Date of Protocol Version: **Ver5.1; 20/Mar/2018**

Sponsor: Fidmi Medical Ltd.

Principal Investigator: Dr. Dov Wengrower,
Director, Therapeutic Endoscopy Unit. Digestive Diseases Institute
Shaare Zedek Medical Center, Jerusalem

FIDMI MEDICAL LTD.
5 HAESHEL STREET, CAESAREA,
P.O. 3079500
P.O. 3079815
ISRAEL
Webpage: www.Fidmimedical.com

REVISION HISTROY TABLE

REVISION NUMBER	REASON FOR CHANGE	DOCUMENT AUTHOR	RELEASE DATE
1	Initial release.	Tal Lavi, GSAP medical Ltd.	19/Dec/2016
2	a) Better Specifying patients indication for Inclusion: "oropharyngeal dysphagia impairing or anticipated to impair the patients' nutritional status" b) specifying "visit in patient facility" to be performed by sub-investigator c) GERD abbreviation typo + adding IFU to the abbreviation d) Adding version control to the PI signature page e) 'V7' instead of 'V5' typo in the Schematic of study design f) Changing Early withdraw criteria 9.2.3.6 to "Inability to complete Fidmi device gastrostomy placement" g) Adding Packaging, Labeling and Storage (5.4) h) Visit 1 can be performed up until 2 weeks before insertion procedure i) Elaborating Intended Use (5.3) to subjects with functioning digestive system j) Adding to the procedural tasks that the patient would be instructed by the staff with the home Instructions to Use (10.1.1) k) Un-merging the PEG Insertion/Removal Form into two separated forms(10.1.1) l) Update of 'Visits Procedure Chart' per current protocol (X-ray imaging) m) Adding "Apotropos signed authorization documents (when applicable)" to the required Source Documents list (13.5.2) n) Adding further elaborations on "screen failure subjects" (9.3.1)	Tal Lavi, GSAP medical Ltd.	14/Feb/2017
3	a) Adding elaboration in case a Gastrostom replacement (10.1.2, Visit 6) b) Adding to follow-up visits 6 &7 (10.1.2) that: *An endoscopic examination is not required but may be performed on a need base, and following the investigator discretion.	Tal Lavi, GSAP medical Ltd.	23/Apr/2017
4	Changing inclusion age criteria from 80 to 90 years old to increase patient potential for the study	Keren Smulovitz, GSAP medical Ltd.	29/May/2017

REVISION NUMBER	REASON FOR CHANGE	DOCUMENT AUTHOR	RELEASE DATE
4.1	Adding Shaare Zedek Medical Center to the study (multi-site study)	Tal Lavi, PhD GSAP medical Ltd.	20/Nov/2017
5.1	Adding an option to Home abdominal X-ray evaluation at visit 7 – performed by Medix at Home, phone call follow up	Tal Lavi, PhD Gsap medical Ltd.	20/Mar/2018

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1. SIGNATURES

Sponsor Signature: _____ Date: _____

Principal Investigator Agreement:
I have carefully read and understood the provisions of this protocol – Version5.1 ___and I am prepared to follow them in every detail in the conduct of this study.

Principal Investigator Signature: _____ Date: _____

2. LIST OF ABBREVIATIONS

Abbreviation	Name
AE	Adverse Event
BMI	Body Mass Index
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
ER	Emergency Room
GERD	Gastroesophageal Reflux Disease
ICF	Informed Consent Form
IFU	Instructions For Use
INR	International Normalised Ratio
IRB	Institutional Review Board
GI	Gastrointestinal
MOH	Ministry of Health
NA	Not Available
PEG	Percutaneous Endoscopic Gastrostomy
PI	Principal Investigator

3. PROTOCOL SYNOPSIS

Protocol Number	FM-01
Protocol Title	Safety and Usability Evaluation of the Fidmi Low-Profile Enteral Feeding Device
Participating Countries	IL
Study Type	Interventional
Study Design	The Fidmi trial is an early First In Human feasibility Open Label single center study consists of Single Group Assignment, to evaluate the safety and preliminary efficacy of Fidmi Low-Profile Enteral Feeding Device as a treatment for adult patients with a need for enteral feeding (Percutaneous Endoscopic Gastrostomy placement).
Investigational Study Device	Fidmi Feeding Device, by Fidmi Medical Ltd.

