CLINICAL STUDY PROTOCOL

ASTA Study

ASSESSMENT OF A SONIC TOOTHBRUSH ON THE ABRASION OF THE GINGIVAL TISSUE.

STUDY IDENTIFICATION No. 2020-A02614-35

Effects of a sonic toothbrush on the gingival tissues. A 3-month prospective, controlled clinical study.

DEVICE IDENTIFICATION: Philips Sonicare ProtectiveClean®

Final Version 3.0 of 21/09/2021

This protocol has been written in accordance with the current ICH GCP.

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2 ABBREVIATIONS AND DEFINITIONS

ADA	American Dental Association
AE	Adverse Event
AG	Attached Gingiva
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
ASADE	Anticipated Serious Adverse Device Effect
BOP	Bleeding On Probing
b	buccal
CF	Consent Form
CFG	Cervical Free Gingiva
CRF	Case Report Form
CRO	Contract Research Organization
CTM	Clinical Trial Material
D	Distal
EC	Ethics Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FU	Follow-up
GA	Gingival Abrasion
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	Gingival Inflammation
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization

ITT	Intent to treat (analysis)
IGC	Intensity of gingival coloring
L	Lingual
m	Mesial
MT	Manual toothbrush
p	Palatal
PFG	Papillary Free Gingiva
PD	Pocket Depth
PP	Per Protocol
REC	Gingival margin RECession
RIPH	Recherche impliquant la personne humaine
TEP	Time Evaluation Period
PI	Plaque index
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
ST	Sonic Toothbrush
USADE	Unanticipated Serious Adverse Device Effect
UST	Ultrasonic toothbrush
ZOI	Zone Of Interest

3 PROTOCOL SUMMARY / SYNOPSIS

Study Name	ASTA
Study Title	Effects of the sonic toothbrush on the abrasion of the gingival tissue. A 3-month prospective and controlled clinical study.
Study no.	2020-A02614-35
Investigational Products:	• Sonicare ProtectiveClean® HX6848/92 with C2 Optimal Plaque Defense head HX9022/10 (electric toothbrush) • Pierre Fabre Inava 20/100 (manual toothbrush)
Sponsor	Philips France Commercial
Coordinating Investigator	Dr. Francis Mora, DDS, PhD Rothschild Hospital 5 rue Santerre 75012 Paris France
Investigational site	Hôpital Rothschild, AP-HP, Service d'Odontologie, 5 rue Santerre, 75012 Paris France
Study type	Category 2 of Research involving human subjects (RIPH2), Post-market for a dental device (other than health products).
Methodology	This is a randomized, monocentric, examiner-blind, two-arm, parallel, controlled clinical research study. It aims to assess gingival abrasion by the comparison of pre- to- post-brushing after a single brushing and after 12 weeks of daily home brushing using a macro-relief scoring based on photographs of the gingiva. The study also aims to assess plaque removal, gingival inflammation, gingival recession and gingival color after 12 weeks. To enter the study, adult male and female subjects attending the service of odontology at Rothschild hospital (Paris, France) will refrain from all oral hygiene procedures for 24 hours. Subjects will have the study procedure explained to them both orally and by written instructions. Eligible patients will give their written consent to participate before being included into the study. Following a baseline clinical examination for collection of the following periodontal parameters: plaque control record (PCR), bleeding on probing (BOP), gingival recession (REC), and probing pocket depths (PD), the subjects will be randomized into two balanced groups, test group assigned to the Sonicare ProtectiveClean® HX6848/92 with C2 Optimal Plaque Defense head HX9022/10 (electric toothbrush) and control group assigned to the Pierre Fabre Inava 20/100, a reference manual toothbrush. Subjects will be instructed to brush their teeth for one minute under supervision with their assigned toothbrush and a sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL) with a low level of abrasion to minimize bias due to toothpaste abrasivity. After brushing, they will again be evaluated for primary and secondary outcomes (post-brushing). Subjects will be dismissed from the study site with their assigned toothbrush and toothpaste, and instructed to brush twice daily at home for the next 12 weeks. The subjects will be instructed to brush for two minutes during each tooth brushing. The subjects will report to the study site after 12 weeks of product use, at which time

	they will be re-evaluated for gingival abrasion, as well as for plaque removal, gingival inflammation, gingival recession and gingival color. Data (photographs and clinical measurements) will be collected, i.e. primary and secondary variables of each patient, by blinded examiners.
Number of patients	30 per group, 60 in total
Visits	1. Inclusion (D1) 2. Follow-up (D90)
Primary objective and endpoint	**Primary objective** To compare the gingival abrasion (GA) after toothbrushing between the sonic toothbrush Sonicare ProtectiveClean® with Optimal Plaque Defense head (test group) and a conventional manual toothbrush (control group) in regular consecutive patients attending the Service of Odontology at Rothschild hospital (Paris, France) **Primary endpoint** Gingival Abrasion (GA) assessed as modification in the gingival surface based on macroscopic photographs of each gingival quadrant at each time point. Observers will score those photographs in a double-blind manner by comparing the different photographs with a photonumerical reference scale used as standard. Five parameters will be assessed on a 0-3 scale (erythema, inflammation, bleeding, recession and erosion) resulting in a 15 points scale (from 0 - no abrasion, to 15 - severe gingival abrasion). Modifications in the gingival surface are defined by a macro-relief scoring based on photographs of the gingiva pre-operatively, immediately after the first brushing sequence and 90 days later
Secondary objectives and endpoints	**Secondary Objective** To compare : 1. the plaque control 2. the gingival inflammation 3. the gingival recession 4. the gingival color obtained by using the sonic toothbrush Sonicare ProtectiveClean® with Optimal Plaque Defense head (test group) and by using a conventional manual toothbrush (control group) in regular consecutive patients attending the Service of Odontology at Rothschild hospital (Paris, France); **Secondary Endpoints** 1. plaque control measured by the Plaque Control Record 2. gingival inflammation measured by Bleeding On Probing 3. gingival recession defined as the distance from the cemento-enamel junction to the gingival margin and measured in millimeters using a manual periodontal probe (HuFriedy PCP UNC 15 probe, Chicago, IL, USA) 4. gingival color change based on sensory analysis.

Eligibility criteria	**Inclusion criteria** 1. Dentate males and females must be at least 18 years and not more than 75 years of age 2. Patient able to understand and sign the informed consent prior to starting the study 3. Patient with a minimum of 3 teeth in each of the 4 quadrants and no/or pockets >4 mm 4. Ability and willingness to comply with all study requirements. **Non-inclusion criteria** 1. Pregnancy 2. Patient with cervical restorations 3. Current smoker 4. Patient with orthodontic banding 5. Patient with oral lesions or periodontal diseases 6. Patient who has been deprived of his/her freedom by administrative or legal decision or who is under trusteeship/guardianship 7. Patient already using an electric toothbrush 8. Patient with conditions or circumstances, which may prevent completion of study participation or interfere with analysis of study results, such as history of non-compliance, or unreliability; 9. Patient with non-plaque induced gingival diseases or localized gingival ulceration 10. Thin gingival phenotype 11. Patients with cardiac pacemakers to prevent any interference between the power toothbrush and the implantable cardiac device.
Method of administration	After screening, clinical examination, informed consent collection and randomization, a blinded examiner will provide each patient a manual toothbrush or a sonic toothbrush depending on his/her allocation group (control or test group). The examiner will orally explain the appropriate tooth brushing technique, the frequency and duration of tooth brushing (twice a day, 2 mins). Each participant will receive a tube of sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL). At the end of the study, each patient will give back the used toothbrushes and tubes of toothpaste to the blinded examiner.
Treatment scheme	**Visit 1 (V1)**: (D0) screening, patient's information on the study protocol, inclusion, randomization, baseline oral measurements, supply of investigational device, oral hygiene instructions, and dental photographs. **Visit 2 (V2):** (D90) Collection and verification of investigational device, oral measurements and dental photographs.
Study Duration	Inclusion period: 6 Months

	Total study duration: 9 Months
Study Schedule	Q2 2021 – Q1 2022
Statistical methods	The test and control groups will be compared on the primary and secondary outcomes of the study. Normality tests (e.g. Kolmogorov-Smirnov or Shapiro-Wilk test) will be used to assess the normality of the distribution. According to data distribution, t-test or Mann-Whitney u-test will be applied for continuous variables, such as the gingival abrasion and gingival relief scoring. For categorical variables, Pearson's Chi square test or Fisher's Exact test will be used. Within group, tests will be used to explore the time effect, i.e. evolution between baseline and post-baseline measurements. Wilcoxon's test or Student's test for pairwise comparisons will be used, depending on the normality of the distribution. A p value < 0.05 will be considered statistically significant. The sample size calculation has been based on a preliminary study evaluating the primary criteria (macro-relief scoring changes between D0 and D90 after manual compared to electric brushings). In this preliminary study, we have measured a threshold value of $\Delta E = 0.67$ on the primary criteria between manual brushing and electric brushing, associated with a standard deviation of 0.84. Using a bilateral two-group test with a 0.05 two-sided significance level and a power (1- ß) of 0.80 yielded a sample size of 25 subjects per group (34 subjects when considering a power (1- ß) of 0.90). We added 20% for potential dropouts. Thus, 30 subjects per group will be evaluated, i.e. 60 subjects will be required in total.

Visits / Tasks	Screening/baseline	Follow-up
	Day 1	Day 90
Patient information and informed consent signature	X	
Inclusion/exclusion criteria	X	
Randomization	X	
Investigational device supply	X	
Plaque Control Record (PCR)	X	X
Inflammation assessment (BoP)	X	X
Gingival recession assessment (REC)	X	X
Pocket depth probing (PD)	X	X
Gingival abrasion (GA)	X	X
Gingival coloring variation assessment	X	X
Dental photograph	X	X
Oral hygiene instructions	X	
Investigational device collection		X
Assessment of toothbrush usage (patient reported)		X
Assessment of toothbrush usage (brush wear assessment)		X
Adverse events collection		X

Figure 1: Flow chart of the course of the study.

4 INTRODUCTION

4.1 Background and rationale

Gingival recession is defined as the apical shift of the gingival margin with respect to the cemento-enamel junction it is associated with attachment loss and with exposure of the root surface to the oral environment (Cortellini and Bissada, 2018). The etiology of gingival recessions remains unclear. Among predisposing factors tooth brushing has been suggested. A few systematic reviews support or refute the association between tooth brushing and gingival recession. In one systematic review, among the 18 examined studies, one concluded that the toothbrushes significantly reduced recessions on facial tooth surfaces over 18 months, two concluded that there appeared to be no relationship between tooth brushing frequency and gingival recession, while eight studies reported a positive association between tooth brushing frequency and recession. Several studies reported potential risk factors like duration of tooth brushing, brushing force, frequency of changing the tooth-brushing technique (Cortellini and Bissada, 2018).

