Trial Protocol

Trial N° 16.21.CLI

NPDI Code N° DNHS-100135

A prospective multi-center study comparing the performance of the Dysphagia Detection System (DDS) in detecting impaired swallowing safety and efficiency as compared to the clinical reference method - videofluorosopic swallowing study (VFSS)
PORSCHE

Version:	**Amendment**
N°	**02**
Date:	**25 September 2017**
Sponsor	Nestec Ltd Avenue Nestlé 55 CH-1800 Vevey Switzerland

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3 PROTOCOL AMENDMENT VERSION 02

Section		***Change***	***Rationale***
Synopsis	Primary/Secondary Endpoints	Removed mention of # of boluses following each endpoint. Changed the order of secondary endpoints: The sensitivity & specificity for swallow safety using moderate barium (MOD-Ba) is now secondary endpoint #2 followed by efficiency endpoints	Reduced # of boluses per thin and mildly thick consistency. Thus determined mention of bolus per consistency was redundant here. Aligned on clincial priority: safety of swallowing has priority over efficiency of swallowing
Synopsis	Secondary Objective	Added in Secondary Objective from Section 8.3	Missing from Synopsis
Synopsis	Exploratory Endpoints	Added additional Exploratory Endpoint: Impact of VFSS results on Nutritional Management	Explore the relationship between VFSS findings and nutritional decisions
Synopsis	Trial Design	Removed 'for thin (THIN-Ba boluses)' from the statement 'The study is designed as operationally seamless to facilitate the updating of the threshold on the ROC curve for swallowing safety if required.	Clarification that the design pertains to not just the thin boluses.
Synopsis	Trial Design	Increase enrollment from 800 to 900 (with a maximum enrollment increased from 1150 to 1300).	Update to statistical plan increased the number of study samples needed.
Synopsis	Trial Design	Added 'At the last interim analysis a sample-size re-estimation will be carried out in order to compensate for design parameters like accuracy and prevalence that may be slightly different from the values assumed during trial design.'	Added clarification should design parameters assumed during the trial design not be met, then a sample size re-estimation is necessary.
Synopsis	Procedure	Decrease of boluses from 6 to 5 thin barium stimulus and decrease from 6 to 4	Sensitivity and specificity end-points are changed from evaluation at bolus

		boluses of barium thickened to mildly thick	(swallow) level to a patient level following FDA advice. The algorithms for THIN-Ba, MILD-Ba and MODERATE-Ba are based on anaylsis of up to 4, 3 and 3 swallows per patients for each consistency respectively. One additional bolus in each consistency will be collected to compensate for bolus-level data lost due to unreadable VFSS signals (Rationale: According to the analysis of Exploratory trial with more than 4000 boluses, up to 14% of boluses were missing golden standard (VFSS) rating mainly due to insufficient quality of VFSS videos).
Synopsis	Procedure	4, 3 and 3 boluses for THIN-Ba, MILD-Ba and MOD-Ba will be analyzed using the classifier algorithms for sensitivity/specificity results. According to the exploratory trial, VFSS data for safety or efficiency can be missing for up to 14% boluses due to quality of VFSS recording. To compensate for potential losses of boluses due to missing gold standard (VFSS) data, 5, 4 and 4 boluses will be collected for the three consistencies respectively. Clarification of when subject will be followed after the study procedure. Redefined 'within 2 business days' and deleted 'for approximately 1 day' after the study procedure.	See above Standardized wording across the protocol of when a subject will be followed after the study procedure.
Synopsis	Trial Population	Increase enrollment to 900 (from 800) with a maximum	Update to statistical plan increased the number of

		enrollment increased to 1300 from 1150).	study samples needed.
Synopsis	Inclusion Criteria	Removed from the patient group of stroke patients the qualifier of 'with scores 0 or 1 on question 1a of NIHSS'	Deemed duplicative with Inclusion Criteria : Subject able to give voluntary, written informed consent to participate in the clinical investigation and from whom consent has been obtained / or a consultee has consented on the subjects behalf in line with nationally agreed guidelines concerning adults unable to consent for themselves. Additionally not all sites use NIHSS scoring.
Synopsis	Trial Visits	Added (up to 2 weeks prior) at end of the following sentence : Consent must be obtained prior to the study procedure. Clarification of when subject will be followed after the study procedure. Redefined 'within 2 business days' and deleted 'for approximately 1 day' after the study procedure.	Added clarification of time a subject may be consented prior to the study prodedure. Standardized wording across the protocol of timeframe a subject will be followed after the study procedure.
Synopsis	Statistical Method	Change of specificity from 'of at least 55%' to 'greater than 50%'	The targeted sensitivity and specificity of about 90%/ 60% is maintained, however to avoid substantial sample size increase due to change from bolus to patient level endpoint, use of a broader confidence interval is proposed for specificity.
Synopsis	Statistical Method	Change of the type-I error from 5% to '2.5% (one-sided)'.	Clarification requested by FDA
Synopsis	Blinded Mid-Course Enrichment	Section header : Blinded Mid-Course Enrichment is removed. The following is removed : A further inclusion/exclusion criteria based on the screening test (using Dysphagia screening as per usual site-specific protocol)	As per FDA recommendation, The Blinded Mid-Course Enrichment is abandoned, but the study will continue to monitor the prevalence in the Trial. The plan to

		results may be imposed. This will be reflected in a formal protocol-amendment and will be implemented before the first interim analysis. Replaced by : The study population should be representative of the device intended use population (at risk of dysphagia). According to the published literature, estimated prevalence of dysphagia in the target population varies from 20-50%. The necessity to carry out VFSS may result in sites selecting patients at higher risk than in the intended target population (such as those already assessed by SLPs). We therefore blindly monitor the prevalence and retrain sites as necessary in order to ensure that they recruit at-risk patients (not only those already assessed as dysphagic by SLPs).	consider change in recruitment criteria is also no longer relevant
6	Table 1 : Sequence of Study Procedures	'Swallow Exam of up to 5 (not 6) sips of thin barium…' and 'Swallow Exam of up to 4 (not 6) sips of mildly-thick barium	Sensitivity and specificity end-points are changed from evaluation at bolus (swallow) level to a patient level following FDA feedback. The algorithms for THIN-Ba, MILD-Ba and MODERATE-Ba are based on anaylsis of up to 4, 3 and 3 swallows per patients for each consistency respectively. One additional bolus in each consistency will be collected to compensate for bolus-level data lost due to unreadable VFSS signals. Standardized wording

		Clarification of when subject will be followed after the study procedure. Redefined 'within 2 business days after the study procedure.'and deleted 'approximately 1 day after all exams are complete.'	across the protocol of when a subject will be followed after the study procedure.
8.2 & 8.4	Primary/Secondary Endpoints	Removed mention of # of boluses following each endpoint. Changed the order of secondary endpoints: The sensitivity & specificity for swallow safety using moderate barium (MOD-Ba) is now secondary endpoint #2 folowed by efficiency endpoints	Reduced # of boluses per thin and mildly thick consistency. Thus, the mention of bolus per consistency was redundant here. To align on clincial priority: safety of swallowing has priority over efficiency of swallowing.
8.5	Exploratory Endpoints	Added additional Exploratory Endpoint: Impact of VFSS results on Nutritional Management (% patients with diet changes (advanced/more conservative))	Explore the relationship between VFSS findings and nutritional decisions for future trials on dysphagia.
9	Procedure	Decrease of boluses from 6 to 5 thin barium stimulus and decrease from 6 to 4 boluses of barium thickened to mildly thick. Added '4, 3 and 3 boluses for THIN-Ba, MILD-Ba and MOD-Ba will be analyzed using the classifier algorithms for sensitivity/specificity results. According to the exploratory trial, VFSS data for safety or efficiency can be missing for up to 14% boluses due to quality of VFSS recording. To compensate for potential losses of boluses due to missing gold standard (VFSS) data, 5, 4 and 4 boluses will be collected for	same as in the synopsis same as in the synopsis

		the three consistencies respectively'.	
10	Trial Population	Increased enrollment to 900 (from 800) with a maximum enrollment increased to 1300 from 1150.	same as in synopsis
10.1	Subject Inclusion Criteria	Removed from the patient group of stroke patients the qualifier of 'with scores 0 or 1 on question 1a of NIHSS'	same as in synopsis
12.1	Screening	Added a timeframe prior to study procedure may be consented '…provide their consent to particiapte in the study 'within 2 weeks of the study procedure.'	Added clarification of time a subject may be consented prior to the study prodedure.
12.3	Baseline Assessment	Removed the following data to be collected for stroke patients : Modified Rankin Scale and Barthal Index Added the following data to be collected for parkinson patients (if available) : Functional Independence Measurement	The patient scales deemed necessary for data collection were reassessed.
12.5	Swallow Exam	Up to 5 (*not 6*) boluses of thin barium and up to 4 (*not 6*) boluses of mildly thick barium	same as in synopsis
12.7	Post Exam	Clarification of when subject will be followed after the study procedure. Redefined 'within 2 business days' and deleted 'approximately 1 business day' after the study procedure.	Standardized wording across the protocol of when a subject will be followed after the study procedure.
14.2	Success Criteria and hypothesis testing	Change of specificity from 'of at least 55%' to 'greater than 50%' Change of the type-I error from '5%' to '2.5% (one-sided)'.	same as in synopsis same as in synopsis
14.3	Threshold Optimization	Added: 'The study population should be representative of the device intended use population (at risk of dysphagia). According to the published literature, estimated prevalence of dysphagia in the target population varies from 20-	same as in synopsis