Study Purpose	To evaluate the safety and effectiveness of the Fidmi PEG device: insertion, long term utilization, dismantling and removal
Study Population	15 adult patients, male or female suffering from dysphagia, who are scheduled for PEG (Newly PEG insertion (minimum 10 patients) and PEG replacement involving endoscopy procedure)
Study Procedures	15 Consecutive adult patients with need for enteral feeding Scheduled for PEG with protocol sedation. The patients will attend the following: Visit 1: Screening and Enrollment Visit 2: Insertion or replacement in the Endoscopy suite, Visit 3: Follow up after 2 days (sub-investigator visit in patient facility) Visit 4: Follow up after 1 month (sub-investigator visit in patient facility) Visit 5: Follow up after 2 month (phone call) Visit 6: Follow up after 3 months and Fidmi device removal Visit 7: Follow up after 4 months, X-ray and termination
Study Endpoints	**Safety Endpoints:** 1. Number of Participants With Treatment-Related Adverse Events as Assessed by CTCAE v4.0 through study completion. 2. Number of participants requiring unscheduled hospital readmission related to Fidmi Feeding device through study completion. **Performance Endpoints:** <u>Primary</u>: **3.** Number of accidental dislodgements during study follow up until device removal at 3 months. **4.** Number of unscheduled internal tube replacements (only clogged tubes) until device removal at 3 months. **5.** Patient Pain on the Visual Analog Scale during device removal at 3 months. **6.** Number of uneventful (flawless) insertions and removals of Fidmi PEG device during device placement (Day 0) and device removal (3 month). <u>Secondary</u>: 7. Device placement procedure time length at Day 0 (from endoscope intubation to end of procedure).

	8. Ease of the device placement procedure (Scored by the investigator performing the procedure using the 10-point Visual analogue scale satisfaction) at Day 0. 9. Ease of the device removal procedure (Scored by the investigator performing the procedure using the 10-point Visual analogue scale satisfaction) at 3 months. 10. Ease of the internal tube replacement (Scored by the patient/caregiver) using the 10-point Visual analogue scale satisfaction) until device removal at 3 month. 11. Validate (True/False) correct (color) selection of *'Measuring Cannula'* at Day 0 by residual tube measurement [design endpoint]
Study Methods of Appraisal	<u>Safety assessment</u> Safety assessment will be based upon monitoring the Adverse events, which will be collected throughout the trial (placement, chronic utilization, removal procedure and post removal follow up) Adverse events encountered will be reported as categorized below in accordance with reviewing Ethics Committee and Competent authority requirements. <u>Complication</u> **Placement complication**: excessive stoma wound bleeding, over tightened external bumper, gastric and/or esophageal laceration, device unintended disassembly, need for more than one needle puncture **Short-term complications (post placement)** [Time Frame: 1week] [Designated as safety issue: Yes] Stomal complication (wound infection, peristomal leakage, hypergranulation, pressure ulcer, any skin lesion adjacent to external bumper). Tube complication (accidental dislodgement, tube leakage, buried bumper, gastric outlet obstruction, dumping syndrome). **Long-term complications** [Time Frame: 3 month] [Designated as safety issue: Yes]

Stomal complication (wound infection, peristomal leakage, hypergranulation, pressure ulcer, any skin lesion adjacent to external bumper).
Tube complication (accidental dislodgement, tube leakage, buried bumper, gastric outlet obstruction, dumping syndrome).

Post removal complication
Bowel obstruction, Bowel peroration, GI bleeding, painful defecation

USIBILITY STUDY MEASURES

Placement

1. Procedure time length (from endoscope intubation to end of procedure).
2. Difficulty of the procedure in general compared to routine procedure [Time Frame: Intra-procedural] Scored by the endoscopist on a 10-point Visual Analogue Scale).
3. Endoscopic measurement – clear, simple and decisiveness of color scale evaluation, accurate length estimation.
4. Need for additional needle puncture (sheath kink, loss of visualization).
5. Ease of device insertion through the esophagus [questioner].
6. Ease of tube exteriorization through abdominal wall [questioner].
7. Placement location in the gastric body (low (pre pyloric) mid, high).
8. External bumper connection - Tactile feedback, confidence in secured connection [questioner].
9. Measurement and evaluation of the Residual Tube at the end of the procedure – ensure residual is not "over protruding".