Large cohort studies have demonstrated that high standards of oral hygiene are essential for oral health, prevention and treatment of periodontal diseases. The most common means of removing plaque at home is tooth brushing. Substantial plaque reduction can be achieved by manual brushing and/or a variety of power toothbrushes (ADA, 2019; Rosema et al., 2016) with the aim of improving plaque removal efficiency. A Cochrane systematic review on powered toothbrushes (Heanue et al., 2003), which has been updated (Heanue et al., 2003; Yaacob et al., 2014), claimed that only oscillating-rotating brushes are safe and have better clinically effects in terms of plaque removal and inflammation reduction. It is understood that tooth brushing requires the application of shear forces to remove plaque and can damage the superficial keratinized epithelial layer of the gingival tissue and create a background of gingival lesions (De Nutte et al., 2018). Superficial gingival abrasions can be expected to heal naturally, but it is unclear to what extent gingival abrasion caused by tooth brushing is associated with gingival recession. Due to the possible causal relationship between tooth brushing, gingival abrasion and gingival recession, an assessment of gingival tissue abrasion and recession in manual and power brush users is required to help establish whether there could be an association between these factors (Rosema et al., 2014). In addition, the use of high frequency sonic brushes has been considered safe and has produced satisfactory results in reducing gingival and plaque indices compared with conventional brushes used by patients with gingivitis and periodontitis (Costa et al., 2007). To our knowledge, no previous studies have provided information on the effects (abrasion) of tooth brushing on gum tissue.

The Philips Sonicare DiamondClean® power toothbrush is more effective than the ADA Reference manual toothbrush to reduce supra gingival plaque and gingival inflammation by routine manual toothbrush users (Delaurenti et al., 2017). Based on a sample of 154 randomized subjects the Philips Sonicare FlexCare® Platinum toothbrush with Premium plaque control brush head significantly reduces gingival inflammation, gingival bleeding, and plaque following two and six weeks of home use, when compared to manual tooth brushing alone (Jenkins et al., 2017). Recently, a randomized and examiner-blind study (Ccahuana-Vasquez et al., 2018) comparing the reduction of gingivitis and plaque over an 8-week period shows that oscillating-rotating electric rechargeable brush handle (Oral-B® PRO 1000, D16U) with a round brush head with angled bristles (Oral-B® CrossAction, EB50) performed better than a premium sonic brush (Philips Sonicare DiamondClean® Toothbrush with AdaptiveClean brush head). Opposite conclusions are produced by Starke *et al*. and by Mirza *et al*., comparing the benefits in terms of plaque and bleeding reduction with the Philips Sonicare DiamondClean® Smart powered toothbrush and the Oral-B Genius 8000 powered toothbrush following a 42-day home-use period (Mirza et al., 2019; Starke et al., 2017). The advantage of using high-frequency, high-amplitude sonic powered toothbrushes is to decrease plaque and gingivitis significantly more effectively than manual toothbrushes (de Jager et al., 2017) but not more than the oscillating-rotating power toothbrush according to a recent single-Centre study, randomized, examiner-blind, parallel group design (Lv et al., 2018). A meta-analysis based on six studies and a total of 462 subjects concludes that the benefits in terms of bleeding and plaque reduction, in dental surfaces hard to clean such as lingual and

proximal mandibular surfaces, are higher when using a sonic powered toothbrush than when using a manual toothbrush (Grender et al., 2013).

Philips Sonicare brush heads work with sonic technology: High-speed vibrations in the toothbrush handle power up to 62,000 brush movements per minute that whip up the toothpaste into gentle cleaning bubbles, driving them deep between the teeth and the gum for additional cleaning. The sonic toothbrush Philips Sonicare ProtectiveClean has an intuitive pressure sensor that helps patients to guide their brushing technique. One of the advantages of using this toothbrush is that pressure sensor provides real-time feedback so patient will adopt a softer touch to protect teeth and gums. This toothbrush works on 2 modes to remove plaque gently and effectively. On some Philips Sonicare sonic brushes, a program named “Gum Care” also adds an extra minute of reduced-power brushing to gently massage the gums, improving gum health. In addition, the BrushSync feature tracks brush head effectiveness based on brushing time and pressure and alerts patients when it is time for replacement.

The toothbrush head Philips Sonicare Optimal Plaque Defense possesses densely-packed, high-quality bristles that remove up to 7x more plaque than a manual toothbrush (Philips Oral Healthcare, unpublished data). This brush head works with a sonic technology, high-speed vibrations in the toothbrush handle power up to 62,000 brush movements per minute that whip up the toothpaste into gentle cleaning bubbles, driving them deep between the teeth and the gum for cleaning. Philips Sonicare ProtectiveClean has an intuitive pressure sensor that helps patients to guide their brushing technique. This pressure sensor provides a real-time feedback, thus encouraging the subject to adopt a softer touch in order to protect his/her teeth and gums. This feature is one of the benefits of using this toothbrush. This toothbrush works on 2 modes to remove plaque gently and effectively. The Gum Care mode also adds an extra minute of reduced -power brushing to gently massage the gums, improving gum health

The Philips Sonicare Optimal Gum Care brush head was found to be superior to a manual toothbrush in reducing gingival inflammation and gingival bleeding. A recent clinical study compared the plaque removal efficacy of Philips Sonicare 2 Series versus a manual toothbrush. One-hundred and thirty-three (133) healthy adults (mean age 40.7 years, 103 females and 30 males) were included in a parallel, examiner-blinded clinical trial. Eligible subjects were non-smokers, aged 18-65 years who were routine manual toothbrush users. Enrolled participants had a minimum average plaque following 3-6 hours of plaque accumulation. All subjects were dispensed study products per randomization, either Philips Sonicare 2 Series power toothbrush or a manual toothbrush. Study subjects assigned to the Sonicare treatment group were instructed to brush at home twice daily for two minutes using the ‘Clean’ mode. Study subjects assigned with the manual toothbrush were instructed to brush twice daily per their regular technique. 3-6 hours plaque accumulation and plaque removal was assessed during a second visit 14 days after the initial visit. Safety was assessed per subject report and intraoral examination. The results of this study showed that Philips Sonicare 2 Series was statistically superior to manual toothbrush in reducing plaque including posterior interproximal areas (Milleman et al., 2014, unpublished data). However, electric toothbrush heads become less effective after 3 months of use.

Usually patients brush their teeth with a toothpaste. To minimize the bias of using abrasive toothpaste the choice of a sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL) with a low degree of abrasion as defined by the relative dentine abrasion (RDA) was made. RDA –is an index of tooth abrasion by toothpaste. The RDA scale ranges from 0 to 250. The 0-70 range is considered as low abrasion, i.e. safe for cement, dentine and enamel (González-Cabezas et al., 2013). According to this standard, toothpastes with an RDA value below 250 can be used safely for a lifetime. However, the RDA value is only one of the factors that cause tooth wear during brushing. An *in vitro* study concludes that, regardless of the properties of the toothpastes (desensitizing and/or anti-erosive) the lower surface abrasion is associated with higher concentration of Ca^{2+} and PO_4^{3-}, presence of Sn^{2+}, higher percentage weight of solid particles, smaller particle size, and lower wettability (João-Souza et al., 2017).

Therefore, the aim of this study is to compare the gingival abrasion of a sonic toothbrush (Sonicare ProtectiveClean® Optimal Plaque Defense head) as test group with a conventional manual toothbrush (control group) in regular patients attending the Service of Odontology of the Hôpital Rothschild (AP-HP).

4.2 Investigational Product indications and contra-indications

Indications

Electric toothbrushes are intended for all patients today and specially for (Sussalan et al., 2018):

- Orthodontic patients;
- Those who are on supportive periodontal therapy;
- Patients with prosthodontic or dental implants;
- For hospitalized patients;
- Individuals with low manual dexterity, such as children and the handicapped.

Contraindications

- Thin gingival phenotype
- Patients with cardiac pacemakers -As they can result in electrical interference with the normal functioning of implantable cardiac devices.

4.3 Risk-Benefit Assessment

The investigational and control devices used in this study are standard devices that are normally used for routine oral hygiene. Very few adverse effects are expected. On the other hand, 50% of the patients may benefit from using the investigational product as it is expected to perform better than a conventional toothbrush in terms of plaque removal and gingival abrasion. The clinical procedures performed are standard procedures.

5 STUDY OBJECTIVES

5.1 Primary Objective and Endpoint

5.1.1 Primary objective

Primary endpoint variables will be used to assess and to compare the gingival abrasion of a sonic toothbrush (Sonicare ProtectiveClean® Optimal Plaque Defense head) in a test group with a conventional manual toothbrush (control group) in regular patients attending the Service of Odontology of the Hôpital Rothschild (AP-HP). These variables will be recorded at the mandible and at the maxillary on the buccal aspects of teeth 6, 4, 3, 1 in each quadrant. If one these teeth is missing, the adjacent mesial tooth will be evaluated. If ever the adjacent mesial tooth is missing the distal tooth is chosen.

5.1.2 Primary endpoint

Evaluation of the gingival abrasion (GA): Macro-relief scoring.

A first method for the evaluation of gingival abrasion (GA) will consist in a method of macro-relief scoring of gingival tissue as described previously by Perin *et al*. with skin tissue. This evaluation consists of acquiring macroscopic views of each investigated surface and then classifying them by observers according to a reference groups of defined abrasion intensity. This evaluation scoring,

using photo grading technique, allow delayed and blinded scoring, independent of whole-subject appearance, thus decreasing subjectivity (Perin et al., 2000).

The macro-relief gingival abrasion scoring technique consists of acquiring macroscopic photographs of each gingival quadrant at each time point. Observers will score these photographs in a double-blind manner by comparing the different photographs with a photonumerical reference scale used as standard. This scale, composed of 5 criteria each scored from 0 to 3, has already been retained by observers as being representative of the different grades of gingival abrasion. The final score will from 0 (no abrasion) to 15 (severe gingival abrasion).

5.2 Secondary Objectives and Endpoints

5.2.1 Secondary objectives

The secondary objectives aim at assessing the effects of a sonic toothbrush versus a conventional manual toothbrush in terms of plaque elimination, gingival inflammation reduction minimizing gingival recession on the gingival tissue of patients in routine dental treatments.
Another secondary objective aims to compare gingival abrasion evaluation techniques.

5.2.2 Secondary endpoints

The investigator will perform the assessment of evolution of secondary objectives after 90 days, using the following endpoints:

- ✓ Comparison of gingival color;
- ✓ Presence of plaque -Plaque index, PI - (Silness and Löe, 1964)
- ✓ Presence of inflammation BOP (Ainamo and Bay, 1975)
- ✓ Presence and/or amount of gingival recession (REC).

5.2.2.1 Changes in gingival color

The evaluation of gingival coloring will be conducted by trained examiners and will consist in extracting each individual visual component of the gingival surface color, based on sensory analysis. This method has already been applied to describe the intensity of skin coloring (red /green/blue component) as well as luminosity, the brightness and transparency (Musnier et al., 2004) and will be applied to each subject's gingival tissue.
Photographed views will be taken according to the standard shooting protocol used in the hospital department, which ensures that all photographs are made in the axis to facilitate proper recording with minimal distortion. A control of image reproducibility will be done by an examiner with image analysis software. A previous study (Kerner et al., 2007) has shown that this method is highly correlated with clinical measurements. During photo shooting, an internal colored reference chart will be photographed in the vicinity of the photographed gingival tissue, as extensively explained by Van Poucke et al in 2010 (Van Poucke et al., 2010).