		50%. The necessity to carry out VFSS may result in sites selecting patients at higher risk than in the intended target population (such as those already assessed by SLPs). We therefore blindly monitor the prevalence and retrain sites as necessary in order to ensure that they recruit at-risk patients (not only those already assessed as dysphagic by SLPs).'	
14.4 (section removed)	Blinded Mid-Course Enrichment	Section 14.4 : Blinded Mid-Course Enrichment is removed. The following is removed : 'A further inclusion/exclusion criteria based on the screening test (using Dysphagia screening as per usual site-specific protocol) results may be imposed. This will be reflected in a formal protocol-amendment and will be implemented before the first interim analysis'.	same as in synopsis
14.4	Sample Size Calculations	'if a high.risk population with at least 60% to 70% prevalence is sampled and if at least 30% of the swallows coming from Dysphagis patients show impaired safety' changed to 'If approximately 35% patients show impaired safety' Change from '...then a power of 90% can be achieved with 700-800 (from 500 to 600) subjects under a fixed design. Increased sample size : Considering that data from additional 100 to 200 subjects may be used for threshold calibration, the starting sample size is 900	Clarification /simplification Revised power calculation Revised power calculation

		(from 800) subjects. Added : A sample size re-estimation will be carried out at the last interim analysis.	 Clarification of last interim analysis
14.7	Central Blinded VFSS Assessors	Added 'if the consensus can not be reached due to a noisy VFSS signal, the bolus will be rated as missing VFSS'.	Added clarification for VFSS rating process
14.8.1	Full Analysis Dataset	'For this trial, ITT population is defined as the population able to complete 'at least 3 boluses' is changed to 'at least one' THIN-Ba bolus.' Added : Missing data will be reported and sensitivity analysis carried out. Added : The THIN-Ba consistency boluses (up to 4) with available simultaneous VFSS and DDS data per patient will be included into the analysis. As will the MILD-Ba and the MOD-Ba consistency boluses (up to 3 each) with simultaneous VFSS and DDS data per patient.	Reflect change of endpoint from bolus to patient level: algorithms should produce patient-level result if at least one bolus is completed. Clarification Clarification
17.6	Retention of Data	Change from 'Records can be in paper or electronic format.' to 'The eTMF is the official regulatory file for the study and will be used for monitoring the study and by FDA for any inspections (audits) under the Bioresearch Monitoring (BIMO) program. The only paper files included in the official regulatory file will be all original signed informed consent forms.'; (also added eTMF to Section 4: Abbreviations)	Clarification of official records format for the study.

4 ABBREVIATIONS

AE	Adverse Event
CPM	Clinical Project Manager
CRA	Clinical Research Associate (synonym: trial monitor)
CRO	Contract Research Organization
CRF	Case Report Form
CSE	Clinical Swallow Evaluation
DDS	Dysphagia Detection System
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDQF	Electronic Data Query Forms
EM	Electromagnetic
eTMF	Electronic Trial Master File
FEES	Fiberoptic Endoscopic Evaluation of Swallowing
FIM	Functional Independence Measurement
GCP	Good Clinical Practice
GSD	Group Sequential Design
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IRB	Institutional Review Board
iSC	Independent Statistical Center
ITT	Intent-To-Treat
MBS	Modified Barium Swallow
MD	Medical Doctor
NPV	Negative Predictive Value
NRC	Nestlé Research Centre
PM	Project Manager
PP	Per-protocol
PPV	Positive Predictive Value
RCRI	Regulatory & Clinical Research Institute, Inc. (CRO for this trial)
ROC	Receiver Operating Characteristic (curve)
SAE	Serious Adverse Event
SLP	Speech Language Pathologist
SOP	Standard Operating Procedures
UADE	Unanticipated Adverse Device Effect
TUC	Thicken Up Clear
VFSS	Videofluoroscopic Swallowing Study

5 SYNOPSIS

TRIAL TITLE	A prospective multi-center single-blinded study comparing the performance of the Dysphagia Detection System (DDS) in detecting impaired swallowing safety and efficiency as compared to the clinical reference method - videofluoroscopic swallowing study (VFSS).
TRIAL N°	16.21.CLI
TRIAL OBJECTIVES AND ENDPOINTS	**Primary objective** The primary objective is to validate the DDS against the VFSS for detecting swallow safety problems using thin barium stimulus (THIN-Ba). **Primary endpoint** The primary efficacy of the DDS will be measured as specificity and sensitivity obtained from comparing the DDS predicted swallow safety outcome with the clinical reference standard VFSS swallow safety outcome (binary) for thin barium (THIN-Ba) boluses **Secondary Objective** The secondary objective is to validate the DDS against the VFSS for detecting swallow efficiency problems using thin stimulus (THIN-Ba) and swallowing safety and efficiency using mild and moderately thick stimuli. Swallowing efficiency described the ability to clear a bolus through the pharynx in 2 swallows or less without leaving residue in the throat. The impaired swallowing efficiency is defined as at least 50% residue as determined by VFSS. **Secondary endpoints** At the final analysis, if the primary endpoint meets statistical significance then formal testing and analysis for the following secondary endpoints will be carried out in a hierarchical fashion in the specified order: 1. The sensitivity & specificity for swallow safety using mild barium (MILD-Ba) 2. The sensitivity & specificity for swallow safety using moderate barium (MOD-Ba) 3. The sensitivity & specificity for swallow efficiency using THIN-Ba 4. The sensitivity & specificity for swallow efficiency using MILD-Ba 5. The sensitivity & specificity for swallow efficiency using MOD-Ba **Exploratory endpoints** • Prevalence of boluses resulting in “grey” outcomes of the classifier for safety and efficiency of the swallows on thin (THIN-Ba) and thickened stimuli (MILD-Ba and MOD-Ba) • Prevalence of impaired swallowing safety and efficiency of the swallows of thin (THIN-Ba) and thickened stimuli (MILD-Ba and MOD-Ba) as determined by VFSS at bolus and participant levels. • Positive and Negative predictive value (PPV and NPV) of detecting swallow safety and efficiency problems using DDS and using THIN-Ba, MILD-Ba and MOD-Ba stimuli. • Prevalence of impaired swallowing safety and efficiency of the swallows of thin (THIN-Ba) and thickened stimuli as determined by VFSS at bolus and patient level by the following predetermined subgroups: stroke, other neurological diseases, other patients. • Timing and Outcome of the dysphagia screening as per usual care protocol of the study site • Timing and Outcome of the dysphagia Clinical Swallow Assessment (CSE) by SLP (speech language pathologist) where applicable as per usual care protocol of the study site • Impact of VFSS results on Nutritional Management • DDS accuracy in terms of AUC, sensitivity and specificity by sub-group (Stroke, Other Neurological Diseases and Others) for swallow safety and efficiency problems for all consistencies (THIN-Ba, MILD-Ba, MOD-Ba) **Safety Endpoints** All adverse events (AEs) will be observed during and within two business days following the study procedure.

TRIAL DESIGN	An operationally seamless single-arm, prospective, multicenter, single-blinded for central outcomes assessors trial to test DDS in assessing swallowing safety and efficiency in patients at risk of oropharyngeal dysphagia. The study is designed as operationally seamless to facilitate the updating of the threshold on the ROC curve for swallowing safety if required and to validate the DDS classifier with a fixed threshold using an independent validation set. The study has been planned to enroll and study approximately 900 patients (maximum enrollment 1300) with the possibility of early stopping for futility or success. The trial will start with the frozen classifier based on a fixed threshold derived using ROC curve from the completed exploratory trial. The clinical trial will initially start as a 3-look group sequential design (GSD). At the first interim, sensitivity and specificity will be calculated based on the fixed threshold. If the Area under the ROC curve at the first interim is above 75% but the sensitivity and/or specificity are low then the threshold will be revised based on the first interim data. In this case, the validation will exclude the data used for the first interim, i.e. the validation trial will start with the first patient enrolled after the first interim analysis data cut-off date. In case the fixed threshold from the completed exploratory trial data is not revised using the first interim data, the trial continues as planned. At the last interim analysis a sample-size re-estimation wil be carried out in order to compensate for design parameters like accuracy and prevalence that may be slightly different from the values assumed during trial design. If the classifier cannot analyze the signal (e.g. due to signal-to-noise level), it will result in a “grey” outcome of the classifiers. The prevalence of “grey” outcomes among analyzed boluses for safety and efficiency classifier on thin (THIN-Ba) and thickened stimuli (MILD-Ba and MOD-Ba) at site level will be monitored centrally during the trial. *Blinding*: VFSS analysis, considered in this study as the clinical reference method (gold standard), will be performed by an independent and central VFSS assessment laboratory which will be blinded to the DDS results. The interim analyses will be carried out in an unblinded fashion by an independent statistical center (iSC) while the interim decisions will be made by an independent data monitoring committee (iDMC). The iDMC will also monitor the prevalence of swallow safety problems in a blinded manner throughout the course of the Trial. *Procedure:* DDS signals and VFSS will be recorded simultaneously (for the same bolus) using barium contrast agent stimuli prepared in three consistencies: thin, mildly-thick and moderately-thick. Subjects will undergo VFSS with simultaneous DDS using up to 5 boluses of thin barium stimulus (“THIN-Ba”), and up to 4 boluses of barium thickened to mildly (“MILD-Ba”) thick and up to 4 boluses of moderately (“MODERATE-Ba”) thick barium consistencies using TUC (Resource Thicken Up Clear, Nestlé Health Science). 4, 3 and 3 boluses for THIN-Ba, MILD-Ba and MOD-Ba will be analyzed using the classifier algorithms for sensitivity/specificity results. According to the exploratory trial, VFSS data for safety or efficiency can be missing for up to 14% boluses due to quality of VFSS recording. To compensate for potential losses of boluses due to missing gold standard (VFSS) data, 5, 4 and 4 boluses will be collected for the three consistencies respectively . The DDS signals will be sent to a dedicated application software installed at the CRO, which interprets the acceleration data and displays the examination result. The VFSS recording will be sent to CRO and provided for blinded assessment by the independent central VFSS laboratory. Consent must be obtained within 2 weeks prior to the study procedure. The study procedure of simultaneous VFSS and DDS measurement will be completed in one day and the subject will be followed within 2 business days after the study procedure to monitor for adverse events.
TRIAL POPULATION	The study has been planned to enroll and study approximately 900 (maximum enrollment 1300) patients at risk for oropharyngeal dysphagia of non-congenital, non-surgical, and non-oncologic origin that meet all the inclusion and exclusion criteria and are considered eligible to be entered into this clinical investigation.