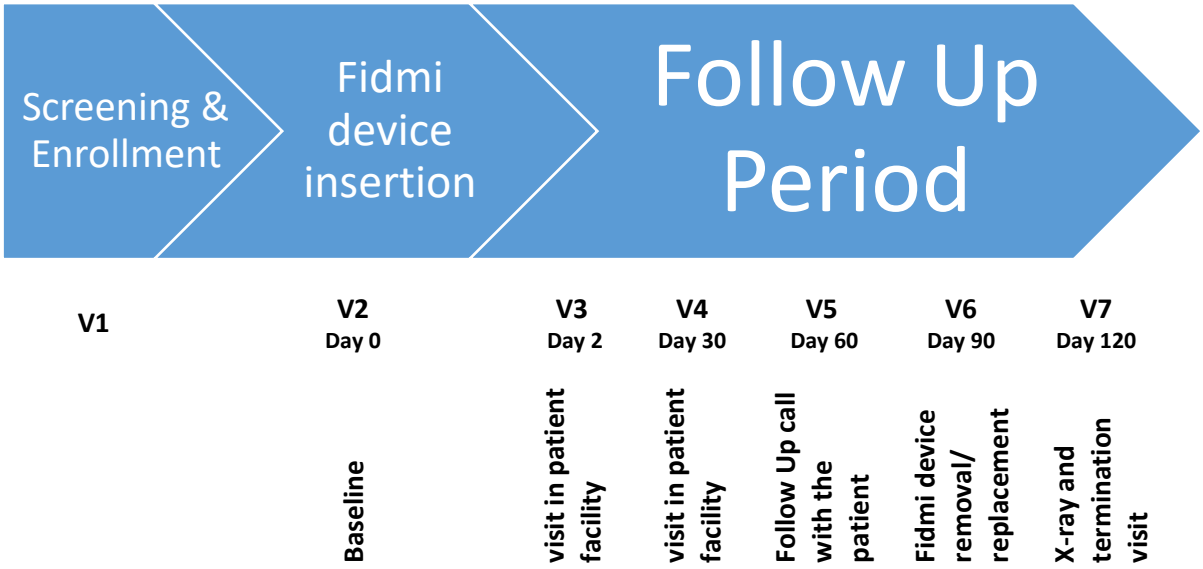
Post placement utilization. [Time Frame: 3 months]

10. Patency of disposable tube (partial or clogged tubes).
11. Disposable tube performance (ease of replacement, jammed tube, leakage).
12. Patency of the affixed main tube which is defined as time period between device placement and need for re-intervention (e.g. - flushing).
13. Measurement and evaluation of the Residual Tube at follow up visits – ensure residual is not "over protruding".
14. Patient discomfort during long term use (Granulation tissue at the insertion site, limitation, esthetic etc.)

	Removal 15. Dismantling - tactile feedback (Obvious, vague scale). 16. Force needed for bumper-less shaft extraction compared to standard skin level removal of collapsible bumper graded: similar harder, lighter, much lighter, negligible (comparable to endoscope withdraw from esophagus. 17. Patient discomfort during the procedure. **Bumper flanges expulsion** 18. Sensation in communicating patients.
Inclusion/ Exclusion Criteria	**Inclusion Criteria:** 1. Male or female patient 18 up to 90 years. 2. Consecutive adult patients suffering from oropharyngeal dysphagia impairing or anticipated to impair the patients' nutritional status with need for enteral feeding (PEG). 3. Ability to give informed consent for the study by patient or legal guardian. 4. Willingness to undergo 4 follow up visits 1, 3 and 4 months following PEG insertion/replacement, as well as unscheduled sick visits. **Exclusion Criteria:** 1. Pregnancy (all women of child-bearing age would be questioned and told by the consenting physician regarding that criteria). 2. All current practice PEG contraindication 3. Acute gastrointestinal bleeding 4. Extreme obesity patients (BMI>40) 5. Emergency endoscopy 6. Infectious disease local or systemic (e.g.- sepsis, pancreatitis) 7. Known esophageal pathology (e.g.- stenosis, eosinophilic esophagitis, varices, achalasia, reflux) 8. In case of PEG replacement: lack of a well healed gastrostomy or Infection around the insertion site. 9. Known gastric pathology that may prevent safe device insertion, feeding, removal and Bumper flanges expulsion according to the investigator discretion. 10. Any history of bowel obstruction, pseudo-obstruction. 11. Crohn's disease

	12. Severe GERD, recurrent vomiting 13. Inability to tolerate sedated upper endoscopy due to cardio-pulmonary instability or other contraindication to endoscopy 14. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study.
Study Duration	Per Patient: between 120 days±14 days, depending on the interval between pre-operative visit (inclusion) and day of operation. Total 8 months to recruit and treat 15 patients.
Statistical Analysis Plan	NA. Feasibility safety study. Descriptive statistics will be provided.

4. SCHEMATIC OF STUDY DESIGN



5. INTRODUCTION – BACKGROUNG AND DEVICE DESCRIPTION

5.1 BACKGROUND & GENERAL DESCRIPTION

Over 17.6 million stroke, Parkinson's, cancer and multiple sclerosis patients have poor control over their swallowing muscles and are unable to safely consume enough food. This swallowing disorder is called dysphagia. If untreated dysphagia can lead to aspiration pneumonia - food leakage into the lungs, which can even cause death. In addition, patients may require a long-term (for years) solution for feeding to deliver nutrition, liquids and medications directly into the stomach.