Regarding the periodontal parameters, a full-mouth examination will be performed.

5.2.2.2 Probing pocket depth (PD)

PD will be measured before the test/control treatment by one and the same examiner by using the PCP-UNC 15 (Hu-Friedy® Chicago, IL, USA) probe throughout the study. The probing depth will be assessed at the buccal aspects of teeth 16,14,13,11. All measurements will be adjusted to the nearest 1.0 mm.

5.2.2.3 Gingival margin recession (REC)

Gingival margin recession will be measured from the cemento-enamel junction to the marginal position of the gingiva with PCP-UNC 15 (Hu-Friedy® Chicago, IL, USA) probe. The measurements will be assessed at the middle of the buccal gingival recession.

5.2.2.4 Bleeding on marginal probing (BOP)

Gingival inflammation (GI) will be assessed as bleeding on marginal probing (BOP) using the index as described by Ainamo & Bay (Ainamo and Bay, 1975). GI uses a 0 to 3 scale to measure the presence of inflammation or not on six sites (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, and disto-lingual) on all teeth, according to the following criteria: 0: absence of inflammation; 1: visible inflammation and no bleeding; 2: visible inflammation and bleeding on probing; 3: obvious inflammation and spontaneous bleeding.
BOP is considered as dichotomous variable. BOP uses 0 and 1 scale. 0: no bleeding on probing; 1: bleeding on probing including 4 sites per tooth. The percentage of bleeding will be calculated as following: number of sites with bleeding / number of sites assessed X 100.

5.2.2.5 Plaque index (PI)

Plaque index (PI) described by Silness & Löe (Silness and Löe, 1964) uses 0 to 4 classes to assess the presence of plaque or not on six sites (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, and disto-lingual) on all teeth, according to the following criteria: 0: absence of plaque; 1: non visible plaque but detectable with a probe; 2: visible plaque not detectable in the interproximal areas; 3: visible plaque in interdental spaces also.

6 STUDY DESIGN

6.1 Type of study

This will be a monocentric, interventional, reference-controlled, randomized, single blind, and superiority study.

The examiner will be blind regarding the investigational products.

6.2 Study Design

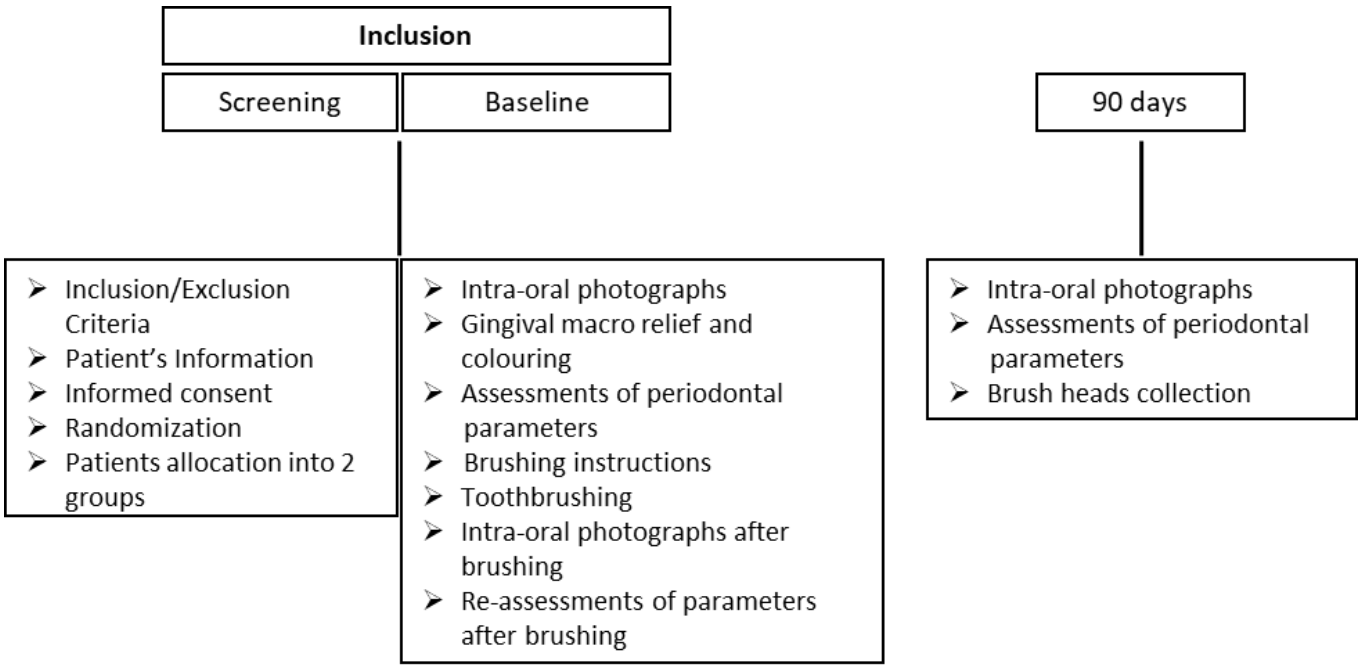

Figure 2: Study diagram

6.3 Treatment groups

The choice of the tooth brushing instrumentation and the brush group will be done randomly by one operator. In addition, these groups will be selected for brushing with or without instructions of the operator with manual or electric toothbrush. The Examiner will be blind and, at any stage of the measurements not informed of the distribution / repartition of the brush group / selected devices.

✓ Brush group 1: Sonicare ProtectiveClean® toothbrush (HX6848/92 Philips) equipped with a C2 Optimal Plaque Defense head (HX9022/10 Philips) + oral hygiene instructions + Manufacturer's instructions + sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL Colgate-Palmolive) with a low degree of abrasivity.

✓ Brush group 2: Inava® 20/100 (Code ACL: 3401561130767) manual toothbrush + oral hygiene instructions + Manufacturer's instructions + sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL Colgate-Palmolive) with a low degree of abrasivity (= 79).

	1st Group: Electric toothbrush + manufacturer's instructions + professional recommendations + sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL)
	2th Group: Manual toothbrush + manufacturer's instructions + professional recommendations + sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL)

6.4 Randomization

Patients will be enrolled sequentially. Patients will be randomized to use either Philips Sonicare ProtectiveClean® or Pierre Fabre Inava® 20/100 toothbrushes (1:1) at inclusion in accordance with a central randomization table generated using a validated computer program. Randomization will be stratified by study site and performed using, a permuted block of 4. Each randomization number will be assigned when a screened patient will be deemed eligible. Toothbrush allocation only depends on the time sequence in which patients enter the study, thus minimizing the selection bias. Treatments will be allocated in accordance with the randomization number assigned to the patient.

6.5 Blinding /Unblinding

At first the eligible patients are randomized. After this step, the data for each patient of two groups (test and control) are collected. The examiner, laboratory and statistical procedures will be blind to the treatment.

6.6 Time and repartition of tooth brushing procedures

The randomization of the toothbrush and the brush group will be performed as previously described by the operator (see section 6.4). Subjects will receive a Sonicare ProtectiveClean® toothbrush (HX6848/92 Philips) equipped with a C2 Optimal Plaque Defense head (HX9022/10 Philips) or a standard manual toothbrush (Pierre Fabre Inava® 20/100) and a sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL). The brushing duration will be inconspicuously measured in seconds with a stopwatch, while the participants are brushing. The mean duration of brushing will be 30 seconds per quadrant for manual or power brushers. All participants with their assigned toothbrush (being either the Philips Sonicare ProtectiveClean® 6809/04 or Inava® 20/100) will brush with manufacturers / professional recommendations. They will use a sodium monofluorophosphate (1450 ppm F) toothpaste. At the beginning of the study three and/or four 75 ml tubes of toothpaste will be given to each patient. It has been calculated that the dose of toothpaste per brushing was 1.21 g on average i.e. 217.8 grams for 90 days (Precisa®100C-3000D). The tubes of toothpaste are weighed at the beginning (average 108 g) and at the end of this study. It is thus possible to measure the global quantity of toothpaste used and the possible effect of this use on the surface texture of the gum tissue.
Thus, brushing time for the whole mouth will be 2 minutes for each patient from both toothbrush groups. The evaluation time and the consequences of brushing will be assessed immediately and 90 days later.

7 SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Informed Consent

An informed consent form, written in accordance with the Declaration of Helsinki (see Appendix 1) and applicable laws of the country of interest will be obtained from all patients.

The patient will sign the informed consent form before being enrolled into the study, i.e. before screening assessments or any other study-related activity. The Investigator will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information sheet. The patient will be given sufficient time to consider the study implications before deciding whether to participate. Should there be any amendments to the final protocol such that this would directly affect the patient participation in the study, e.g. a change in any procedure, the informed consent

form will be amended to incorporate this modification and an informed re-consent will be obtained from the patient.

7.2 Eligibility Criteria

The volunteers will be informed on the background of the study and a written explanation will be given concerning the objectives and the involvement methods. They all will request to give their written consent prior the enrolment into the study.

Each patient entering the study must comply with all of the primary inclusion criteria and will be excluded if one or more exclusion criteria is met.

7.2.1 Inclusion Criteria

1. Dentate males and females must be at least 18 years and not more than 75 years of age
2. Patient able to understand and sign the informed consent prior to starting the study
3. Patient with a minimum of 3 teeth in each of the 4 quadrants and no/or pockets >4 mm
4. Ability and willingness to comply with all study requirements.

7.2.2 Non-inclusion Criteria

1. Pregnancy
2. Patient with cervical restorations
3. Current smoker
4. Patient with orthodontic banding
5. Patient with oral lesions or periodontal diseases
6. Patient who has been deprived of his/her freedom by administrative or legal decision or who is under trusteeship/guardianship
7. Patient already using an electric toothbrush
8. Patient with conditions or circumstances, which may prevent completion of study participation or interfere with analysis of study results, such as history of non-compliance, or unreliability;
9. Patient with non-plaque induced gingival diseases or localized gingival ulceration
10. Thin gingival phenotype
11. Patients with cardiac pacemakers to prevent any interference between the power toothbrush and the implantable cardiac device.

7.3 Withdrawal and Early Discontinuation Criteria and Procedures

When the study is terminated for a given patient, the nature of termination will be documented (scheduled end or early termination/discontinuation). In the event of premature termination/discontinuation, justification will be provided and the name of the decision maker for the discontinuation will be documented.

If the study as a whole is prematurely terminated or suspended, the Independent Ethics Committees (IEC) and the appropriate regulatory authorities will be promptly informed and provided with the reasons for termination or suspension by the Sponsor.