INCLUSION CRITERIA	• Adult subjects (over 18 years of age)
	• Hospitalized subjects or outpatients identified as at risk of oropharyngeal dysphagia (using local practice)
	• Patients belong to one of the following groups:
	  o Stroke patients
	  o Traumatic brain injury
	  o PD (Parkinson Disease) stage III or higher by Hoehn and Yahr scale
	  o MS (Multiple Sclerosis) above age 60
	  o AD (Alzheimer Disease) or other Dementia
	  o Other medically complex hospitalized subjects not covered by the exclusion criteria and identified as at risk of dysphagia
	• Subject is able to comply with VFSS protocol to diagnose dysphagia
	• Subject is able to give voluntary, written informed consent to participate in the clinical investigation and from whom consent has been obtained / or a consultee has consented on the subjects behalf in line with nationally agreed guidelines concerning adults unable to consent for themselves.

EXCLUSION CRITERIA	• Presence of nasogastric / nasojejunal feeding tube at the time of VFSS test • Currently has a tracheostomy, or has had a tracheostomy in the past year • Had posterior cervical spine surgery and/or carotid endarterectomy in the last 6 months • Had significant surgery to the mouth and/or neck, for example resection for oral or pharyngeal cancer, radical neck dissection, anterior cervical spine surgery, orofacial reconstruction, pharyngoplasty, or thyroidectomy. Routine tonsillectomy and/or adenoidectomy are not excluded • Experienced non-surgical trauma to the neck (e.g., knife wound) resulting in musculoskeletal or nerve injury in the neck. • Received radiation or chemotherapy to the oropharynx or neck for cancer. • Allergy to oral radiographic contrast media (specifically barium) • Distorted oropharyngeal anatomy (e.g. pharyngeal pouch) • Cognitive impairment that prevents them from being able to comply with study instructions and procedures • Known to be pregnant at the time of enrollment • Currently has significant facial hair at the location of sensor adherence and are unwilling/unable to be shaved • Any patients the local investigator finds that participation would not be in patients' best interest
DEVICE	Dysphagia Detection System (DDS)
DEVICE DESCRIPTION	The NHSc (Nestle Health Sciences) Dysphagia Detection System (DDS) is a portable, non-invasive device designed for use at the bedside. The investigational DDS has three basic components: a Sensor Unit (suspended on a necklace), a Sensor Fixation and a PC for collecting data. The Sensor Unit consists of a dual-axis accelerometer in a plastic housing that is attached to the front of a patient's neck just below the thyroid cartilage by the single-use, disposable fixation unit (Sensor Fixation). The Sensor Unit is connected via a cable to an A/D converter which then connects via cable to the PC. The PC collects the examination data, which is then sent to dedicated application software (installed at the CRO), which interprets the acceleration data and displays the examination result. During an assessment, a patient takes a series of sips as directed by a clinician. Each sip is processed and transferred to the application software on the PC. The data are stored and then sent to the CRO. These data are subsequently analyzed and the system outputs an assessment of swallowing safety and efficiency.
STUDY DURATION	This study is expected to require approximately 18 months to complete.
TRIAL VISITS	Consent must be obtained prior to the study procedure (up to 2 weeks prior). The study procedure of simultaneous VFSS and DDS measurement will be completed in one day and the subject will be followed within 2 business days after the study procedure to monitor for adverse events. The sequence of Study Procedures is described in the Table 1.

STATISTICAL METHODS

Success criteria and hypothesis testing

The success criteria for the DDS device validation trial is that the sensitivity is greater than 80% with a specificity greater than 50%. Here the sensitivity and the specificity will be estimated using an independent validation dataset. Thus the following one-sided hypothesis testing will be carried out:

$$H_0 : H_0^{se} \cup H_0^{sp} \text{ vs.}$$

$$H_A : H_A^{se} \cap H_A^{sp}$$

Where

H_0^{se} : Sensitivity ≤ 0.8; H_A^{se} : Sensitivity > 0.8; H_0^{sp} : Specifictiy ≤ 0.50; H_A^{sp} : Sensitivity > 0.50

The same hypothesis test as above will be applied to the secondary endpoints. If the primary hypothesis meets statistical significance then hypothesis testing for secondary endpoints will be carried out in a hierarchical fashion to ensure that the type-I error is controlled at the 2.5% level (one-sided).

Threshold optimization

The validation trial will start with the frozen classifier based on a fixed threshold derived using the ROC curves obtained using the 10,000 test datasets following a random splitting (80:20) of the Phase-0 data.

At the first interim, sensitivity and specificity will be calculated based on the fixed threshold. If the Area under the ROC curve at the first interim is above 75% but the sensitivity and/or specificity are low then the threshold will be revised based on the first interim data. In this case, the validation will exclude the data used for the first interim, i.e. the validation trial will start with the first patient enrolled after the first interim analysis data cut-off date. In case the fixed threshold from the phase-0 data is not revised using the first interim data, the trial continues as planned.

Power analysis using simulations (described in statistical plan) show the impact of prevalence on power. The targeted prevalence of swallow safety problems using THIN-Ba (primary endpoint) is between 0.3 and 0.4. Throughout the course of the trial prevalence of swallow safety and efficiency problems will be monitored closely by the Data Monitoring Committee (DMC) in a blinded fashion.

The study population should be representative of the device intended use population (at risk of dysphagia).According to the published Literature, estimated prevalence of dysphagia in the target population varies from 20-50%. The necessity to carry out VFSS may result in sites selecting patients at higher risk than in the intended target population (such as those already assessed by SLPs). We therefore blindly monitor the prevalence and retrain sites as necessary in order to ensure that they recruit at-risk patients (not only those already assessed as dysphagic by SLPs).

6 TRIAL PLAN

Table 1: Sequence of Study Procedures

Study Procedures
Written informed consent
Inclusion/exclusion criteria review
Schedule VFSS with simultaneous DDS
Prepare all swallowing substances and portion into cups: thin barium, and mildly and moderately -thick barium using a mixture of TUC and barium (can be done in advance as per study manual instructions)
Swallow Exam of up to 5 sips of thin barium simultaneously recorded using both the VFSS and DDS
Swallow Exam of up to 4 boluses of mildly-thick barium simultaneously recorded using both the VFSS and DDS
Swallow Exam of up to 4 boluses of moderately-thick barium simultaneously recorded using both the VFSS and DDS
Upload the subject's study files (VFSS recording, DDS signal recording, acoustic soundtrack recording to a secure site for retrieval from the Sponsor or designee.
AE assessment within 2 business days following the study procedure

7 INTRODUCTION

Oropharyngeal dysphagia is a symptom of a swallow dysfunction that provokes difficulty or inability to form or move the alimentary bolus safely from the mouth to the esophagus. It can include oropharyngeal aspiration (the entry of secretions, food, or drink from the oropharynx into the trachea or the lungs) and choking (the subsequent mechanical obstruction of pulmonary air flow)[1].

Oropharyngeal dysphagia is a prevalent condition in several at-risk populations. We focus on oropharyngeal dysphagia of non-congenital, non-surgical and non-oncological origin which is prevalent in post-stroke patients, patients with neurological or neurodegenerative diseases such as Parkinson disease (PD), multiple sclerosis (MS), critically ill patients in intensive care units (ICUs) and elderly patients especially those with history of community-acquired pneumonia.

Oropharyngeal dysphagia is an important contributor to morbidity and mortality. It leads to impaired quality of life and nutritional and respiratory complications associated with poorer prognosis. Early identification of oropharyngeal dysphagia and aspiration risk is critical for management of dysphagia and its clinical consequences.

A recent retrospective review of National Hospital Discharge Survey data demonstrated a significant association between dysphagia and both hospital length of stay and mortality in a heterogeneous hospital population. The same study estimated the national annual cost of dysphagia in hospitalized patients to be over $500 million.[2]

The AHA Stroke and VA/DoD Stroke Rehabilitation Guidelines recommend assessment of swallowing before the patient begins eating, drinking, or receiving oral medications (AHA Class I; Level of Evidence B). Screening for dysphagia is also recommended by European Stroke Organization, NICE, and by German, Swiss and Austrian guidelines. The Joint Commission (JCAHO) guidelines state, “A screen for dysphagia should be performed on all ischemic/hemorrhagic stroke patients before [they are] given food, fluids, or medication by mouth.” Their rationale is that 27%-50% of stroke patients develop dysphagia, 43%-54% of stroke patients with dysphagia will experience aspiration, 37% of patients who develop aspiration will develop pneumonia, and if not part of a dysphagia diagnosis and treatment program, 3.8% of those will die. Other adverse effects that can be avoided include malnutrition and increased length of hospital stay.

