed with difficulty

Adverse events from FNE: Yes | No | Comments: ……..

C) **TRANSLARYNGEAL ULTRASOUND (TLUS) FINDINGS**

Date of TLUS:……..3 adequate videos of more than 10 sec: Yes | No

Objective Findings:

Normal Bilateral Vocal Cord mobility: Yes | No

If NO Unilateral Vocal Cord immobility: Yes | No

If YES, LEFT or RIGHT

If palsy: is there a glottic gap? Yes | No

Other findings / comments: ……..

Reported difficulty of TLUS: None| Somewhat | Moderate | Very

Adverse events from TLUS: Yes | No | Comment: ……..

(E) Clinical Research Form (CRF): Video Evaluations TLUS vs FNE

Clinical Research Form (CRF): Video Evaluations TLUS vs FNE

Evaluator 1 | 2 | 3

TITLE: THE UTILITY OF APPLICATION-BASED TRANSLARYNGEAL ULTRASONOGRAPHY (TLUS) FOR LARYNGEAL ASSESSMENT IN CHILDREN AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL: A PROSPECTIVE STUDY

Date of Assessment: ..... **VIDEO NO: .....**

Q1: TRANSLARYNGEAL ULTRASOUND (TLUS):

Normal Bilateral Vocal Cord mobility: Yes | No *If yes, skip following questions & proceed to Q2*

If NO, Unilateral Vocal Cord immobility: Yes | No

If YES, LEFT or RIGHT

If palsy: is there a glottic gap? Yes | No

Other findings / comments: .....

Q2: FLEXIBLE NASENDOLARYNGEAL ENDOSCOPY (FNE):

Normal Bilateral Vocal Cord mobility: Yes | No *If yes, skip following questions*

If NO, Unilateral Vocal Cord immobility: Yes | No

If YES, LEFT or RIGHT

If palsy: is there a glottic gap? Yes | No

Other findings / comments: .....

(F) Ethics approval form

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

07 April 2021

HREC REF: 202/2021

Dr Shazia Peer
ENT Surgery
H53 OMB
Groote Schuur Hospital
Observatory
7925

Email: Shazia.peer@uct.ac.za

Dear Dr Peer

PROJECT TITLE: THE UTILITY OF APPLICATION-BASED TRANSLARYNGEAL ULTRASONOGRAPHY (TLUS) FOR LARYNGEAL ASSESSMENT IN CHILDREN AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL: A PROSPECTIVE STUDY

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Subject to adding a sentence why they may contact the HREC.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 and 06 July 2020, found on the following website link:
http://www.health.uct.ac.za/fhs/research/humanethics/about

Approval is granted for one year until the 30 April 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

(G) Annual Progress Report

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.4.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	16/3/22

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14 March 2022		
HREC REF Number	202/2021	Current Ethics Approval was granted until	30 April 2022
Protocol title	The utility of application-based translaryngeal ultrasonography (TLUS) for laryngeal assessment in children at Red Cross War Memorial hospital: A prospective study		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	x No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	A/Prof Shazia Peer		
Department / Office Internal Mail Address	Division of Otorhinolaryngology (ENT Surgery) Department of Surgery. Shazia.Peer@uct.ac.za		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

1.1 Does this protocol receive US Federal funding?	☐ Yes	X No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	X No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please **(tick ✓)**appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ✓***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	X
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	N/A
Billing Address of Sponsor:	
Vat Number:	
Contact person	
Telephone number	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Email Address	
2. **Internal Journal Billing:**	
Fund Number:	N/A
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

1. FHS011 Deviation form to add co-investigator Dr Divya Ramyead
2. Updated Protocol with CRF and consent

3. Protocol status (tick ✓)

X	Open Enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	10
Number of participants enrolled, since last HREC Progress report (continuing review)	
Additional number of participants still required	30

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	

6. Cumulative summary of participants

Total number of participants who provided consent	10
Number of participants determined to be ineligible (i.e. after screening)	4

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Number of participants currently active on the study	10
Number of participants completed study (without events leading to withdrawal)	10
Number of participants withdrawn at participants' request (i.e. changed their mind)	n/a
Number of participants withdrawn by PI due to toxicity or adverse events	n/a
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	n/a
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	
nil	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	
nil	

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
This study is still ongoing as we need to recruit more participants. This has taken time due to covid and restrictions on outpatient clinic numbers. This has changed now, and we expect to get our numbers by July 2022.

8. Protocol violations and exceptions (tick ✓ all that apply)

X	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

X	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
nil

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	X Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	X Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	X Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	X No
If yes, please explain:	

12. Level of risk (tick ✓)

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
X	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
n/a

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**			
☐ Yes	☐ No		X Not Applicable – N/A
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	X No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	14 March 2022

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

International Journal of Pediatric Otorhinolaryngology:

Author guidelines

Article structure

Abstract

For Full Length Articles (Research Papers) a structured abstract, by means of appropriate headings (e.g. Objectives, Methods, Results, Conclusion), should provide the context or background for the research and should state its purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations. Abstracts for Case Reports should not exceed 100 words and should not have a structured format. Abstracts for Review Papers may be structured or non-structured depending on author preference.

Subdivision - numbered sections

Divide your article into clearly defined and numbered sections. Subsections shouldbe numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should bedescribed.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices

If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq.

(A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

Title. Concise and informative. Titles are often used in information-retrievalsystems. Avoid abbreviations and formulae where possible.
Author names and affiliations*.* Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. Ensure that the e-mailaddress is given and that contact details are kept up to date by the corresponding author.
Present/permanent address*.* If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grantnumber zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

Artwork

Electronic artwork

General points

- Make sure you use uniform lettering and sizing of your original artwork.
- Embed the used fonts if the application provides that option.
- Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size the illustrations close to the desired dimensions of the published version.
- Submit each illustration as a separate file.

A detailed guide on electronic artwork is available.

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format. Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings, embed all used fonts.

TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.

TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.

TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.

Please do not:

- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
- Supply files that are too low in resolution;
- Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article. Please indicate your preference for color: in print or online only. Further information on the preparation of electronic artwork.

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Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article.
Please avoid using vertical rules.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full.
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Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given. Example: '…..as demonstrated [3,6]. Barnaby and Jones [8] obtained a different result…. '

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Examples:

Reference to a journal publication:
[1] J. van der Geer, J.A.J. Hanraads, R.A. Lupton, The art of writing a scientificarticle, J. Sci. Commun. 163 (2010) 51–59.
Reference to a book:
[2] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, NewYork, 2000.
Reference to a chapter in an edited book:
[3] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article,in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304.
Reference to a website:
[4] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/, 2003 (accessed 13.03.03).
Reference to a dataset:
[dataset] [5] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1, 2015. http://dx.doi.org/10.17632/xwj98nb39r.1.