7.3.1 Discontinuation Criteria Related to the Study

Criteria for discontinuation / termination of the entire clinical study include (non-exhaustive list):

- Unexpected high frequency of adverse (device) reactions / adverse (device) effects during the study which does not justify a continuation of the study
- Patients cannot be recruited in sufficient numbers

7.3.2 Discontinuation Criteria Related to the Study Site

Discontinuation of the clinical study in an individual study site may occur because of various reasons including but not limited to:

- Failure of the Investigator to comply with the EN ISO 14155:2011, ICH GCP E6 (rev2), and/or applicable regulatory requirements;
- Submission of knowingly false or incomplete information from the site to Philips, the Study Monitor or authorities;
- Repeated non-compliance with protocol requirements including insufficient data quality (missing data in Case Report Forms (CRFs) occurring repeatedly);
- Failure of the Investigator at a site to enroll patients into the study at an acceptable rate;
- Personnel change without appropriate information to the Sponsor.

7.3.3 Discontinuation Criteria related to the Patient

Patients will be advised in the informed consent forms that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's / Sponsor's discretion at any time, when the withdrawal is considered to be in the interest of the patient. In the event of a patient dropping out of the study or withdrawing from the study, the withdrawal/study termination page in the CRF has to be completed. On the withdrawal page of the CRF the Investigator should record the date of the withdrawal, the person who initiated withdrawal and the reason for withdrawal.

The following are reasons for patient dropout/withdrawal:

i) Withdrawn by the Investigator due to:
- Adverse Event, Serious Adverse Event
- Protocol deviation (e.g. administration of an excluded treatment, failure to comply with scheduled visits, …)
- Pregnancy

ii) At the patient's request due to:
- An Adverse Event / Device Effect for which the Investigator did not consider removal necessary;
- Withdrawal of consent.

8 INVESTIGATIONAL PRODUCT

All specified devices and products to be used in the study will be provided by Philips Sonicare.

8.1 Name and Description of the Investigational Product

In this study both products, Philips Sonicare ProtectiveClean® and the manual toothbrush (Pierre Fabre Inava® 20/100) will be used within the indications. The test sites will be treated with the investigational device following the instructions of this protocol.

Investigational devices will be made available to the investigation site by the Sponsor. If any defect in the Investigational Product is observed, the study manager or monitor will be informed. A sodium monofluorophosphate (1450 ppm F) toothpaste (elmex® SENSITIVE PROFESSIONAL) will be provided to the patient.

8.1.1 Indications for use

The indication studied is using of an electric toothbrush Philips Sonicare ProtectiveClean® HX6848/92 associated with a C2 Optimal Plaque Defense head HX9022/10, in routine oral hygiene and to assess the possible effects on hard and soft tissue.

8.1.2 Duration of treatment

The overall duration of the study for the patient will be 90 days from the time of the baseline.

8.1.3 Packaging and Labelling

The boxes will be labelled in accordance with ISO 14155:2011 (Paragraph 5.10). Labels will indicate that the device is exclusively intended for use in the study and will identify the study number, Sponsor and patient code.

8.2 Storage

The Investigational Products will be supplied to the pharmacist or any other designated person. Investigational products can be stored at room temperature in a dry area. Non-adherence with the storage conditions could alter the performance of the Investigational Product.

8.3 Instructions for Use

The instructions for use of Philips Sonicare ProtectiveClean® and Pierre Fabre Inava® are provided in the products notices (see appendices in sections 19.2 and 19.3). The investigators will give the patients the following oral hygiene instructions:

Place the bristles against the teeth at a 45° angle, towards the gum line and start brushing. Depending on the allocation group the following instructions will be given:

Electric toothbrush: Apply light pressure and move the brush head slowly horizontally without scrubbing across the teeth to brush all dental surfaces in a regular movement. It is not necessary to do any other movement. The ProtectiveClean Sonicare® brush will generate small vibrations every 30 seconds so the patient can adjust the pace of his movement to the global brushing time of 2 minutes.

Manual toothbrush: The “rolling” modified Bass technique should be used: the head of the brush must be rotated upwards on the lower teeth and downwards on the upper teeth towards the occlusal surface. The occlusal surfaces are cleaned using the scrub technique (the toothbrush is swept along the teeth backwards and forwards). In palatal/lingual sites a slight horizontal movement can be combined with a vertical translation as described above.

8.4 Investigational Product Accountability

The pharmacist or any other appropriate health professional, who is designated by the Investigator, will be responsible for recording the receipt and administration/dispensing of all Investigational Product supplies as well as for the storage and allocation of these supplies. Investigational Product supplies should be counted by the Site Monitor during monitoring visits.

In accordance with the applicable regulations, the Investigator and/or other appropriate designated worker will keep an inventory of all clinical trial material (CTM) received. All used and unused CTM will be accounted for in an Inventory Form provided to the Investigator by the Site Monitor. CTM inventory forms will be examined and reconciled by the operator (Dr Rangé) at the end of the study.

A copy of the completed Inventory Form will be retained in the Investigator's study file, and a copy will be filed in the Sponsor's Trial Master File.

These records should include dates, quantities, batch/serial numbers, expiry dates, and the Investigational Product and study patients. Investigators should maintain records that document adequately that the patients were provided with the Investigational Products specified by the protocol.

8.5 Destruction / Retrieval of Surplus Investigational Products

The site monitor will be responsible for the retrieval of used and surplus / unused Investigational Product. In all cases, an Investigational Product accountability form will be completed.

8.6 Concomitant Therapy

No concomitant therapy will be prohibited by the current protocol.

9 STUDY SCHEDULE

9.1 Flow chart

Visits / Tasks	Screening/baseline	Follow-up
	Day 1	Day 90
Patient information and informed consent signature	X	
Inclusion/exclusion criteria	X	
Randomization	X	
Investigational device supply	X	
Plaque Control Record (PCR)	X	X
Inflammation assessment (BoP)	X	X
Gingival recession assessment (REC)	X	X
Pocket depth probing (PD)	X	X
Gingival abrasion (GA)	X	X
Gingival coloring variation assessment	X	X
Dental photograph	X	X
Oral hygiene instructions	X	
Investigational device collection		X
Assessment of toothbrush usage (patient reported)		X
Assessment of toothbrush usage (brush wear assessment)		X
Adverse events collection		X

Figure 2: Flow chart of the course of the study.

9.2 Investigators' meeting and Calibration

Before starting the study, the examiners / operators will be trained and calibrated to implement an identical procedure. Every member of the investigation team is a former trainee of the European post graduate program in periodontics, which should ensure homogenization of periodontal measurements, thereby limiting the investigator's bias.

9.3 Procedures at Each Visit

Study procedures are described in the tabular overview provided in Section 6.2.

A maximum of 2 visits will be scheduled as follows:

- Screening/Baseline visit at Day 1 (D1), with baseline oral assessment in case of inclusion
- Follow-up visit: at 90 days

Screening/Baseline Visit (Day 1):

This initial study phase consists of a pre-screening of the patients. During routine visits, possible patients will be selected. The patients will be informed on the background of the study and a written explanation will be given concerning the objectives and the study procedures. They all will request to give their written consent prior to enrolment into the study.

The following procedures will apply:

- Explanation to the patient of the purpose of the study and planned oral hygiene procedures;
- Inclusion/Non-Inclusion criteria;
- Patient agreement to comply with study requirements and informed consent form signing;
- Randomization;
- Supply of the Investigational Product (by the operator);
- Plaque measurement (PI)
- Inflammation assessment (BOP);
- Gingival recession assessment (REC);
- Pocket depth probing (PD);
- Dental Photographs and analyze of Gingival macro relief coloring (GA);
- Tooth brushing session;
- Oral Hygiene Instructions.

Subsequent visit date will be scheduled at the end of this visit.

Follow-up visit at 90 Days

The following procedures will apply:

- Plaque measurement (PI)
- Inflammation assessment (BOP);
- Gingival recession assessment (REC);
- Pocket depth probing (PD);
- Dental Photographs and analyze of Gingival macro relief coloring (GA);
- Dental photograph;
- Toothbrush collection (by the operator);
- Assessment of toothbrush usage (patient reported);
- Assessment of toothbrush usage (brush head wear assessment);

- Assessment of toothpaste usage (paste weighed)
- Adverse events collection.

9.4 Assessment of Compliance.

Upon completion of clinical assessments, all manual toothbrushes as well as all brush heads will be collected by the operator, and the age of the brush or brush head will be assessed by asking the participants the number of weeks the brush or brush head was used. After completion of the study, the operator will assess all manual toothbrushes as well as all brush heads for brush wear according to the method described by Conforti *et al*. on a 0–4 scale (Conforti et al., 2003).

10 STUDY AND TREATMENT DURATION

10.1 Duration per patient

The overall study duration for each patient is 90 days after baseline.

10.2 Study period

Overall study duration: 9 Months, including 6 Months inclusion period and 90 days of patient participation after last inclusion.

11 STATISTICS

11.1 Planned Analysis

The description of all parameters recorded will be presented by group and for overall population.

Quantitative parameters will be described using the following summary descriptive statistics: number of non-missing values, mean, standard deviation, median, first and third quartiles, and minimum and maximum values.

Qualitative parameters will be described overall using frequencies and percentages. Percentages will be calculated on the number of non-missing observations.

The test and control groups will be compared on the primary and secondary outcomes of the study.

It will be proven that the test group is superior to the control group.

First, normality tests (e.g. Kolmogorov-Smirnov or Shapiro-Wilk test) will be used to assess the normality of the distribution. According to data distribution, t-test or Mann-Withney u-test will be applied for continuous variables, such as the gingiva abraded and gingival relief scoring.

For categorical variables, Pearson's Chi square test or Fisher's exact test will be used.

Within a certain group, tests will be used to explore the time effect, i.e. evolution between baseline and post-baseline measurements. Wilcoxon’s test or Student’s test for pairwise comparisons will be used, depending on the normality of the distribution.

Any imbalance between-treatment groups in baseline measurements, despite randomization, will be researched and this analysis will be performed using Student’s test or Wilcoxon’s test for quantitative parameters and Chi-square test or a Fisher’s exact test for qualitative parameters.

In case of any imbalance observed, an ANCOVA including the treatment group with the baseline as covariate(s) for quantitative parameters or a logistic regression with the same parameters will be done instead.

In order to provide unbiased and informative findings, no replacement of missing values is planned for any parameters. In all applicable cases, reported analysis will mention the number of missing values for each outcome relatively to the considered analysis set.

11.2 Level of significance

The level of significance for all comparisons is set at 0.05 using two-tailed tests.

Confidence level is set at 0.95 (two-sided) for all primary and secondary endpoints.

11.3 Patient selection for analyses

There will be three analysis populations defined for the study:

- The Safety population (SAF) will include all patients who signed an informed consent form.

  Safety analyses will be performed on the SAF population.

- The Full Analysis Set (FAS) population will include all patients who signed an informed consent form and performed the study procedures, whatever their assigned treatment group by randomization.

  Description of demographic and baseline characteristics as well as analyses of primary and secondary endpoints (other than safety endpoints) will be performed on the FAS population.