In a prospective 15-hospital study in North America, use of a formal dysphagia screening protocol, which incorporated an evidence-based screening tool, was associated with improved compliance with dysphagia screenings and a significantly reduced risk of pneumonia.[3]

Although a wide variety of swallow screening and assessment tests are available for use, none have acceptable sensitivity and specificity to ensure accurate detection of dysphagia. [4]

Several reviews have shown a lack of consensus regarding the best screening instrument to use[5,6,7]. Most bedside swallowing examinations have been shown to lack sufficient sensitivity to be used for screening purposes, regardless of the patient populations examined. No bedside screening protocol has been shown to provide adequate predictive value for the presence of aspiration. Several individual exam components have demonstrated reasonable sensitivity, but reproducibility and consistency of these protocols was not established[6]. Dysphagia screening validation studies reported in the literature have a number of serious limitations[5]. It is also important to note that between one-third and one-half of patients who aspirate following stroke are silent aspirators (i.e., penetration of food below the level of the true vocal cords, without cough or any outward sign of difficulty)[4].

In 2010, The Joint Commission withdrew the dysphagia screening performance standard for acute stroke because the National Quality Forum could not endorse it, stating that there are “no

standards for what constitutes a valid dysphagia screening tool, and no clinical trials have been completed that
identify the optimal swallow screening". Dysphagia screening was removed from the "Get with the Guidelines" stroke guidelines[5]. However, removal from the Joint Commission recommendations does not mean that screenings should not be performed, indeed the Joint Commission recommends further research to improve dysphagia screening methods.

The Nestlé Health Science (NHSc) objective is to develop a new medical device - Dysphagia Detection System (DDS) - to provide clinicians with an objective and non-invasive method to detect impaired swallowing in patients at risk of oropharyngeal dysphagia of non-congenital and non-surgical and non-oncological origin. A good screening test needs to have a high sensitivity and high negative predictive value (NPV)[8]. The operating characteristics of screening methods must be established against a clinical reference standard – validated, accurate and reliable dysphagia assessment methods.

The DDS swallowing impairment detection algorithm has been developed in the exploratory (Phase 0) clinical trial in 332 subjects and reached targeted performance characteristics. VFSS was used as clinical reference method. The DDS algorythms detect impaired swallowing safety and impaired swallowing efficiency at thin, mild and moderate stimuli (6 algorythms – for safety or efficiency for each of 3 consisetncies). Swallowing safety describes risk of penetration-aspiration which describes impaired airway protection. The impaired swallowing safety is defined as PAS ≥ 3. As determined by VFSS. Swallowing efficiency described the ability to clear a bolus through the pharynx in 2 swallows or less without leaving residue in the throat. The impaired swallowing efficiency is defined as at least 50% residue as determined by VFSS.

The purpose of this prospective clinical trial is to validate DDS against the clinical reference standard for detecting swallowing impairment (VFSS).

8 TRIAL OBJECTIVES AND ENDPOINTS

8.1 Primary objective

The primary objective is to validate the DDS against the VFSS for detecting swallow safety problems using thin stimulus (THIN-Ba).

8.2 Primary endpoint

The primary efficacy of the DDS will be measured as the sensitivity & specificity obtained from comparing the DDS predicted swallow safety outcome with the clinical reference standard VFSS swallow safety outcome (binary) for thin (THIN-Ba) boluses.

Swallowing safety describes risk of penetration-aspiration which describes impaired airway protection. The impaired swallowing safety is defined as PAS ≥ 3 as determined by VFSS. (The PAS - Pentration Aspiration Scale – is provided in the Appendix B)

8.3 Secondary objective

The secondary objective is to validate the DDS against the VFSS for detecting swallow efficiency problems using thin stimulus (THIN-Ba) and swallowing safety and efficiency using mild and moderately thick stimuli.

Swallowing efficiency described the ability to clear a bolus through the pharynx in 2 swallows or less without leaving residue in the throat. The impaired swallowing efficiency is defined as at least 50% residue as determined by VFSS.

8.4 Secondary endpoints

At the final analysis, if the primary endpoint meets statistical significance then formal testing and analysis for the following secondary endpoints will be carried out in a hierarchical fashion in the specified order:

1. The sensitivity & specificity for swallow safety using mild barium (MILD-Ba)
2. The sensitivity & specificity for swallow safety using moderate barium (MOD-Ba)
3. The sensitivity & specificity for swallow efficiency using THIN-Ba
4. The sensitivity & specificity for swallow efficiency using MILD-Ba
5. The sensitivity & specificity for swallow efficiency using MOD-Ba

8.5 Exploratory endpoints

The analysis on the following tertiary endpoints will be considered as exploratory:

- Prevalence of boluses resulting in “grey” outcomes of the classifier for safety and efficiency of the swallows on thin (THIN-Ba) and thickened stimuli (MILD-Ba and MOD-Ba)
- Prevalence of impaired swallowing safety and efficiency of the swallows of thin (THIN-Ba) and thickened stimuli (MILD-Ba and MOD-Ba) as determined by VFSS at bolus and participant levels.
- Positive and Negative predictive value (PPV and NPV) of detecting swallow safety and efficiency problems using DDS and using THIN-Ba, MILD-Ba and MOD-Ba stimuli.
- Prevalence of impaired swallowing safety and efficiency of the swallows of thin (THIN-Ba) and thickened stimuli as determined by VFSS at bolus and patient level by the following predetermined subgroups: stroke, other neurological diseases, other patients.
- Timing and Outcome of the dysphagia screening as per usual care protocol of the study site
- Timing and Outcome of the dysphagia Clinical Swallow Evaluation (CSE) by SLP (speech language pathologist) where applicable as per usual care protocol of the study site.
- Impact of VFSS results on Nutritional Management (% patients with diet changes (advanced/more conservative)).
- DDS accuracy in terms of AUC, sensitivity and specificity by sub-group (Stroke, Other Neurological Diseases and Others) for swallow safety and efficiency problems for all consistencies (THIN-Ba, MILD-Ba, MOD-Ba)

8.6 Safety endpoints

All adverse events (AEs) will be observed from the time the consent form is signed through the exit of the subject from the study.

9 TRIAL DESIGN

An operationally seamless single-arm, prospective, multicenter, single-blinded for central outcomes assessors trial to test DDS in assessing swallowing safety and efficiency in patients at risk of oropharyngeal dysphagia.

The study is designed as operationally seamless to facilitate the updating of the threshold on the ROC curve for swallowing safety for thin (THIN-Ba) boluses if required and to validate the DDS classifier with a fixed threshold using an independent validation set.

The trial will start with the frozen classifier based on a fixed threshold derived using ROC curve from the completed exploratory trial. The clinical trial will initially start as a 3-look group sequential design (GSD). At the first interim, sensitivity and specificity will be calculated based on the fixed threshold. If the Area under the ROC curve at the first interim is above 75% but the sensitivity and/or specificity are low then the threshold will be revised based on the first interim data. In this case, the validation will exclude the data used for the first interim, i.e. the validation trial will start with the first patient enrolled after the first interim analysis data cut-off date. In case the fixed threshold from the completed exploratory trial data is not revised using the first interim data, the trial continues as planned.

If the classifier cannot analyze the signal (e.g. due to signal-to-noise level), it will result in a "grey" outcome of the classifier. The prevalence of "grey" outcomes among analyzed boluses for safety and efficiency classifier on thin (THIN-Ba) and thickened stimuli (MILD-Ba and MOD-Ba) at site level will be monitored centrally during the trial.

Blinding
VFSS analysis, considered in this study as the clinical reference method (gold standard), will be performed by an independent and central VFSS assessment laboratory which will be blinded to the DDS results. The interim analyses will be carried out in an unblinded fashion by an independent statistical center (iSC) while the interim decisions will be made by an independent data monitoring committee (iDMC). The iDMC will also monitor the prevalence in a blinded manner throughout the course of the Trial.

Procedure
DDS signals and VFSS will be recorded simultaneously (for the same bolus) using barium contrast agent stimuli prepared in three consistencies: thin, mildly-thick and moderately-thick.
Subjects will undergo VFSS with simultaneous DDS using up to 5 boluses of thin barium stimulus ("THIN-Ba"), and up to 4 boluses of barium thickened to mildly ("MILD-Ba") thick and up to 4 boluses of moderately ("MODERATE-Ba") thick consistencies using TUC (Resource Thicken Up Clear, Nestlé Health Science).
4, 3 and 3 boluses for THIN-Ba, MILD-Ba and MOD-Ba respectively will be analyzed by algoriythms for sensitivity/specificity results. According to the exploratory trial, VFSS data for safety or efficiency can be missing for up to 14% boluses due to quality of VFSS recording. To compensate for potential losses of boluses due to missing gold standard (VFSS) data, 5, 4 and 4 boluses will be collected for the three consistencies respectively.

The DDS signals will be sent to dedicated application software installed at the CRO, which interprets the acceleration data and displays the examination result. The VFSS recording will be sent to CRO and provided for blinded assessment by the independent central VFSS laboratory.

10 TRIAL POPULATION

The study has been planned to enroll and study approximately 900 patients at risk for oropharyngeal dysphagia of non-congenital, non-surgical, and non-oncologic origin that meet all the inclusion and exclusion criteria and are considered eligible to be entered into this clinical investigation (maximum enrollment 1300 with the possibility of early stopping for futility or success).