The type of feeding tube and its placement depends on various factors, including the patient's clinical condition and the length of time enteral feeding is needed (1). There are two categories of enteral feeding tubes: nasoenteric and enterostomy tubes. Nasoenteric tubes are placed either nasally or orally, typically in patients requiring short-term nutritional support, usually for less than 30 days. Enterostomy tubes are placed into the stomach or small bowel through an incision in patients requiring nutritional support over an extended period of time, usually greater than 30 days. The enterostomy feeding tubes can be divided into two

main groups: Gastrostomy tubes, placed into the patient's stomach; and Jejunal feeding tubes, placed into the duodenum or proximal jejunum using a variety of techniques.

Currently, the most common enteral Gastrostomy feeding is obtained through Percutaneous Endoscopic Gastrostomy (PEG) tubes. The initial placement is performed with the help of an endoscope that ensures correct positioning in the stomach. The PEG tube passes through the skin of the abdomen in an opening called stoma, and it is held in place by a semi-rigid bumper. PEG tubes are increasingly used for enteral feeding procedures, although they are troubled by several shortcomings:

Problem #1: Frequent dislodgement. During their total lifetime, 12.8% cases (2) of PEG tubes with soft inner bumper undergo accidental dislodgement, as patients may pull out the tube or the long tubing is displaced during patient transfers, physical therapy or by catching on sheets or bed railings. If a PEG tube is dislodged prior to the tract maturation, specifically within the first 30 days after initial placement, then an emergency intervention is required to recover the stoma. Complications within the procedure are likely to affect the stomach that can separate from the abdominal wall with the open gastrostomy leaking gastric contents into the peritoneal cavity. Delayed dislodgements have to be treated with the PEG tube being reinserted urgently (within the next 12 hours) to prevent the abdominal stoma from closing. The procedure must be undertaken in the hospital, adding workload to the patients and the healthcare system. PEG pull-outs require an emergency department visit, a level 3 surgical procedure, a replacement gastrostomy tube, and a radiographic confirmation of tube positioning. (2).

Problem #2: Difficult replacement. Physicians recommend changing standard PEG tubes after an average period of 6 months. The replacement is performed in a hospital room by pulling out the tube. It is a very painful and unpleasant procedure. Internal bumpers are not very soft to avoid issues with dislodgement and therefore the "pull" technique" is harmful and risky for patients. In 7.6% of cases, there are major complications such as gastrointestinal (GI) tract perforation (3) which can lead to peritonitis, infection, GI bleeding. Minor complications such as stoma leaking and bleeding, and skin dermatitis arise in 24% of replacement cases (4).

Problem #3: Tube clogging. Obstruction is a common complication of enteral tube feeding. PEG tubes become clogged during their lifetime in approximately 45% cases (5) due to difficulties in cleaning and flushing the inner cavity properly. Tube clogging happens slowly, and progressively increases the duration of the feeding from 10 minute up to 1 hour. In addition, this has unpleasant and frustrating consequences for the patient and the caregiver, and compromises nutrient delivery.

Currently there are many solutions in the market for long-term enteral feeding, however none of them provide comfort and autonomy to their users, since they have a high probability of dislodgement, clogging, leakage and are bulky:

i. **Standard PEG tubes** suffer from the paradox requirement of the inner bumper that should be both rigid to hold the device in place and soft to enable an easy removal by traction, avoiding injury to the patient. As a result, to avoid the risk of internal injury, traditional PEG tubes are subject to dislodgment. Moreover, these are long tubes that easily clog and are uncomfortable for the patient as they may be pulled out during transfers, physical activities, or caught on sheets and bed railings. Physicians recommend replacing PEG tubes after 6 months to prevent complications.

ii. **Standard Gastronomy tube (replacement): tubes with balloon bumpers are subject to dislodgement**, as they can deflate, rupture, burst or leak. This implies an emergency intervention since the device should be replaced within 6-12 hours to prevent the stoma from closing and avoid a repeat PEG procedure. The lifespan is only 3 months, and the replacement procedure needs to be performed in hospitals.

iii. **Replacement devices**, that are either gastrostomy tubes or low-profile devices, can be inserted only after PEG tract is matured (3 months after initial placement). The time of use is up to 3 months, and the replacement procedure needs to be performed in hospitals. The tube is retained by an internal bumper consisting either of an inflatable balloon or of a non-balloon collapsible bumper. Retention balloons allow easy tube removal and eliminate the risk of tract perforations from rigid bumpers.

Non-balloon bumpers are more difficult to insert and remove and may easily dislodge due to collapsible, small, dome-shaped bumper.