- The per protocol (PP) population will include patients from the FAS population without major protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data. Deviations involving possible bias regarding the primary endpoint analysis will be considered as major deviations. Protocol deviations will be further defined in the statistical analysis plan.

  The PP population will be used for the supportive analyses of the primary and main secondary endpoints (other than safety endpoints).

11.4 Description of baseline characteristics

Appropriate descriptive methods (means, standard deviations, minimum, median, maximum, lower and upper quartiles, number of observations, percentages and 95% confidence intervals) will be used to describe demographics data and other baseline characteristics.

These analyses will be performed on the SAF population. Some parameters could also be described on FAS and/or PP populations if more than 10% are excluded from SAF population.

11.5 Analysis of the primary endpoint

All parameters listed in Section 5.2.2 will be documented and compared between treatment groups.

Macro-relief scoring: The technique consists of acquiring macroscopic photographs of each gingival quadrant at each time point. Observers will score those photographs in a double-blind manner by comparing the different photographs with a photonumerical reference scale used as standard. This scale will first be retained by observers as being representative of the different grades of gingival abrasion: from 0 (no abrasion) to 15 (severe gingival abrasion) according to the following table:

Score / Criteria	0	1	2	3
Erythema	None	Small (surface 0 to ¼)	Medium (surface ¼ to ½)	Large (surface > ½)
Inflammation	None	Small (surface 0 to ¼)	Medium (surface ¼ to ½)	Large (surface > ½)
Bleeding	None	Slight	Moderate	Severe/expanded
Recession	None	Small (≤ 2 mm)	Medium (3 to 5 mm)	Large (> 5mm)
Erosion	None	Slight	Moderate	Severe/expanded

11.6 Analysis of the secondary endpoints

All parameters listed in Section 5.1.2 will be documented and compared between treatment groups.

Gingival coloring intensity: The technique consists of acquiring macroscopic photographs of each gingival quadrant, including an internal colored reference chart in the vicinity of the photographed gingival tissue, at each time point. Next, using an image analysis software, each photograph will be calorimetrically reconverted to be recalibrated following the colored reference chart. Then, the coloring intensity in each zone of interest [marginal (cervical free gingiva, CFG), interdental (papillary free gingiva, PFG) and mid-gingival (attached gingiva, AG)] around each tooth in each quadrant, will be extracted by observers in a double-blind manner using the color picker tool.

All parameters listed in Section 5.2.2 will be documented and compared between treatment groups.

11.7 Analyses of safety endpoints

Safety will be assessed with the collection of adverse events throughout the study. The number and percentage of patients with at least one AE will be calculated with its 95% confidence interval (CI). All the AEs will also be described by system organ classes (SOC) and preferred terms (PT) and will be classified as serious or not, related to the device or not. All the serious AEs related to the device will be described. A listing describing the following data will be provided: classification as SAE, intensity, imputability to procedure, imputability to Investigational Product, action taken, corrective treatment, outcome, delay of occurrence and duration.

The safety analyses will be performed on the SAF population.

11.8 Sample Size

The sample size calculation is based on a preliminary study evaluating the primary criteria (macro-relief scoring changes between D0 and D90 after manual compared to electric brushings). In this preliminary study, we have measured a threshold value of ΔE = 0.67 on the primary criteria between manual brushing and electric brushing, associated with a standard deviation of 0.84. Using a

bilateral two-group test with a 0.05 two-sided significance level and a power (1- ß) of 0.80 yielded a sample size of 25 subjects per group (34 subjects when considering a power (1- ß) of 0.90).

We can add 20% for potential dropouts. Thus, 30 subjects per group is evaluated, i.e. 60 subjects are required in total.

11.9 Criteria for the termination of the study

See section 7.3.

12 SOURCE DATA AND SOURCE DOCUMENTS

12.1 Definitions

12.1.1 Source Documents

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments involved in clinical study).

12.1.2 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

12.1.3 Direct Access

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are relevant to evaluation of a clinical study.

12.2 Permission of Access

The Investigator will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections, by providing direct access to primary patient data (i.e. source data) which support the data on the study's eCRFs, e.g. general practice charts, hospital notes, appointment books, original laboratory records.

Because this enters within the realm of patient confidentiality, this fact must be included in the Informed Consent Form to be signed by the patient in line with the General Data Protection Regulation (EU) 2016/679 (GDPR).

Any party, e.g. local and foreign regulatory authorities, the Sponsor and/or authorized representatives of the Sponsor such as monitors and auditors, with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Sponsor proprietary information.

13 ASSESSING AND REPORTING OF ADVERSE EVENTS

13.1 Definitions

According to the article R. 1123-39 1°; 2°; 6°; and 8° of the French public health code, the following definitions apply:

13.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, user or other persons, whether or not related to the Investigational Product. This definition includes events related to the Investigational Product or the comparator and events related to the procedures involved.

13.1.2 Adverse Reaction (AR)

An adverse reaction is defined as an adverse event related or likely to be related to the investigational product".

13.1.3 Serious Adverse Event/Reaction (SAE/SAR)

An adverse event/reaction that

- results in death,
- is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect,
- is an important medical event.

*Planned hospitalization for a pre-existing condition, or a procedure required by the clinical study protocol, without serious deterioration in health, is not considered a SAE.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical/medically significant events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually also be considered serious.

13.1.4 Unexpected Serious Adverse Reaction (USAR)

An unexpected adverse reaction is any adverse reaction whose nature, severity or outcome does not match with the information relating to the products, acts performed, and methods used during the research.
For each adverse reaction, the sponsor must assess whether or not it is unexpected.
The assessment of the unexpected nature of an adverse reaction is made on the basis of the information described in the protocol or instructions for use, relating in particular, if applicable, to the acts and methods practiced or in products being researched or used for research purposes.

If the adverse reaction relates to a health product used for the purposes of the trial, it is appropriate in order to determine the unexpectedness of this effect, to refer to the information contained in the relevant standards if the product is used in accordance with these standards [for example the summary of product characteristics of marketing authorization (Marketing Authorization) for a drug, when that drug is used, as part of the test, in accordance with this MA].

13.1.5 New security event

Any new data or information that could result in:

- A re-evaluation of the benefit risk ratio of the risks of the research or the Investigational Product
- Modifications of the use of the Investigational Product, the study conduct or the study documents
- A temporary or permanent halt of the research
- A modification of the research protocol or any similar research protocol

13.2 Organization and evaluation

The study period during which (serious) adverse events will be recorded/reported is defined as the period from patient inclusion to the end of study participation.

The clinical course of each (serious) adverse event will be followed up until the event (or its sequelae) resolves or stabilizes at a level acceptable to both the Investigator and Sponsor,

Every effort will be made by the Investigator to explain each AE and assess its causal relationship to the Investigational Product. The Investigator will use the following definitions and categories to assess adverse events:

Seriousness:

- No: no fulfilment of Serious AE criterion
- Yes: fulfilment of SAE criterion (see section 13)

Severity/Intensity:

- Mild: Transient or mild discomfort, no modification of procedure or medical intervention required
- Moderate: Discomfort causes interference with usual activities, no or minimal modification of procedure or medical intervention required
- Severe: Inability to work or to do usual activity, medical intervention indispensable

There is a distinction between the terms “severe” and “serious” for an AE. Severe is a measurement of intensity; thus, a severe reaction is not necessarily a SAE. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs listed in section 13.1.3.

Action undertaken in regard to the Investigational Product:

- None
- Investigational Product postponed
- Investigational Product discontinued

AE therapy:

- Yes: remedial treatment necessary
- No: remedial treatment unnecessary

Final outcome:

- Recovered without sequelae
- Recovered with sequelae
- Ongoing
- Unknown
- Death
- Improving/worsening

Causality (relationship with the Investigational Product):

- Certain: temporal correlation plausible, other causes excluded
- Probable: temporal correlation reasonable, other causes unlikely
- Possible: temporal correlation reasonable, other causes possible, not assessable
- Unlikely: No temporal correlation, other causes probable, not assessable
- Not related: definitely no causal relationship (see section 10.1.8)

13.3 Role of the Investigators

All AEs occurring during the study period set out in this protocol, observed by the Investigator or reported by the participant, will be recorded in the eCRF (adverse event form) according to the general instructions for completion.

If the AE is Serious (see Section 13.1.3), the investigator must complete the “Serious Adverse Event” form at the time the SAE is detected, in addition to the “Adverse Event” form in the e-CRF.

The investigator will notify the sponsor, as soon he/she becomes aware of all SAEs (whether or not attributed to the product under investigation), new safety issues, without waiting for results of clinical outcome or of additional investigations, unless if the protocol specifies that the event does not need immediate notification.

The initial SAE report will be as complete as possible, including date of onset and end date, severity, seriousness, assessment of relatedness to IP, other suspect drug or device, study procedures and action taken.

The initial notification of a serious adverse event to the sponsor is the subject of a written report and must be followed quickly by one or more detailed written report(s) in order to follow the evolution of the case or add information.

Any information not available at the time of the initial SAE report will be documented on a follow-up report and SAE will be followed up until resolution or the event is considered stable. The SAE forms must be printed and supplied immediately (within max. 24 hours after SAE awareness) to the vigilance department of Philips:

Philips consumer Support
Xavier James
+33 1 57 32 40 51
consumersupport@philips.com

13.4 Role of the Sponsor

The Sponsor will be responsible for continuous safety evaluation of the Investigational Product, which includes the evaluation of seriousness and causality between the SAE and the IP or the procedure or the concomitant treatment.

In addition, the Sponsor will evaluate the unexpectedness or expectedness of SAEs.

In compliance with the pertinent legal requirements, safety data or new elements which may significantly modify the risk-benefit ratio of the investigational product or which may lead to modify the conditions of use of the IP (new security events) will be notified immediately to the competent authority if required.

The sponsor is in particular responsible for:

- The continuous assessment of the safety of any experimental element of the research, no matter if they are acts performed or products used;
- the implementation of written procedures to guarantee:
  - the quality of the collection of research safety data;
  - documentation, evaluation, validation, and archiving of this data;
- the transmission to the relevant CA and EC of the safety data required by the regulations;
- the management and evaluation of adverse events including: collection, evaluation of data, assessment of the severity of all adverse events transmitted by the investigator and their causal link to the research. All adverse events for which the investigator or sponsor considers that a plausible causal relationship with the research exists, are considered suspected adverse reactions. When the causality assessments performed by the investigator and the sponsor differ, both are mentioned in the case declaration to the AC and the EC.;
- the assessment of the unexpected nature of the AEs;
- the quick notification to all the investigators concerned, to the relevant EC and AC of all new security events (any data that could affect the safety of participants, have an impact on the conduct of the test or modify the research authorization);
- keeping detailed records of all adverse events reported to it by the investigator(s); said records being susceptible to be transmitted to the ANSM, upon request.