10.1 Subject inclusion criteria

It is important to carefully consider whether a subject is suitable for enrollment into this clinical study. Fulfillment of the inclusion and exclusion criteria for each subject will be documented by a qualified member of the investigative staff before any study procedure is performed.

- Adult subjects (over 18 years of age)
- Hospitalized subjects or outpatients identified as at risk of oropharyngeal dysphagia (using local practice)
- Patients belong to one of the following groups:
    - Stroke patients
    - Traumatic brain injury
    - PD (Parkinson Disease) stage III or higher by Hoehn and Yahr scale
    - MS (Multiple Sclerosis) above 60 y.o.
    - AD (Alzheimer Disease) or other Dementia
    - Other medically complex hospitalized subjects not covered by the exclusion criteria and identified as at risk of dysphagia
- Subject is able to comply with VFSS protocol to diagnose dysphagia
- Subject able to give voluntary, written informed consent to participate in the clinical investigation and from whom consent has been obtained / or a consultee has consented on the subjects behalf in line with nationally agreed guidelines concerning adults unable to consent for themselves.

10.2 Subject exclusion criteria

Any of the following criteria would render a subject ineligible for inclusion:

- Presence of nasogastric / nasojejunal feeding tube at the time of VFSS test
- Currently has a tracheostomy, or has had a tracheostomy in the past year.
- Had posterior cervical spine surgery and/or carotid endarterectomy in the last 6 months.
- Had significant surgery to the mouth and/or neck, for example resection for oral or pharyngeal cancer, radical neck dissection, anterior cervical spine surgery, orofacial reconstruction, pharyngoplasty, or thyroidectomy. Routine tonsillectomy and/or adenoidectomy are not excluded
- Experienced non-surgical trauma to the neck (e.g., knife wound) resulting in musculoskeletal or nerve injury in the neck.
- Received radiation or chemotherapy to the oropharynx or neck for cancer.
- Allergy to radiographic contrast media (specifically barium)
- Distorted oropharyngeal anatomy (e.g. pharyngeal pouch)
- Cognitive impairment that prevents them from being able to comply with study instructions and procedures
- Currently has significant facial hair at the location of sensor adherence and are unwilling/unable to be shaved
- Known to be pregnant at the time of enrollment.
- Any patients the local investigator finds that participation would not be in patients' best interest

10.3 Subject discontinuation criteria

A subject may be discontinued from the trial for the following reasons:

1. A subject can withdraw consent to participate the trial at any time without reprisal
2. Investigator's decision to discontinue subject's participation to the trial if, to the opinion of the Investigator, continuation in the trial would be detrimental to the subject's wellbeing. Should the Investigator's decision be based on an AE or a SAE, this event must be reported in the appropriate manner
3. Sponsor or Independent Ethics Committee (IEC)/Institutional Review Board (IRB) decides to terminate trial

If the subject withdraws consent from the study, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4 Subject replacement

Not applicable

10.5 Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, study device safety problems, insufficient participant recruitment, when the safety of the participants is doubtful or at risk, respectively or at the discretion of Nestlé-Investigator. In addition, Nestlé retains the right to discontinue development of the study device at any time.

If a study is prematurely terminated or discontinued, Nestlé will promptly notify each study site investigator. After notification, the investigator must contact all active participating subjects and the participating study team members/staff (if applicable) within two weeks. As directed by Nestlé, all study materials must be collected and all (e) CRFs completed to the greatest extent possible.

11 INVESTIGATIONAL DEVICE

11.1 Investigational Device Description

The NHSc Dysphagia Detection System (DDS) is a portable, non-invasive device designed for use at the bedside. The clinical trial will be performed with an investigational device architecture which is adapted to the constraints of the trial methodology (i.e. simultaneous measurement in VFSS suite).

The investigational DDS has three basic components: a Sensor Unit (suspended on a necklace), a Sensor Fixation and a PC for collecting data. The Sensor Unit consists of a dual-axis accelerometer in a plastic housing that is attached to the front of a patient's neck just below the thyroid cartilage by the single-use, disposable fixation unit (Sensor Fixation). The Sensor Unit is connected via a cable to an A/D converter which then connects via cable to the PC. The PC collects the examination data, which is then sent to dedicated application software (installed at the CRO), which interprets the acceleration data and displays the examination result.

During an assessment, a patient takes a series of sips as directed by a clinician. Each sip is processed and transferred to the application software on the PC. The data are stored and then sent to the CRO. These data are subsequently analyzed and the system outputs an assessment of swallowing safety and efficiency.

11.2 Storage and Labeling

Investigational device will be provided to the site(s) when all the mandatory trial documents have been made available. All components will be labeled as investigational. The investigational device components should be stored in secured location where only study personnel can access the device for use.

11.3 Device Accountability

The investigational device will be supplied to Investigator by and under the responsibility of the Sponsor. The Investigator at the trial site will inventory and acknowledge receipt of all shipments of investigational device. The Investigator will keep accurate records of the investigational device. These records will report any investigational device accidentally or deliberately destroyed. Device malfunctions or failures will be recordered. The investigational device will not be used outside of the study protocol.

At trial closure, all used and unused study supplies and the investigational device will be counted and returned to the Sponsor, or destroyed with their written permission. Any discrepancies between the investigational device returned and the expected balance must be justified.

12 TRIAL ASSESSMENTS AND PROCEDURES

12.1 Screening

Subjects identified to have risk of dysphagia via the standard institutional screening / diagnostic methods will be assessed for study inclusion. Subjects appearing to meet all study inclusion and exclusion criteria will be approached to provide their consent to participate in the study within 2 weeks of the study procedure.

12.2 Informed Consent

If a patient is deemed unable to provide informed consent, then consent must be obtained from a legally authorized representative, family member, or other locally recognized representative. Patients will be considered to be enrolled once their informed consent is signed.

12.3 Baseline Assessment

The subjects' eligibility status will be documented on the Case Report Form (CRF). For women of childbearing potential a pregnancy test must be performed to confirm study eligibility. The date and result of the test will be recorded on the CRF.

After obtaining confirmation of the subjects' eligibility for study participation, the following data will be collected and recorded on the CRF:

- Demographics
- Relevant medical and surgical history
- Primary admission diagnosis *(list of diagnosis of special interest: stroke, TBI, SCI (spinal cord injury), PD, MS, Dementia, Pneumonia, COPD)*
- Time from admission to VFSS study procedure
- Secondary diagnosis and dates of diagnosis (Y/N) :Stroke, PD, MS, Dementia, TBI, Pneumonia, COPD
- Patients had invasive mechanically ventilated (Y/N, if yes duration of ventilaton)
- Dysphagia screening by Nurses (date of latest screening and results)
- Dysphagia assessment by SLP (date of latest assessment and results)

- Recent Instrumental dysphagia diagnostics on file (e.g. VFSS, FEES, other – date and results
- Nutritional management
- For stroke patients: NIH Stroke S (if available)
- For parkinson patients: Funcitional Independence Measurement (if available)

12.4 Preparation

Prior to initiating any of the swallow exams the thin liquid barium, mildly-thick barium and moderately-thick barium swallowing substances will be prepared in accordance with the Validation Study Manual (provided to each site at the Site Initiation Visit). The mixed consistencies can be stored unrefrigerated (room temperature) for up to 6 hours or If necessary, refrigerated for up to 24 hours and left at room temperature for approximately 20 minutes before administration to a study subject. (Re-refrigeration is not permitted).

Approximately 5 oz of each of the substances will be poured into study supplied cups. The thin barium and mildly-thick barium will each be poured into cups, whereby the subject will take several sips of each of the substances from a cup. Moderately-thick barium needs to be taken using a spoon.

12.5 Swallow Exam

At the time of the scheduled VFSS, the subjects will be brought to the VFSS suite and prepared for the study.

DDS signals and VFSS will be recorded simultaneously (for the same bolus) using barium stimuli prepared in three consistencies: thin, mildly-thick and moderately-thick. The exams will be performed in the following order:

1. Up to 5 boluses of thin barium simultaneously recorded by DDS and VFSS

2. Up to 4 boluses of mildly-thick barium recorded by DDS and VFSS

3. Up to 4 boluses of moderately-thick barium recorded by DDS and VFSS

The thin barium, and mildly-thick barium tests will be administered using a cup. The moderately-thick barium tests will be administered with a spoon.

The full swallow should be recorded in a lateral view using continuous/25 or 30 frames per second screening.
Subject should be positioned correctly throughout the swallow exam i.e. seat upright with a neutral head position.
There should be no use of swallowing strategies throughout the study procedure e.g. head turns or chin tucks.

Detailed instructions on how to perform the DDS procedure are included in the Study Manual.

Only study personnel delegated and trained to properly apply the accelerometry sensor and operate the computer that will collect all channels of data (accelerometry, videofluoroscopy, audio soundtrack) will conduct the exams for this study. An audio soundtack will be only used when necessary to identify the swallow on VFSS.

12.6 VFSS Stopping Rules

- If the PAS is equal to or greater than 6 on 3 consecutive bolus trials of the same consistency, that consistency should be stopped and the investigator (or trained and authorized designee) can decide if it is safe to move to the next consistency or if the study needs to be stopped.

    - *Penetration Aspiration Score Definitions:*

        6: Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway.

        7: Material enters the airway, passes below the vocal folds & is not ejected from the trachea despite effort

        8: Material enters the airway, passes below the vocal folds & no effort is made to eject

- A 'Stop' may be applied at any time if the Investigator (or trained and authorized designee) feels it is unsafe for the patient to continue.

- If VFSS time exceeds 3 minutes the procedure must be stopped.