Table 1– Comparison of existing technologies

Properties	PEG	Standard Gastronomy tube	Replacement Device/tube	GFeed (all in one)
Initial placement	+	−	−	+
Replacements	−	−	−	+
Prevents dislodgment	−	−	−	+
No ruptures during insertion/extraction	−	−	+−	+
Painless Replacement & Removal	−	−	+	+
No endoscopy or other confirmation	−	−	+−	+
Secures tract during replacement	−	−	−	+
No Complications	−	−	−	+
Avoid clogging	−	−	−	+
Patient comfort	−	−	+	+
Lifetime	6 months	3 months	3 months	2 years

A major drawback of the current marketed solutions is the short time of use, 13% of the tubes are dislodged unexpectedly (6). Other replacements occur due to defective valves, shafts and ruptured balloons or bumpers. Consequently, the annual price of the device is significantly increased, and secondly patients can suffer from some serious complications: mucosal or tissue injury. Estimates of the incidence of clogged feeding tubes range widely, from 12.5-45% over the life of the existing tubes (7).

5.2 DEVICE DESCRIPTION

Fidmi device is an enhanced enteral feeding device that stays securely in place and maintains tube patency during treatment. Fidmi presents a discrete feeding device for patients suffering from dysphagia. Fidmi Device is the first presented "low-profile device from day 1", easily hidden under clothing and not limiting mobility. Unlike other solutions, Fidmi device is resistant to dislodgement due to a semi-rigid internal bumper, and avoids clogging thanks to a disposable insert to deliver the nutrition. Video: http://www.Fidmimedical.com/peg-device-for-initial-placement

Fidmi device consists of **1)** a rigid-core silicone bumper that prevents dislodgment, **2)** a disposable internal tube replacement for a daily nutrition supply and prolonged patency, and **3)** an external flexible bolster that keeps the stoma site ventilated and stable. The disposable insert is placed inside the feeding port and is replaced every 1-2 weeks to avoid clogging,

extend the product life, and improve the cleanliness and hygiene of the tube. Disposable tube replacement is easy and safe and can be done by the patients themselves or their caregivers as the tract is never compromised and there is no need for a physician verification. The device is eventually removed in a simple procedure that can be done by the caregiver or patient himself. Fidmi device a tool dismantles the internal bumper into small parts that are naturally expelled from the body for trauma free-removal (Figure 1 right panel).

Figure 1 - Fidmi device

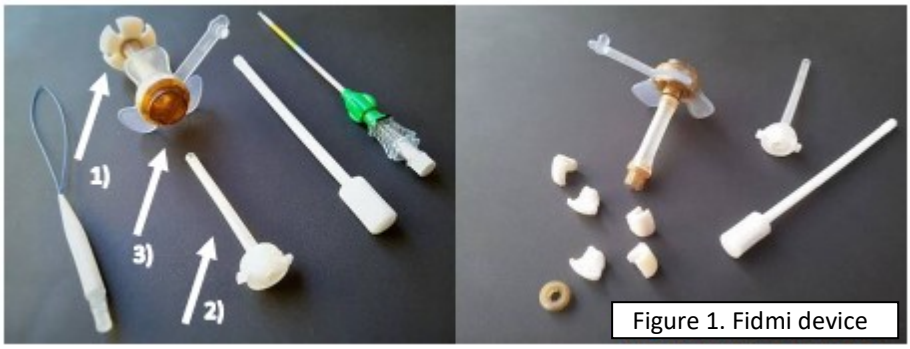


Figure 1. Fidmi device

Product: Fidmi Medical boasts a comprehensive solution for initial placement, replacement, and complete removal of PEG tubes. Fidmi device is a low-profile cosmetic design internal feeding device that simplifies the tube insertion, maintenance and improves the patient mobility. It is discrete, so can be easily hidden under clothing. Fidmi device specifications are provided in Table 2.

Table 2 – Specification

Specifications	
Class	Class IIb
Low profile tube	Yes
French Size	20
Feeding tube length	2.2- 6CM
Balloon capacity	N/A
Materials	Silicon/ Polyurethane
Color	Length is color indicated
Accessories	Long disposable tube, gastric-J disposable tube, stomach decompression disposable tube

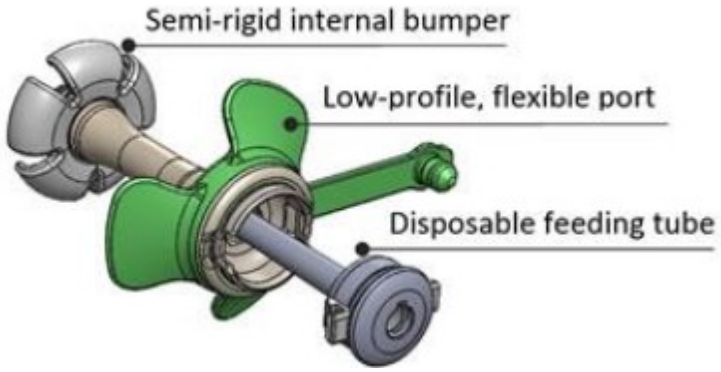
The device consists of three main parts (Figure 2):

i. The internal bumper is rigid enough to prevent dislodgment during the normal use and stay in place from the initial insertion.