13.5 End of study

The final study report will be written by the Sponsor following a reference plan and will be provided to the competent authority as well as the ethics committee in a one year period after the end of the research, defined as the date of the last visit of the last patient. This period will be shortened to 90 days in case of an early study termination.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Quality Control

14.1.1 Definition

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study-related activities have been fulfilled.

Quality Control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14.1.2 Study Monitoring

Authorized, qualified representatives of the Sponsor will set up and visit investigational sites at regular intervals as defined in the monitoring plan to verify adherence to protocol and local legal requirements, to perform source data verification and to assist the Investigator in his/her study related activities. Refer also to section 12.2 regarding permission of access.

At each patient inclusion or theoretical follow-up visit, the monitor will connect to the eCRF to check the filling of data by the Investigator according to the monitoring guidelines established by the Sponsor.

In case the visit has not been completed by the study site, a query will be made to the Investigator by phone or by e-mail or fax.

The frequency of eCRF monitoring will be based on the scheduled dates of patient visits more or less the window specified by the protocol.

During the monitoring of eCRF, the following routine checks will be conducted:

- The actions to be taken during the last central monitoring have been completed
- The data entry into the eCRF: missing data, incorrect data, transcription of paraclinical examinations
- Generate queries
- Check that the issued queries were processed within 7 days of issuance
- Check for study withdrawals and patients lost to follow-up
- Check data consistency in relation to each other
- Check for serious and non-serious adverse events

In the case of a non-reported serious adverse event, the Investigator will be notified and notification to the vigilance department will be done within one business day. Other documents (results of additional tests, hospital discharge file) will be collected and sent as soon as possible.

The Monitor will send the Investigator (via email with read-receipt, mail or fax) details of the problems encountered and issued queries. Without any news, the Monitor will contact the Investigator by phone for a reminder.

14.2 Quality Assurance

14.2.1 Definition

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with the protocol and pertinent regulatory requirements.

14.2.2 Audit

An audit is a systematic and independent review of study related activities and documents to determine whether the evaluated study related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, designated Standard Operating Procedure (SOPs), and the applicable regulatory requirements.

An independent audit at the study site may take place at any time during or after the study. The clinical Investigator(s) will allow auditing of their clinical investigation procedures.

14.2.3 Inspection

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsors and/or clinical research organization facilities or at any other establishments deemed appropriate by the regulatory authorities.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Independent Ethics Committee (IEC)

This is an independent and properly constituted body whose responsibility is to ensure that the safety and well-being and human rights of the subjects participating in a clinical study are protected. The term 'independent ethics committee' is used synonymous with 'research ethics committee' and 'institutional review board (IRB)'.

Before initiating a study, the Investigator should have written and dated approval / favorable opinion from the competent ethics committee for the study protocol (and amendments) according to local requirements, written informed consent form, consent form updates, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. Approval will be given in writing with reference to the final protocol number and date.

15.2 Protocol amendments

All amendments to the clinical study protocol will be agreed upon between the Sponsor and the Investigator and will be recorded with a justification for the amendment. The Investigator or the Sponsor should not implement any deviation from, or changes of, the protocol without mutual agreement, prior review from the IEC and competent authority of a respective amendment. The only exceptions are where necessary to eliminate an immediate hazard to study patients, or when the changes involve only administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)).

The party initiating an amendment will clearly confirm it in writing and it must be signed and dated by the Sponsor and the Principal Investigator. Protocol amendments will be submitted to the appropriate IECs and competent authorities in line with applicable regulatory requirements.

15.3 Patient Information Leaflet and Written Informed Consent Form

In order to obtain and document the patients' informed consent, the Investigator must comply with current regulatory requirements and comply with ICH GCP E6 (R2) directives and the norm EN ISO 14155:2011 and requirements of the Declaration of Helsinki.

Prior to any study-related activity, patients shall be informed in a fair and honest manner using understandable terms, of study objectives and constraints, any potential risks, required monitoring and safety measures and of their right to refuse to participate in the study or to withdraw their consent at any time.

The study participants must voluntarily sign and date an informed consent form prior to any study-related activity.

The written informed consent form must be dated and signed by the person who made the patient's information and obtained his/her informed consent.

The patient shall be given a copy of the patient information leaflet and consent form signed by both parties. The original shall be held by the Investigator. A new consent form shall be signed by study participants, if necessary, in the event of any substantial amendment to the protocol concerning study objectives, design, population, laboratory tests or significant administrative aspects.

The written information must include the patient's right to request a correction to the personal information and data collected, to require that errors be corrected, to know who is in charge of data archiving and who can access to this information.

15.4 Financing and Insurance

The costs necessary to perform the study will be agreed upon with each Investigator and will be documented in a separate financial agreement which will be signed by the Investigator and the Sponsor, prior to the study commencing.

Philips has subscribed an insurance policy with the insurance company HDI Global SE for all patients taking part in the trial under the policy number 01011555-14010.

All Investigators will receive a copy of the insurance certificate and the insurance policy; the latter must be known to the patients and made available on request.

15.5 General reporting obligation

In line with local legal requirements, the Sponsor will inform the federal authority and/or local competent authorities of the planned clinical trial in writing before the beginning of the study. Changes in the information initially submitted to these authorities, e.g. change in participating Investigators, duration of the study, premature study termination will be notified to the said authorities in line with the applicable local legislation.

15.6 Conduct of the Study

This clinical study will be conducted in accordance with the Declaration of Helsinki (relevant version – revised 64th WMA General Assembly, Fortaleza, Brazil, October 2013 - Appendix 1). Furthermore, compliance with this protocol, Standard Operating Procedures, ICH GCP E6 (Rev2) and with local laws and regulations relevant to clinical research not carried out on health products in the country of conduct is observed.

15.7 Investigator's Brochure

The Investigator Brochure is replaced by the Instructions For Use.

15.8 Personal Data and Data Protection

All data obtained in the context of the clinical trial are subject to data protection in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR). The patient's name and other personal data will be pseudonymized.

It will be ensured that eCRFs or other documents, e.g. copies of reports on special findings transmitted to the Sponsor are also pseudonymized.

Data storage for statistical assessment will also be performed only under the patient's study identification. Only the Investigator will have the means to identify a patient's name / other personal details via the study identification.

If it becomes necessary in the course of the study to identify a patient's name for medical reasons, all individuals involved are subject to an obligation to maintain secrecy.

Personal data will be stored and processed in accordance with the above mentioned General Data Protection Regulation requirements.

15.9 Data handling and record keeping

15.9.1 Completion of electronic Case Report Forms (eCRF)

Electronic CRFs developed by CLINFILE will be used to collect clinical data from each site. All data entered into the eCRF will be stored on a secure platform.

According to EN ISO 14155:2011/Cor 1:2011, section 6.8 and ICH GCP E6, the Investigator shall ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

Since electronic databases will be used, written procedures will be implemented to:

- Establish and document requirements for the electronic clinical data system to receive and process data
- Verify and validate that the requirements for the electronic clinical data system can be consistently met
- Ensure attributability, completeness, reliability, consistency and logic of the data entered
- Ensure accuracy of reports
- Ensure that data changes are documented and that there is no deletion of entered data
- Maintain a security system that prevents unauthorized access to the data, both internally and externally
- Maintain a list of individuals who have access to the electronic data system as well as the dates of access and privileges granted to each user
- Ensure that all completed eCRFs are signed by the site Principal Investigator or authorized designee
- Maintain adequate backup, retention and retrievability of the data, and train users on proper use of the systems

All data collected in eCRFs during the trial will be documented in a pseudonymous way and patients will only be identified by patient numbers and initials (only the first letter of the last name, the first letter of the first name). No directly nominative data will be collected.

All information on eCRFs will be traceable to source documents, which are generally maintained in the patient's file. Any original document or object, including questionnaires proving the existence or accuracy of a data or fact recorded during the research, is defined as a source document.

eCRF Completion Guidelines describing the format of the data to be entered into the eCRFs by the site will be available.

Access to add or change data in all eCRFs is limited only to the study site personnel.

Coming up to the end of study, eCRF will be physically locked on an ongoing basis by the CLINACT Data Manager as patients are identified as screening failures or as they discontinue the study.

The Investigator will review and sign off on each subject's eCRF once all eCRFs have been completed, reviewed, monitored, and all queries are resolved.

15.9.2 Data management

A Data Management Plan (DMP) will be drafted to establish and document the overall plan for data management activities in the study from clinical database design, through data collection, to data finalization and clinical database archiving to ensure completeness, correctness, and consistency of the data.

Automated edit checks that are programmed within the eCRF are triggered at the time of data entry. These checks will include out-of-range checks, missing data checks and checks for data inconsistencies. The site is expected to correct or confirm all flags. The CLINACT Site Monitor and/or Data Manager will follow up on any flagged responses directly with the site. The CLINACT Data Manager will be responsible for ensuring that all data management activities are complete in the database before study time-points.

15.9.3 Archiving

Essential documents will be retained for the periods required by applicable national and international legal legislation but not less than 15 years after routine/premature termination of a clinical study.

The final report shall be retained for at least 2 years after the Investigational Products are removed from the last market. The informed consent forms and all the original (raw) data will be retained by the Investigator for at least 15 years.

15.10 Confidentiality

The aim and contents of the study, in addition to its results, will be treated as confidential by all persons involved in the clinical trial according to local regulation.

15.11 Responsibilities

The responsibilities of the Investigator, Monitor and Sponsor of the clinical trial as regards handling of data, storage of data, planning, assessment and quality assurance are regulated by the ICH GCP E6 and apply also to this clinical trial.

16 FINAL REPORT AND PUBLICATION POLICY

The Sponsor and relevant parties shall agree on the final study report.

It is expected that the results of the study will be published as scientific literature. For this reason, the clinical study will be registered in the international database ‘Clinicaltrials.gov’.

Results will also be submitted to regulatory authorities. The following conditions are to protect commercial confidential materials (patents, etc.), not to restrict publication.

All information concerning Philips Sonicare ProtectiveClean® and/or Optimal Plaque Defense, such as patent applications, manufacturing processes, basic scientific data or formulation information supplied to the Investigator by the Sponsor and not previously published is considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees not to use it for other purposes without the Sponsor’s written consent.

It is understood by the Investigator that the Sponsor will use the information developed in this clinical study in connection with the development of the Investigational Product and therefore may

be disclosed as required to other Investigators or any appropriate international Regulatory Authorities. In order to allow for the use of information derived from this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this study.

Subject to the formal authorization from the Sponsor, the Investigator will be allowed to publish and/or communicate the results of this study or any other information related to the study. The Sponsor will provide the Investigator with its decision within 60 days after receipt (proof of delivery) of the publication/communication project. A non-response form the Sponsor will be considered as a refusal. During this 60 day period, the Sponsor will have the right to ask for any modification and/or removal of any confidential information that could lead to a prejudice in terms of industrial or commercial operation of the Sponsor's products. Upon request from the Sponsor, the Investigator shall accept to delay the publication and/or communication by 60 additional days to protect the Sponsor's industrial property rights.