If the VFS procedure is stopped due to any of these Stopping Rules, the 1 day follow-up visit must still be completed.

12.7 Post-Exam

After completion of all study-related testing, the site will stop the recording on the study computer and follow specified procedures for saving and uploading all study files to a secure transmission to the CRO as per the Study Manual.

Subsequently, the site will follow their institution's standard of care for further assessing swallowing impairment in subjects with suspected dysphagia.

Follow-up with the study subject will be performed within 2 business days following completion of all the exams to collect data on AEs. If the subject is still hospitalized at this time, this data will be collected via an in-person interview. If the subject has been discharged at the time of follow-up, this data will be collected via a telephone interview.

12.8 Premature trial termination

Should it prove necessary to discontinue the trial prior to completion, the Sponsor will notify the Investigators and the appropriate entities including the IRB/IEC. All relevant trial documentation will be returned to the Sponsor. The investigational device will be sent back.

12.9 Trial completion

After trial completion or termination the Investigator will inform the IEC/IRB of the end of the trial.

13 DATA MANAGEMENT

13.1 Data capture

Data collected by the sites will be entered from the source document into an electronic Case Report Forms (eCRF) within a Title 21 CFR Part-11 compliant Electronic Data Capture system (EDC). Data should be entered in eCRFs within 7 days after the subject's visit.

eCRFs must be signed electronically by the Investigator.

13.2 Access rights

Designated site personnel will create a unique username and password and will be required to request access to the database. Once the site personnel are trained access will be approved and the site personnel will have access the eCRF database. This username/password pair may be used by a single individual only; passwords must not be shared with any other person.

13.3 Coding

The following types of data will be coded using standard dictionaries detailed below.

Type of data	Dataset	Dictionary
Adverse Events	AE	MedDRA
Serious Adverse Events	AE	MedDRA

13.4 Database Lock

Clinical database will be locked after review, query resolution, signatures of the eCRF and determination that clinical database is ready for analysis.

Once the Trial is finished and database is locked, the Clinical Data Manager should follow the database unlock/relock process to document any further change.

14 STATISTICS

14.1 Background

The DDS classifier was built using data from around 300 subjects in a proof-of-concept trial using different bolus consistencies: thin barium (THIN-Ba), mildly thick barium (MILDBa) and moderately thick barium (MOD-Ba).

This pivotal trial aims at validating the Dysphagia Detector System (DDS) with respect to the Video-fluoroscopy test (gold-standard) in detecting swallow safety and efficiency impairments. The core component of the DDS is a statistical classifier algorithm that is able to predict the probability that a swallow was normal or with impaired safety and/or impaired efficiency based on the swallow signals captured using a dual-axis accelerometer sensor.

14.2 Success criteria and hypothesis testing

The success criteria for the DDS device validation trial is that the sensitivity is greater than 80% with a specificity greater than 50%. Here the sensitivity and the specificity will be estimated using an independent validation dataset. Thus the following one-sided hypothesis testing will be carried out:

$$H_0 : H_0^{se} \cup H_0^{sp} \text{ vs.}$$

$$H_A : H_A^{se} \cap H_A^{sp}$$

Where

H_0^{se} : Sensitivity ≤ 0.8; H_A^{se} : Sensitivity > 0.8; H_0^{sp} : Specifictiy ≤ 0.50; H_A^{sp} : Sensitivity > 0.50

The same hypothesis test as above will be applied to the secondary endpoints. Hypothesis will be carried out in a hierarchical fashion to ensure that the type-I error is controlled at the 2.5% level (one-sided).

14.3 Threshold Optimization

The validation trial will start with the frozen classifier based on a fixed threshold derived from the Phase-0 (exploratory) trial data.

At the first interim analysis, sensitivity and specificity will be calculated based on the fixed threshold.
If the Area under the ROC curve at the first interim is above 75% but the sensitivity and/or specificity are low then the threshold will be revised based on the first interim data. In this case, the validation will exclude the data used for the first interim, i.e. the validation trial will start with the first patient enrolled after the first interim analysis data cut-off date. In case the fixed threshold from the phase-0 data is not revised using the first interim data, the trial continues as planned.

Power analysis using simulations (described in statistical plan) show the impact of prevalence on power. The targeted prevalence of swallow safety problems using THIN-Ba (primary endpoint) is between 0.3 and 0.4. Throughout the course of the trial prevalence of swallow safety and efficiency problems will be monitored closely by the Data Monitoring Committee (DMC) in a blinded fashion. The study population should be representative of the device intended use population (at risk of dysphagia).According to the published Literature, estimated prevalence of dysphagia in the target population varies from 20-50%. The necessity to carry out VFSS may result in sites selecting patients at higher risk than in the intended target population (such as those already assessed by SLPs). We therefore blindly monitor the prevalence and retrain sites as necessary in order to ensure that they recruit at-risk patients (not only those already assessed as dysphagic by SLPs)

14.4 Sample size calculations

The power and the sample size to test the hypothesis depends on several unknown parameters:
1. Subject level prevalence;
2. The prevalence of impaired swallows conditional on subject having Dysphagia;
3. The true sensitivity and specificity of the DDS device in detecting swallow impairment; and
4. The optimum threshold on the ROC curve.

Based on estimates from the exploratory study data, if the DDS is assumed to have a sensitivity and specificity of at least 86% and 60% respectively and approximately 35% patients show impaired safety, then a power of 90% can be achieved with 700 to 800 subjects under a fixed design. Considering that data from additional 100 to 200 subjects may be used for threshold calibration, the starting sample size is 900 subjects. A sample size re-estimation will be carried out at the last interim analysis.

14.5 Group Sequential Design

The clinical trial will initially start as a 3-look group sequential design (GSD). The clinical trial will initially start as a 3-look GSD. Alpha-spending will be calculated using Lan-DeMets spending function (with O'Brien-Fleming parameter). At the first interim analysis (IA-1) the threshold on the ROC curve may be re-computed using the ROC curve generated using the IA-1 data, in which case, the validation trial would start afresh following IA-1 using a 2-look GSD. Data included in the IA-1 would no longer be used for the validation phase.

14.6 Interim analysis and Sample Size Reestimation

The overall subject-level prevalence of impaired safety and efficiency as determined by the central lab VFSS reading will be continuously monitored in a blinded fashion. The first interim analysis will be performed when the prevalence can be estimated using a 95% confidence interval of width no more than 15%. If the monitoring is carried out after every 50 subjects have completed the study, the first interim will be carried out around 200 subjects as reflected by the simulation.

Due to uncertainties about the population parameters and their influence on the power, an adaptive sample size re-estimation (SSR) is proposed. Thus if after the first interim the trial continues as a 3-look GSD without changing the threshold, then a SSR would be done at the second interim analysis. If the threshold is changed at the first interim then the SSR will be carried out at the only interim analysis time for the freshly started validation trial post threshold re-calibration. SSR will be carried out using the promising zone approach[16]. Details can be found in the statistical plan.

The interim analyses will be carried out in an unblinded fashion by an independent statistical center (iSC) while the interim decisions will be made by an independent data monitoring committee (iDMC). The iDMC will also monitor the prevalence in a blinded manner throughout the course of the Trial.

14.7 Central Blinded VFSS Assessors

The Swallowing Rehabilitation Research Laboratory at the Toronto Rehabilitation Institute will be performing blinded VFSS assessment. CRO will organize transfer of blinded VFSS records analysis for the Assessors. The VFSS records will be reviewed and analyzed by two trained raters independently of each other to identify penetration-aspiration score (PAS) and residue. If there is disagreement between the two raters regarding penetration-aspiration status, a third trained rater will assess the VFSS(s) in question, and, if necessary, a meeting will be convened to obtain a consensus on any rating disagreements. If the concensus can not be reached due to a noisy VFSS signal, the bolus will be rated as missing VFSS. The Assessors will use a standardized protocol to ensure objectivity and consistency in the assessment of the VFSSs. Following analysis, they will send the subjects' VFSS results to the CRO.

14.8 Datasets to be analyzed

14.8.1 *Full analysis dataset*

For this trial, ITT population is defined as the population able to complete at least 1 THIN-Ba bolus. Missing data will be reported and sensitivity analysis carried out. The analysis of primary and secondary endpoints will be performed to evaluate DDS performance and will be carried out using data from this population. The THIN-Ba consistency boluses (up to 4) with available simultaneous VFSS and DDS data per patient will be included into the analysis. As will the MILD-Ba and MOD-Ba consistency boluses (up to 3 each) with simulultaneous VFSS and DDS data per patient.

14.8.2 *Safety analysis set*

Safety population includes all subjects with documented VFSS exam.

15 HANDLING OF ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol. Adverse event information will be assessed from the time the subject signs the Informed Consent/HIPAA Form through the exit of the subject from the study. AEs will be recorded on the AE page of the (e)CRF.

15.1 Definitions and assessment criteria

15.1.1 *Adverse event*

An AE is any untoward medical occurrence experienced by a subject during this trial regardless of its relationship to the device.

All AEs (regardless of suspected causality) will be assessed from the time the Informed Consent Form is signed through the exit of the subject from the study.

All AEs will be assessed by the Investigator according to:

• Whether the event is an unanticipated adverse device effect (UADE);

• Whether the event is serious (SAE);

• The severity of the event (mild, moderate, severe); and

• The relationship of the event to the device and/or procedure (not related, possibly related, probably related, or definitely related).

Information will also be collected on any treatment of the event and outcome/resolution status of the event. All data concerning AEs will be recorded on the AE CRF.