ii. The disposable feeding tube is used to supply nutrition to the patient. It's recommended to be replaced each 2 weeks by the patient or caregiver without removing the feeding device.

iii. An external flexible port is attached to the tube, allowing easy access for daily care. The device itself does not require replacement and therefore the abdominal tract and the stoma opening are never stressed or compromised. The feeding port has a comfortable and ventilated design that protects the stoma and holds the disposable feeding insert in place.

Figure 2 – Fidmi device model



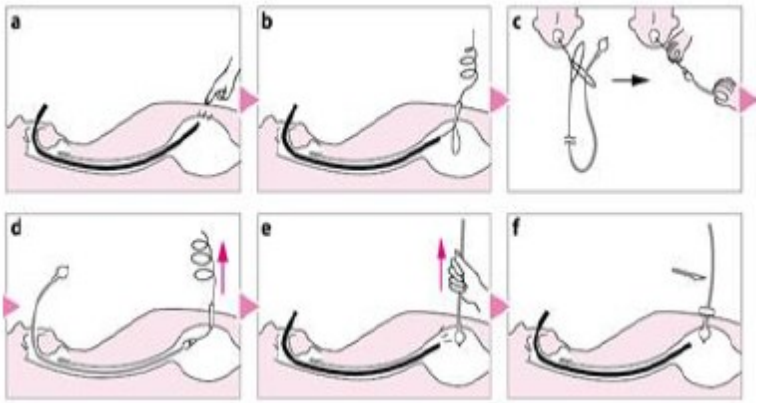
5.3 INTENDED USE AND INDICATIONS FOR USE

Fidmi device is intended to provide nutrition to a patient directly into the stomach through a stoma. The Fidmi PEG device would be investigated in this study on patients suffering from oropharyngeal dysphagia impairing or anticipated to impair the patients' nutritional status, who are scheduled for PEG procedure in order to improve surgical initial insertion, device replacement and removal. Enteral feeding is used in patients who have functioning digestive systems, but are unable to orally ingest adequate nutrients or to meet their metabolic needs.

Fidmi provides the first PEG device with a discrete enteral feeding solution **from Day-1** that overcomes most of the currently suffered shortcomings. Fidmi device can ensure less complications, less follow-up visits, 5 minute replacement, 2 year lifetime.

The device is inserted in a standard PEG procedure and the whole insertion takes up to 45 minutes: a physician places the feeding tube into a patient mouth (a) using the Fidmi device kit – a retrieval snare (Figure 3). The feeding tube is inserted through an incision in the abdomen (d). The internal bumper stops the tube from falling out (e). It rests in the stomach and exits through the skin. The external bolster is then connected allowing an external fixation and stability (f). These features eliminate the need of repeatable replacement of the PEG, reduce clogs and allow medications or nutrition to flow freely. The replacement takes an approximate time of 5 minutes. The unique design stabilizes the device and keep it clean and ventilated. When enteral feeding is no longer required, the device is easily removed: the patient or caregiver pushes the internal bumper using Fidmi device kit, then the internal bumper breaks into 5 pieces that fall into the stomach and naturally expel from the body. The feeding tube and port are easily and safely pulled out allowing the tract to close.

Figure 3– Fidmi device insertion



Additional preclinical results are detailed in the Investigator brochure.

5.4 Packaging, Labeling and Storage

5.4.1 Packaging and Labeling

Packaging and labeling of Fidmi Feeding device (study Investigational Medicinal Product) will be performed in compliance with relevant regulatory requirements of GMP guidelines.

Further details are elaborated in the Investigational Brochure.

In order to be delivered ready for use each 'Patient Pack' are assembled with:

- 1X Measurement pack (Fidmi Medical Stoma Measuring Device), packed in a heat sealable EtO compatible sterilization pouch
- 1X Placement and Feeding pack (Fidmi Medical Enteral Feeding Device), sealed in a rigid tray PET-G blister pack with a Tyvek® lid (heat pressed)
- 5X Disposable Tube Pack (Replaceable Tube Pack), sealed within a rigid tray blister pack with a Tyvek® lid
- 10X Extension tubes.

Packs are plug-sealed and packed in adhesive-sealable wrap packaging pouches/blister pack. These are sealed and labeled with the patient details and expiry time. Device packs are transferred to the site for the clinical usage according to the study protocol.