In accordance with generally recognized principles of scientific collaboration, co-authorship with any Sponsor personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

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18 SIGNATURES

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
_____	Thibaut SALTET DE SABLET (Medical Writer, CLINACT)
_____	Dr Gérard SORBA (Medical Representative, CLINACT)
_____	Florence CARRERE (Statistician, CLINACT - STATITEC)
_____	Dr Francis MORA (Coordinating Investigator)
_____	Dr Marc WATTS (Head of Professional Relations, Philips Personal Health)
_____	Pr Philippe BOUCHARD (Scientific advisor)
_____	Dr Helene RANGE (Scientific advisor)
_____	Dr Gael ROCHEFORT (Scientific advisor)

19 APPENDICES

19.1 Appendix 1: Declaration Of Helsinki (October 2013)

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 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, 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 ad-dressed 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 fulfilment 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 sub-jects 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 minimizes 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 minimize 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 re-searcher, 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 re-search 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 maybe 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 re-searcher, 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 in-formation, 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 in-formed consent, the physician must seek informed consent from the legally authorized 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 in-stead be performed with persons capable of providing in-formed 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 authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally in-capable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that pre-vents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized 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 authorized 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.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

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 in-formed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, reestablishing 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 re-corded and, where appropriate, made publicly available.

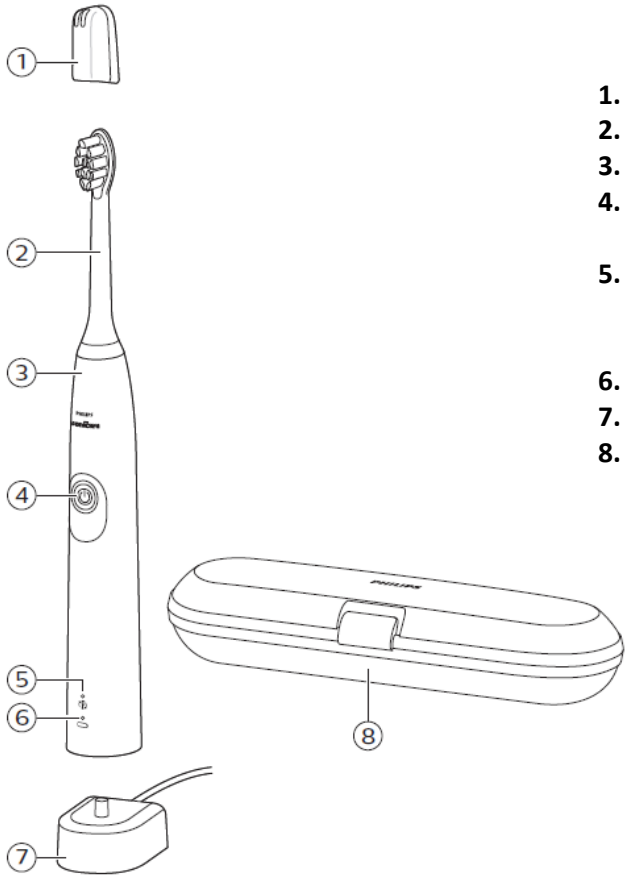
19.2 Appendix 2: Philips Sonicare ProtectiveClean® Instructions for use

Philips Sonicare ProtectiveClean® - ©2014 Koninklijke Philips Electronics NV (KPENV).

The Sonicare toothbrush complies with the safety standards for electromagnetic devices. If you have a pacemaker or other implanted device, contact your physician or the device manufacturer of the implanted device before you use the Sonicare.

Package Insert

General Description



1. Hygienic travel cap
2. Smart brush head
3. Handle
4. Power on/off button
5. Brush head replacement reminder light
6. Battery indicator
7. Charging base
8. Travel case (specific types only)

IMPORTANT

Read this user manual carefully before you use the appliance and save it for future reference.

DANGER

-Keep the charging base away from water.

Do not place or store it over or near water contained in a bathtub, washbasin, sink etc. Do not immerse the charger in water or any other liquid. After cleaning, make sure the charger is completely dry before you connect it to the mains.

WARNING

-The mains cord cannot be replaced. If the mains cord is damaged, discard the charger.

-Always have the charger replaced with one of the original type in order to avoid a hazard.

-Do not use the charger outdoors or near heated surface.

-Check if the voltage indicated on the appliance corresponds to the local mains voltage before you connect the appliance.

-If the appliance is damaged in any way (brush head, toothbrush handle or charger), stop using it. This appliance contains no serviceable parts. If the appliance is damaged, contact the Consumer Care Centre in your country (see chapter 'Warranty and support').

-This appliance can be used by children and by persons with reduced physical, sensory or mental capabilities or lack of experience and knowledge if they have been given supervision or instruction concerning use of the appliance in a safe way and understand the hazards involved. Cleaning and user maintenance shall not be made by children without supervision.

-Children shall not play with the appliance.

CAUTION

-Do not clean the brush head, handle or the charger in the dishwasher.
-If you have had oral or gum surgery in the previous 2 months, consult your dentist before you use the toothbrush.
-Consult your dentist if excessive bleeding occurs after using this toothbrush or if bleeding continues to occur after 1 week of use. Also consult your dentist if you experience discomfort or pain when you use the Philips Sonicare.
-The Sonicare toothbrush complies with the safety standards for electromagnetic devices. If you have a pacemaker or other implanted device, contact your physician or the device manufacturer of the implanted device before to use.
-If you have medical concerns, consult your doctor before you use the Sonicare.
-This appliance has only been designed for cleaning teeth, gums and tongue. Do not use it for any other purpose. Stop using the appliance and contact your doctor if you experience any discomfort or pain.
-The Sonicare toothbrush is a personal care device and is not intended for use on multiple patients in a dental practice or institution.
-Stop using a brush head with crushed or bent bristles. Replace the brush head every 3 months or sooner if signs of wear appear. Do not use other brush heads than the ones recommended by the manufacturer.
-If your toothpaste contains peroxide, baking soda or bicarbonate (common in whitening toothpastes), thoroughly clean the brush head with soap and water after each use. This prevents possible cracking of the plastic.

Electromagnetic fields (EMF)

This Philips appliance complies with all applicable standards and regulations regarding exposure to electromagnetic fields.

Radio Equipment Directive

–Radio Equipment in this product operates at 13.56 MHz

–Maximum RF power transmitted by the Radio Equipment is 30.16dBm

Introduction

Congratulations on your purchase and welcome to Philips! To fully benefit from the support that Philips offers, register your product at **www.philips.com/welcome.**

Brush heads

Your Philips Sonicare comes with one or more brush heads which are designed to deliver superior results for your oral care needs.

Philips Sonicare BrushSync Technology

Your smart brush heads use a microchip to sync with your handle, enabling brush head replacement reminder. For more information regarding the brush head replacement reminder, see 'Features'. This symbol indicates the brush head is equipped with BrushSync technology. (Fig. 2)

Brushing modes

Your power toothbrush is equipped with clean mode.

Clean mode

Clean is a 2–minute mode. It gives you a thorough and complete clean and is recommended to be used with the C2 Optimal Plaque Control brush head.

Intensities

Your power toothbrush gives you the option to choose between low and high intensity.
Note: When you use the toothbrush for the first time, the default setting is the low intensity.

–Press the power button once to turn on the toothbrush.
–Press a second time **within 2 seconds** to change the intensity.
–Press a third time **within 2 seconds** to pause.
After 2 seconds of brushing, pressing the power button again will also pause the toothbrush.

Using your Philips Sonicare

Brushing instructions

1 Press the brush head onto the handle in such a way that the bristles will face the front of the handle. (Fig. 3)
2 Firmly press the brush head down onto the metal shaft until it stops.
Note: it is normal to see a slight gap between the brush head and the handle.
3 Wet the bristles. (Fig. 4)
4 Apply a small amount of toothpaste on the bristles. (Fig. 5)
5 Place the toothbrush bristles against the teeth at a slight angle (45 degrees), pressing firmly to make the bristles reach the gumline or slightly beneath the gumline. (Fig. 6) A change in vibration (and a slight change in sound) alerts you when you apply too much pressure while brushing.
Note; Keep the center of the brush in contact with the teeth at all times.
6 Press the power on/off button to turn on the Philips Sonicare. (Fig. 7)
7 Gently keep the bristles placed on the teeth and in the gumline. Brush your teeth with small back and forth motion so the bristles reach between the teeth. (Fig. 8)
Note: The bristles should slightly flare. Do not scrub.
8 To clean the inside surfaces of the front teeth, tilt the brush handle semi–upright and make several vertical overlapping brushing strokes on each tooth. (Fig. 9)
9 To make sure you brush evenly throughout the mouth, divide the mouth into 4 sections using the Quadpacer feature. (Fig. 10) The quadpacer feature beeps after 30 seconds.
10 Brush for the full 2 minutes following the Quadpacer. (Fig. 11) After 2 minutes, the toothbrush will automatically shut off.
–After you have completed the brushing cycle, you can spend additional time brushing the chewing surfaces of your teeth and areas where staining occurs. (Fig. 12)
Your Phihips Sonicare toothbrush is safe to use on;
–Braces (brush heads wear out sooner when used on braces)
–Dental restorations (fillings, crowns, veneers)
Note; When the Philips Sonicare toothbrush is used in clinical studies, it must be used in the Clean mode (for plaque and gum health claims) with EasyStart turned off.

Features

–EasyStart
–Brush head replacement reminder
–Pressure sensor
–Quadpacer

EasyStart

This Philips Sonicare model comes with the EasyStart feature deactivated. The EasyStart feature gently increases the power over the first 14 brushings to help you get used to the brushing with the Philips Sonicare.

To activate EasyStart see 'Activating or deactivating features'.

Brush head replacement reminder

Your Philips Sonicare is equipped with BrushSync technology that tracks the wear of your brush head. (Fig. 13)
1 When attaching a new smart brush head for the first time the brush head replacement reminder light blinks green three times. This confirms you have a Philips brush head with BrushSync technology.
2 Over time, based on the pressure you apply and the amount of time used, the handle will track brush head wear in order to determine the optimal time to change your brush head. This feature gives you the guarantee for the best cleaning and care of your teeth.
3 When the brush head replacement reminder light lights up amber, you should replace your brush head.
To deactivate the brush head replacement reminder see 'Activating or deactivating features'.

Pressure sensor

Your Philips Sonicare is equipped with an advanced sensor that measures the pressure you apply while brushing. If you apply too much pressure, the toothbrush will provide immediate feedback to indicate that you need to reduce the pressure. This feedback is given by a change in vibration and therefore brushing sensation.
To deactivate the pressure sensor see 'Activating or deactivating features'.

Quadpacer

The Quadpacer is an interval timer that has a short beep and pause to remind you to brush the different sections of your mouth.
Depending on the brushing mode you have selected (see 'Brushing modes'), the Quadpacer beeps at different intervals during the brushing cycle.