All SAEs and UADEs will be reviewed by a Nestlé Health Science Medical Safety Officer (MSO). The MSO's decisions regarding SAE status and device- or procedure-relatedness will be considered final for the purposes of data analysis, regulatory reporting, and publications.

15.1.2 *Serious adverse event*

An AE is considered serious if it meets at least one of the following criteria:

• led to death, or

• led to serious deterioration in the health of the subject, that either resulted in:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- inpatient or prolonged hospitalization ≥ 24 hours, or transfer to the higher intensity of care unit/hospital
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or

• led to fetal distress, fetal death or a congenital abnormality or birth defect.

15.1.3 *Unanticipated Adverse Device Effect (UADE)*

A UADE is any adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death that is not previously identified in nature, severity, or degree of incidence in this Investigational Plan or informed consent,

or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). The Sponsor or designee, in conjunction with the Medical Monitor, will assess all SAEs considered to be device-related to determine if they are reportable to the US Food and Drug Administration (FDA) as a UADE.

The evaluation of "unanticipated" is based on current knowledge and applicable product information and will be assessed by the MSO of the Sponsor.

15.1.4 *Anticipated Adverse Events*

AEs that are anticipated to occur during this clinical trial are believed to be consistent with those associated with underlying disease and/or dysphagia screening tests and VFSS or have been identified by the Sponsor as part of their risk assessment. Anticipated AEs include and are not limited to, the following:

- Choking episode or airway obstruction event requiring emergency response
- Fever
- Congestion and/or shortness of breath
- Chest pain
- Anaphylactic reaction (allergy to the test stimuli)
- New diagnosis of respiratory infection
- Nausea and/or Constipation

Potential AEs that may be specifically related to the investigational device (accelerometry device) include, but are not limited to, the following:

- Allergy, skin reaction, or irritation to the adhesive used for the sensor fixation
- Infection
- Discomfort
- Electrical shock
- Electromagnetic (EM) emission interference with other devices leads to failure of life supporting device*

*see Section 16.3 Mitigation of Risk

15.1.5 *Severity of adverse events*

Severity of AEs will be graded according to the following criteria:

Mild:	Symptoms hardly perceived, only slight impairment of general well-being. Resolves without treatment and with no sequelae.
Moderate:	Clearly noticeable symptom, but tolerable without immediate relief.
Severe:	Overwhelming discomfort and has significant impact on the Subject's usual activities and/or requires treatment.

15.1.6 *Event Relatedness*

AEs will be judged by the Investigator as to their relatedness to the device and/or procedure using the following classifications:

- **Not related:** An AE for which sufficient information exists to indicate that there is no causal connection between the event and the device or procedure. The AE is due to and readily explained by the subject's underlying disease state or is due to concomitant medication or therapy not related to the use of the device or procedure. In addition the AE may not follow a reasonable temporal sequence following the procedure.

- **Possibly related:** There is a reasonable possibility that the AE may have been primarily caused by the device or procedure. The AE has a reasonable temporal relationship to the

use of the device or procedure *and* follows a known or expected response pattern to device or procedure, *but* alternative etiology is equally or more likely compared to the potential relationship to the use of the device or procedure.

- **Probably related:** There is a reasonable probability that the AE may have been primarily caused by the device or procedure. The AE has a reasonable temporal relationship to the use of the device or procedure *and* follows a known or expected response pattern to the device or procedure. Note: This definition assumes no alternative etiology is equally or more likely compared to the potential relationship to the use of the device or procedure.

- **Definitely related:** The AE has a strong causal relationship to the device or procedure. The AE follows a strong temporal relationship to the use of the device or procedure, follows a known response pattern to the device or procedure, and cannot be reasonably explained by known characteristics of the subject's clinical state or other therapies.

Device-related Adverse Event: an AE is considered to be device-related when, in the judgment of the Investigator or the MSO, the clinical event has a reasonable time sequence associated with use of the device and is unlikely to be attributed to concurrent disease or other procedures or medications, or it is reasonable to believe that the device directly caused or contributed to the AE.

Procedure-related Adverse Event: an AE is considered to be procedure-related when, in the judgment of the Investigator or the MSO, it is reasonable to believe that the event is associated with the procedure and is not specific to the device. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

15.2 Reporting of serious adverse events and unanticipated adverse device effects

15.2.1 *Reporting of serious adverse events and UADEs to Sponsor*

Upon awareness of an SAE or UADE, the investigator has to enter the data in the e-CRF within 24 hours. Notification does not depend on whether there is a causal relationship with the study product or not, all SAEs have to be entered within 24 hours after awareness. All SAEs or UADEs occurring until the last trial visit will be similarly reported.

Upon data entry, a first email will be automatically sent to the Clinical Safety Manager. Following emails will be automatically sent when changes or additional information are entered in the e-CRF.

The investigator must electronically sign each SAE and UADE.

In case the e-CRF is not functional, the Clinical Safety Manager must be notified of any SAE or UADE within 24 hours after awareness by the investigator per the fax and/or email address supplied in the source data worksheets.

15.2.2 *Follow up of serious adverse events*

All SAEs and UADEs must be followed up until the outcome is resolved or stable.

In case of SAE(s) persisting beyond trial termination, a follow up visit may be required. If further analyses are required for the evaluation of a potential cause-effect relationship between the device and the AE, all examinations and laboratory analyses will be documented in the (e)CRF or in an attached file.

15.2.3 *Notification*

The Sponsor is responsible for the ongoing safety evaluation of the device.

The Sponsor should promptly notify all concerned Investigator(s)/institution(s) and the Regulatory Authority(ies) of findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter IEC/IRB approval/favorable opinion to continue the trial.

15.3 Reporting

Nestle Health Science must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after receiving notice of the effect.

16 RISK ANALYSIS

16.1 Potential Risks

There are potential risks associated with both VFSS and the study device.

16.1.1 *VFSS Risks*

VFSS involves low levels of radiation exposure. Researchers have quantified the median levels of radiation exposure associated with a VFSS in patient populations. Zammit-Maempel and colleagues[9] reported a median exposure time of 171 seconds and an associated dose of 0.20 millisieverts or mSv, while Moro and Cazzani[10] reported a median exposure time of 149 seconds and an associated dose of 0.35 mSv.

Based on the analysis of 3273 boluses of thin, mild and moderate stimuli from exploratory (Phase 0) trial, the mean VFSS duration per bolus was 3.1, 3.4 and 3.1 sec for healthy and 5.4, 6.3 and 4.9 sec for impaired boluses for thin, mild and moderate stimuli respectively. Taking conservatively highest means of 3.4 sec and 6.3 sec as the reference for healthy and impaired boluses for all consistencies and assuming a high expected prevalence of impaired boluses of 40%, the mean radiation exposure time in the study is estimated to be 1.2 min per subject. Even more conservative calculation based onVFSS duration of mean plus two standard deviations per bolus as described above results in estimated VFSS duration of 2.7 min.

In addition, the VFSS stopping rules in this study requires VFSS to be stopped after approximately total of 3 min of radiation exposure.

Based on the above, the standardized VFSS protocol used in this study specified that all videofluoroscopic data must be collected with not more than 3 minutes of screening time. Interpolating from the relationship Moro published, VFSS time of 2.9 min (174 sec), relates to an effective dose of ~0.44 mSv[11].

On average, a U.S. resident receives an annual radiation exposure from natural sources of about 3.1 mSv. In addition, man-made sources of radiation from medical, commercial and industrial activities contribute roughly 3.1 mSv more to our annual exposure. Computed tomography (CT) scans, which account for about 1.5 mSv, are among the largest of these sources[12].

Radiation exposure during VFSS is approximately 30% of the CT radiation exposure and about 0.9% of the annual maximum permitted by the FDA radiation dose for radioactive drug research[13]. Comparing to background radiation, VFSS radiation exposure is equivalent to 1.7 months of natural exposure.

	Radiation Exposure (mSv)
VFSS (3)	0.44
CT (Computer Tomography) (5)	1.5
Natural "background" radiation (5)	3.1

FDA Regulations on Radioactive drugs research (6)	
Max radiation dose to whole body, active blood-forming organs, lens of the eye, and gonads	
Single dose	35
Annual and total dose commitment	50
Other organs	
Single dose	50
Annual and total dose commitment	150

One such strategy that is popularly used to decrease radiation exposure is reducing the pulse rate of the radiation beam emitted during VFSS. The emitted radiation beam can be either continuous or pulsed. When pulsed, the pulse rate is defined as the number of pulses per second (pps) of the x-ray beam. Pulse rates for fluoroscopy commonly include 30, 15, 7.5, and 4pps. Radiation exposure is reduced as pulse rate is reduced. Specifically, Aufrichtig et al showed average dose reductions of 22% at 15pps and 49% at 7.5pps when compared to doses at 30pps. Decreasing pulse rate also has a direct and proportional effect on the number of unique images in which a swallow is captured. Since the oropharyngeal swallow only lasts approximately 1 second, when pulse rate is decreased from 30 to 15, the number of unique images available to judge swallowing impairment also decreases from 30 to 15. Bonilha and colleagues[14] (2013) reported differences in both judgment of swallowing impairment and treatment recommendations when pulse rates are reduced from 30pps to 15pps to minimize radiation exposure. Differences between PAS scores for the four pulse rates tested (e.g. 24% of disagreements between 30 vs 15 rates) indicate that pulse rate may have a high impact on attributes of the MBSS examination that are used to determine PO status[14].

The standardized VFSS protocol used in this study specified 30 pulse rates and 30 frames per second for all videofluoroscopic data must be collected.