Illustration samples of Device Package Labels:

Fidmi Medical Stoma Measuring Device,
Version: _____ UDI : CT…_____
Sponsor: Fidmi Medical Ltd., 17 Tchelet St. Misgav, Israel
For clinical trial use only
Instruction for Use and Warnings are enclosed inside the kit
0297-17-SZMC Shaare Zedek Medical Center, Dr. Dov Wengrower.
Trial subject ID _____
Storage conditions: Temperature: - 30º C – (+60º C), Humidity: ≤ 90%, Do not store device in direct sunlight
Keep out of reach of children

Fidmi Medical Enteral Feeding Device,
Version: _____ UDI : CT…_____
Sponsor: Fidmi Medical Ltd., 17 Tchelet St. Misgav, Israel
For clinical trial use only
Instruction for Use and Warnings are enclosed inside the kit
0297-17-SZMC Shaare Zedek Medical Center, Dr. Dov Wengrower.
Trial subject ID _____
Storage conditions: Temperature: - 30º C – (+60º C), Humidity: ≤ 90%, Do not store device in direct sunlight
Keep out of reach of children

Replaceable Tube Pack,
Version: _____ UDI : CT…_____
Sponsor: Fidmi Medical Ltd., 17 Tchelet St. Misgav, Israel
For clinical trial use only
Instruction for Use and Warnings are enclosed inside the kit
0297-17-SZMC Shaare Zedek Medical Center, Dr. Dov Wengrower.
Trial subject ID _____
Storage conditions: Temperature: - 30º C – (+60º C), Humidity: ≤ 90%, Do not store device in direct sunlight
Keep out of reach of children

פידמי מכשיר מדידת הסטומה
גרסה:_____מספר מזהה_____
היזם: פידמי מדיקל בע"מ, רחוב תבלת 17, משגב, ישראל
לשימוש בניסוי רפואי בלבד
הוראות שימוש ואזהרות למשתמש מצורפים בערכה 0297-17-SZMC . ,
מרכז רפואי שערי צדק, ד"ר דב ונגרובר
מספר נבדק _____

תנאי אכסון: טמפ' (+60º C) – 30º C - לחות <90%, אין להניח תחת שמש ישירה להרחיק מהישג ידם של ילדים

פידמי מבשיר הזנה תוך בטנית גרסה:_____מספר מזהה_____ היזם: פידמי מדיקל בע"מ, רחוב תכלת 17, משגב, ישראל לשימוש בניסוי רפואי בלבד הוראות שימוש ואזהרות למשתמש מצורפים בערכה SZMC-0297-17. , מרכז רפואי שערי צדק, ד"ר דב ונגרובר מספר נבדק _____ תנאי אכסון: טמפ' (+60º C) – 30º C - לחות <90%, אין להניח תחת שמש ישירה להרחיק מהישג ידם של ילדים

ערכת צינוריות החלפה גרסה:_____מספר מזהה_____ היזם: פידמי מדיקל בע"מ, רחוב תכלת 17, משגב, ישראל לשימוש בניסוי רפואי בלבד הוראות שימוש ואזהרות למשתמש מצורפים בערכה SZMC-0297-17. , מרכז רפואי שערי צדק, ד"ר דב ונגרובר מספר נבדק _____ תנאי אכסון: טמפ' (+60º C) – 30º C - לחות <90%, אין להניח תחת שמש ישירה להרחיק מהישג ידם של ילדים

5.4.2 Transport and Storage

- Temperature: - 30º C – (+60º C), Humidity: ≤ 90%
- Do not store Fidmi Feeding device and Replacement Tubes in direct sunlight
- Place the Disposable Tubes in their box or in a safe, dry, cool place.

6 Potential Risks and Benefits

6.1 Known Potential Risks

Complications from PEG tube placement can be classified as major or minor (8):

Minor complications include:

i. Wound infection,
ii. Peristomal leakage,
iii. Wound leakage,
iv. Wound bleeding,
v. Hemorrhage bleeding
vi. Cutaneous or gastric ulceration,
vii. Pneumoperitoneum,
viii. Temporary ileus,
ix. Aspiration
x. Gastric outlet obstruction.
xi. Clogging
xii. Tube dysfunction

Major complications include:

i. Necrotizing fasciitis,
ii. Esophageal perforation,
iii. Gastric perforation,
iv. Colocutaneous fistula,
v. Buried bumper syndrome,
vi. Inadvertent PEG removal.
vii. Small bowel obstruction
viii. Hepatic injury

6.2 Known Potential Benefits

Fidmi Device will provide simple initial insertion, home replacement and removal procedures and would contribute to improved life quality of the patient.

Fidmi Device is the first presented "low-profile device from day 1", easily hidden under clothing and not limiting mobility.

Fidmi Device overcomes most of the currently suffered shortcomings. Fidmi device can ensure less complications, less follow-up visits, 5 minute replacement, 2 year lifetime.