Activating or deactivating features

You can activate or deactivate the following features of your toothbrush;
–EasyStart
–Brush head replacement reminder
–Pressure sensor
To activate or deactivate these features, follow the instructions below;

EasyStart

1 Put the handle on the plugged–in charger.
2 Press and hold the power on/off button while the handle remains on the charger.
3 Keep the power on/off button pressed until you hear a single short beep (after 2 seconds).
4 Release the power on/off button.
–Triple tone of how–med–high means the EasyStart feature has been activated. The brush head replacement light and battery light will also blink green 3 times in unison to confirm activation.
–Triple tone of high–med–how means the EasyStart feature has been deactivated. The brush head replacement light and battery light will also blink amber 3 times in unison to confirm deactivation.
Note: To achieve clinical efficacy, EasyStart needs to be deactivated.

Brush head replacement reminder

1 Put the handle on the plugged–in charger.
2 Press and hold the power on/off button while the handle remains on the charger.
3 Keep the power on/off button pressed until you hear a series of two short beeps (after 4–5 seconds).
4 Release the power on/off button.

–Triple tone of how–med–high means the Brush head replacement reminder feature has been activated. The brush head replacement light and battery light will also blink green 3 times in unison to confirm activation.
–Triple tone of high–med–how means the Brush head replacement reminder feature has been deactivated. The brush head replacement light and battery light will also blink amber 3 times in unison to confirm deactivation.

Pressure sensor

1 Put the handle on the plugged–in charger.
2 Press and hold the power on/off button while the handle remains on the charger.
3 Keep the power on/off button pressed until you hear a series of three short beeps (after 6–7 seconds).
4 Release the power on/off button.
–Triple tone of how–med–high means the pressure sensor feature has been activated. The brush head replacement light and battery light will also blink green 3 times in unison to confirm activation.
–Triple tone of high–med–how means the pressure sensor feature has been deactivated. The brush head replacement light and battery light will also blink amber 3 times in unison to confirm deactivation.
If you continue holding the power on/off button after the three short beeps, the activate/deactivate sequence repeats.

Battery status and charging

1 Put the pug of the charger in an electrical outlet.
2 Place the handle on the charger.
–The charger will emit 2 short beeps to confirm that the handle is placed properly.
–The flashing light of the battery level indicator shows that the toothbrush is charging.
–When handle is fully charged on the charger, the battery light shows solid green for 30 seconds and switches off.
Note: Your toothbrush comes pre–charged for first use. After first use, charge for at least 24 hours.

Battery status (when handle is not on charger)

When removing the Philips Sonicare from the charger, the battery light at the bottom of the toothbrush will indicate the status of the battery life.
–Solid green LED; full battery
–Flashing green LED; medium battery
–Flashing amber LED and three beeps; low battery
–Flashing amber LED and two sets of five beeps; No brushing sessions left (charge toothbrush).

Cleaning

Note: Do not clean the brush head, handle or travel case in the dishwasher.

Toothbrush handle

1 Remove the brush head and rinse the metal shaft area with warm water. Make sure you remove any residual toothpaste (Fig. 14).
Note: Do not push on the rubber seal on the metal shaft with sharp objects, as this may cause damage.
2 Wipe the entire surface of the handle with a damp cloth.
Note: Do not use isopropyl rubbing alcohol, vinegar or bleach to clean handle as this may cause discoloration.

Brush head

1 Rinse the brush head and bristles after each use (Fig. 15).
2 Remove the brush head from the handle and rinse the brush head connection with warm water at least once a week.

Charger

1 Unplug the charger before you clean it.
2 Wipe the surface of the charger with a damp cloth.

Storage

If you are not going to use your Philips Sonicare for an extended period of time, unplug the charger from the wall socket, clean it and store it in a cool and dry place away from direct sunlight.

Locating the model number

Look on the bottom of the Philips Sonicare toothbrush handle for the model number (HX681x).

Recycling

–This symbol means that this product shall not be disposed of with normal household waste (2012/19/EU) (Fig. 24).

–This symbol means that this product contains a built–in rechargeable battery which shall not be disposed of with normal household waste (Fig. 25) (2006/66/EC). Please take your product to an official collection point or a Philips service center to have a professional remove the rechargeable battery.

–Follow your country's rules for the separate collection of electrical and electronic products and rechargeable batteries. Correct disposal helps prevent negative consequences for the environment and human health.

Removing the rechargeable battery

Warning: Only remove the rechargeable battery when you discard the appliance. Make sure the battery is completely empty when you remove it.

To remove the rechargeable battery, you need a towel or cloth, a hammer and a flat–head (standard) screwdriver. Observe basic safety precautions when you follow the procedure outlined below. Be sure to protect your eyes, hands, fingers, and the surface on which you work.

1 To deplete the rechargeable battery of any charge, remove the handle from the charger, turn on the Philips Sonicare and let it run until it stops. Repeat this step until you can no longer turn on the Philips Sonicare.

2 Remove and discard the brush head. Cover the entire handle with a towel or cloth (Fig. 16).

3 Hold the top of the handle with one hand and strike the handle housing 0.5 inch above the bottom end. Strike firmly with a hammer on all 4 sides to eject the end cap (Fig. 17).

Caution: Be aware of the sharp edges of the battery tabs so as to avoid injury to your fingers.

4 Remove the end cap from the toothbrush handle. If the end cap does not release easily from the housing, repeat step 3 until the end cap is released (Fig. 18).

5 Holding the handle upside down, press the shaft down on a hard surface. If the internal components do not easily release from the housing, repeat step 3 until the internal components are released (Fig. 19).

6 Remove the rubber battery cover.

7 Wedge the screwdriver between the battery and the black frame at the bottom of the internal components. Then pry the screwdriver away from the battery to break the bottom of the black frame (Fig. 20).

8 Insert the screwdriver between the bottom of the battery and the black frame to break the metal tab connecting the battery to the green printed circuit board. This will release the bottom end of the battery from the frame (Fig. 21).

9 Grab the battery and pull it away from the internal components to break the second metal battery tab (Fig. 22).

Caution: Be aware of the sharp edges of the battery tabs so as to avoid injury to your fingers.

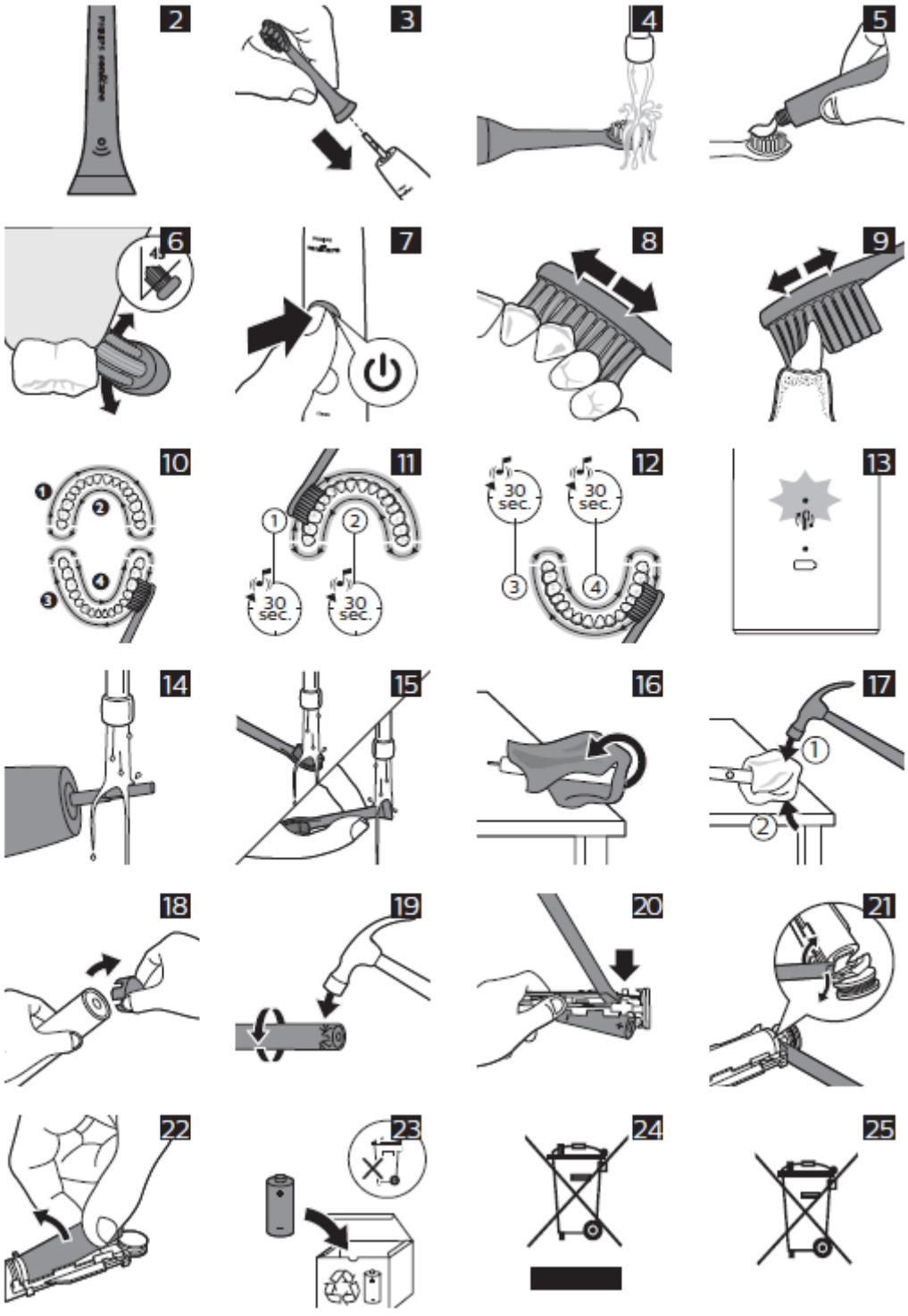
10 Cover the battery contacts with tape to prevent any electrical short from residual battery charge. The rechargeable battery can now be recycled and the rest of the product discarded appropriately (Fig. 23).

Warranty and support

If you need information or support, please visit
www.philips.com/support or read the international warranty leaflet.

Warranty restrictions

The terms of the international warranty do not cover the following;
– Brush heads.
– Damage caused by use of unauthorized replacement parts.
– Damage caused by misuse, abuse, neglect, alterations or unauthorized repair.
– Normal wear and tear, including chips, scratches, abrasions, discoloration or fading.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19.3 Appendix 3: Pierre Fabre Inava 20/100® Instructions for use

Inava 20/100® Pierre Fabre Oral Care France manual toothbrush
Manual toothbrush with bristles with rounded end (diameter: 20/100ème in Tynex®) and soft /ergonomic handle (ACL: 3401561130767).

The INAVA system consists of an INAVA 20 / 100th (ACL: 3401599691391) toothbrush mounted on a lightweight and ergonomic foam handle to facilitate grip of the brush. Indeed, for some people, brushing can become a real journey of the combatant, especially when the hands are painful or lose in dexterity; then simple manipulation can become difficult.

Instructions for use can be found in the following website:
https://fr-fr.pierrefabre-oralcare.com/inava/inava-souple-20100-brosse-dents