16.1.2 *Investigational Device Risks*

Potential risks related to the investigational device (accelerometry device) include, but are not limited to, the following:

- Allergy, skin reaction, or irritation to the adhesive used for the sensor fixation
- Infection
- Discomfort
- Electrical shock
- EM emission interference with other devices leads to failure of life supporting device*
  *see Section 16.3 Mitigation of Risk

16.2 Potential Benefit

There are no guaranteed benefits to participation in this study. The information gained from participation in this study will be used to validate a new non-invasive portable device to be used at the bed-side to detect impaired swallowing thereby it may benefit other patients with the same medical condition in future.

16.3 Mitigation of Risk

Adequate measures including eligibility criteria limitations and extensive bench testing, including electrical safety and EMC testing, biocompatibility assessment, functional testing, and software validation (e.g. EM emission interference with other devices), have been taken to minimize the above mentioned risks. Investigational accelerometry device and VFSS have been used in the

exploratory study (Phase 0) with more than 300 subjects with no serious adverse events related to the device or the swallowing protocol observed. The minor design improvement in the new investigational device has no impact on device safety and performance.

Site and Investigator selection criteria shall include the following:

- Sites that have standardized procedures for, and are accustomed to, caring for patients with dysphagia
- Sites that have SLP on staff, on-site or affiliated VFSS facilities and personnel

The provision for each Investigator to have appropriate training on the investigational device constitutes additional efforts to minimize risk. Furthermore, any risks associated with participation in this clinical study will be minimized and managed in accordance with and full compliance to recognized Good Clinical Practices (GCP), 21 CFR Parts 11, 50, 54, 56, and 812; HIPAA; International Conference on Harmonization (ICH) E6 Good Clinical Practices, and International Organization for Standardization (ISO) 14155.

16.4 Risk Analysis Conclusion

The Sponsor believes that any additional risks beyond other screening tests for oropharyngeal dysphagia presented by this study are very low and that adequate testing, safeguards, and risk monitoring have been incorporated into the study to further minimize and mitigate the risks relative to the potential benefits that may be realized by participation in this study. Thus, the balance of potential risks and benefits associated with the accelerometry device supports further clinical research.

17 SPONSOR AND INVESTIGATOR OBLIGATIONS

17.1 Good Clinical Practice and Declaration of Helsinki

This trial will be conducted in compliance with the International Conference on Harmonization (ICH) guidelines and the ethical principles that have their origin in the Declaration of Helsinki (Appendix A) and its subsequent amendments.

17.2 Independent Ethics Committee/Institutional Review Board Approval

An appropriate IEC/IRB which conforms with the Declaration of Helsinki*and local laws must review and approve the protocol, informed consent, and any other relevant trial documentation prior to enrolment of subjects into the trial. Prior to trial initiation, the Sponsor must have received a letter documenting IEC/IRB approval that specifically identifies the protocol (title and protocol number). A list of IEC/IRB members and affiliations must also be provided to the Sponsor. During the course of the trial, the IEC/IRB must be notified of all subsequent additions to or changes in the trial protocol and the informed consent.

Within 90 days of trial completion (last patient, last visit) or 15 days of early trial discontinuation, the Investigator, Sponsor or designee will inform the IEC/IRB of the end of the trial.

Every SAE or unexpected AE that might affect subject safety must be brought to the attention of the IEC/IRB by the Sponsor/Investigator if required by the relevant IEC/IRB regulations.

17.3 Informed Consent

The Investigator or designee will ensure that each study subject, or his/her legally representative, is fully informed about the nature and objectives of the study and possible risks associated with participation and that signed informed consent is obtained from each potential subject prior to any trial related procedure in accordance with all applicable regulatory requirements. The informed consent process will be documented. The informed consent document used in this study, and any

changes made during the course of the study, must be prospectively approved by the IRB/IEC and Nestlé before use.

Each subject will be given oral and written information in an easily understandable language describing the nature and duration of the trial. This must take place under conditions where the subject has adequate time to consider the risks associated with trial participation.

The informed consent will be signed by the subject (and/or legal authorized representative [guardian, next of kin, or other authorized individual] if applicable) and the Investigator or his/her designee. One signed copy will be given to the subject and the original will be kept in the Investigator's file at the trial site.

17.4 Subject Confidentiality

The Investigator will ensure protection of subject's personal data and that all reports, publications, subject samples and any other disclosures, except where required by law are identified only by a subject identification number and site identification number to maintain subject confidentiality. All subject trial records will be kept safely in an access controlled area. Identification code lists linking subject names to subject identification numbers should preferably be stored separate from subject records. In case of data transfer Nestlé will maintain high standards of confidentiality and protection of subject personal data. Clinical information will not be released without the written permission of the subject, except for monitoring by Regulatory Authorities or the trial Sponsor and their designees.

17.5 Data Reporting and Case Report Forms

The Investigator and/or designee will accurately, completely, and in a timely manner record data resulting from the execution of the protocol on paper or via electronic case report forms (CRFs/eCRFs, respectively) provided by the Sponsor. CRFs will be completed for each subject, all of which must be submitted/provided to the Sponsor at agreed upon intervals.

Case report forms will be supplied in paper or in electronic (eCRF) format via a web-based application, and must be signed and dated by the Principal Investigator by handwritten or electronic signature as appropriate.

17.6 Retention of Data

The Investigator will maintain adequate trial records including eCRFs, medical records, laboratory reports, original signed informed consent forms, investigational product disposition records, safety reports, information regarding participants who discontinued and other pertinent data, such as letters and administrative documents exchanged between the Sponsor and the site. The electronic Trial Master File (eTMF) is the official regulatory file for the study and will be used for monitoring the study and by FDA for any inspections (audits) under the Bioresearch Monitoring (BIMO) program. The only paper files included in the official regulatory file will be all original signed informed consent forms.

All trial records must be retained by the Investigator for the maximum period of time authorized by the hospital, institution or surgery. According to ICH GCP guidelines, essential documents should be retained until at least 2 years after the last approval of a marketing application in the EU and until there are no pending or contemplated marketing applications in the EU or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable local regulatory requirement(s) or according to the Clinical Trial Agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

To avoid any possible errors, the Investigator must contact the Sponsor prior to destruction of any trial records or if leaving the institution where the trial was conducted. The Investigator will notify the Sponsor in the event of accidental loss or destruction of any trial records.

17.7 Deviations from the Protocol/Protocol amendments

The Investigator will not deviate from the protocol without prior written approval from the Sponsor. In case of medical emergencies, the Investigator will use medical judgment and will remove the participant from immediate hazard. The Sponsor and the IEC/IRB will be informed of type of emergency and course of action taken, according to local reporting requirements.

Any permanent changes to the protocol will be formalized in an amended protocol which must be approved by the Sponsor and, if substantial as defined in directive 2001/20/EC, submitted for approval to the IEC/IRB and Health Authorities (the latter if applicable), prior to implementation. If the amendment results in a modification of trial treatment or subject assessments, a new version of the informed consent must be prepared and submitted for approval to the IEC/IRB and Health Authorities (the latter if applicable).

17.8 Trial Monitoring

At agreed upon times during the trial and after the trial has been completed, the Investigator will allow Sponsor representatives to periodically review the eCRF and corresponding office, hospital, and laboratory records (source documents) of each trial subject. Case report forms must be completed by the Investigator on a regular basis and prior to each monitoring visit.

Monitoring visits allow the Sponsor or a mandated CRO to evaluate trial progress, verify accuracy and completeness of eCRFs, resolve any inconsistencies in the trial records, and ensure that all protocol requirements, applicable local laws, ICH guidelines, and Investigator obligations are fulfilled.

17.9 Sponsor Audits

During the trial or after the trial has been completed, the Investigator will allow Sponsor representatives or external auditors to conduct an audit of the trial. The purpose of the audit is to evaluate compliance with Good Clinical Practice (GCP) guidelines, applicable regulations, the trial protocol and the Sponsor's procedures, and to assess accuracy of the trial data.

17.10 Regulatory Agency Inspections

The Investigator may undergo a Regulatory Agency/IEC/IRB inspection during the trial or after the trial has been completed. The purpose of the inspection is to conduct an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial.

Investigator and staff are expected to be available for the inspection and allow access to subject records supporting (e)CRFs and other trial-related documents. If given advance notice of this inspection, the Investigator must contact the Sponsor and CRO immediately. IRB/IEC notification to be completed per local requirements.

17.11 Publications

All topics related to publication are developed in the Clinical Trial Agreement related to the study.

17.12 Insurance Policy

The Sponsor will subscribe a liability insurance covering his and the Investigator's responsibility as well as the responsibility of any person involved in the conduct of the trial, provided there is proper adherence to the protocol. An insurance certificate will be provided by the Sponsor to the IEC if required.

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19 APPENDIX A: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

20 APPENDIX B: PENTRATION ASPIRATION SCALE

Penetration Aspirtaion Scale[1]

Score	Description on videofluoroscopy
1	Material does not enter airway
2	Material enters airway. Remains above vocal cords & is ejected from airway
3	Material is above vocal cords & is not ejected from airway
4	Material enters airway, contacts vocal cords & ejected from airway
5	Material contacts the vocal cords & is not ejected from airway
6	Material passes below the vocal cords & is ejected into larynx or out of airway
7	Material passes below the vocal cords & is not ejected from the trachea despite effort
8	Material enters airway, passes below the vocal cords & no effort is made to eject the material

Reference

1. *Rosenbek J, Robbins J, Roecker E, Coyle J, Wood J. A penetration-aspiration scale. Dysphagia. 1996;11:93-98*