7 TRIAL OBJECTIVE AND HYPOTHESIS

7.1 STUDY OBJECTIVES

To evaluate the safety and effectiveness of the: insertion, long term utilization, dismantling and removal, as a treatment for adult patients with a need for enteral feeding (Percutaneous Endoscopic Gastrostomy).

7.2 HYPOTHESIS

Insertion of Fidmi PEG device will reduce complication rate, reduce tedious patient follow up visits at the hospitals and significantly shorten the time of replacement from currently 45 minutes (in average) to 5 minutes. Above all, Fidmi device lifetime will offer 2 years' time instead of the current 3-6 months.

7.3 STUDY PARTICIPATION DURATION

Overall, under the study protocol, each patient enrolled into the study will undergo a total of 7 visits including 4 follow-up visits during study duration of 120 days±14 days.

7.4 STUDY DURATION

15 patients will be enrolled to the study. We expect enrollment to occur over a 8-month period and the data analysis period of time will be 1 month time.

8 TRIAL DESIGN

8.1 STUDY DESIGN

The Fidmi trial is an early feasibility Open Label single center study consists of Single Group Assignment, to evaluate the safety and preliminary efficacy of Fidmi Low-Profile Enteral Feeding Device as a treatment for adult patients with a need for enteral feeding (Percutaneous Endoscopic Gastrostomy placement).

8.2 STUDY ENDPOINTS

Safety Endpoints:

1. Evaluate incidence of adverse events according to National Cancer Institute (NCI) Terminology Criteria for AE v4.0 common terminology criteria for AE. (CTCAE) during insertion, patient utilization or removal of Fidmi PEG device.
2. Concomitant medications
3. Physical examination (of insertion site).
4. Unscheduled hospital readmission.

Performance Endpoints:

Primary:

5. To evaluate accidental dislodgement during study follow up.
6. To evaluate unscheduled replacement rate (only clogged tubes).
7. To evaluate patient pain during removal.
8. To evaluate of uneventful (flawless) insertion and removal of Fidmi PEG device.
9. The ability to provide prescribed (and not partial) enteral feeding throughout the study period.

Secondary:

10. To evaluate usability by Physician filling a user questionnaire.
11. To evaluate usability by the patient or caregiver during long term use filling a user questionnaire.

12. To be able to validate correct (color) selection of *'Measuring Cannula'* by residual tube measurement [design endpoint]

8.3 USIBILITY STUDY MEASURES

Placement

1. Procedure time length (from endoscope intubation to end of procedure).
2. Difficulty of the procedure in general compared to routine procedure [Time Frame: Intra-procedural] Scored by the endoscopist on a 10-point Visual Analogue Scale).
3. Endoscopic measurement – clear, simple and decisiveness of color scale evaluation, accurate length estimation.
4. Need for additional needle puncture (sheath kink, loss of visualization).
5. Ease of device insertion through the esophagus [questioner].
6. Ease of tube exteriorization through abdominal wall [questioner].
7. Placement location in the gastric body (low (pre pyloric) mid, high).
8. External bumper connection - Tactile feedback, confidence in secured connection [questioner].
9. Measurement and evaluation of the Residual Tube at the end of the procedure – ensure residual is not "over protruding".

Post placement utilization. [Time Frame: 3 months]

10. Patency of disposable tube (partial or clogged tubes).
11. Disposable tube performance (ease of replacement, jammed tube, leakage).
12. Patency of the affixed main tube which is defined as time period between device placement and need for re-intervention (e.g. - flushing).
13. Measurement and evaluation of the Residual Tube at follow up visits – ensure residual is not "over protruding".
14. Patient discomfort during long term use (Granulation tissue at the insertion site, limitation, esthetic etc.)

Removal

15. Dismantling - tactile feedback (Obvious, vague scale).
16. Force needed for bumper-less shaft extraction compared to standard skin level removal of collapsible bumper graded: similar harder, lighter, much lighter, negligible (comparable to endoscope withdraw from esophagus.
17. Patient discomfort during the procedure.

Bumper flanges expulsion

18. Sensation in communicating patients.

19. Complete expulsion fluoroscopically proven by abdominal X-Ray imaging (in case particle/s from the bumper can be seen in the imaging a further follow visit will be scheduled only in case of symptoms related event/s, as per physician discretion)

8.4 SAMPLE SIZE JUSTIFICATION

15 adult patients, males or females, scheduled for PEG (Newly PEG insertion and PEG replacement involving endoscopy procedure). There will be minimum of 10 Newly PEG inserted patients enrolled to the study from the overall sample size.

Due to the small sample size and study early stage, no formal sample size calculation was done for this study.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 STUDY POPULATION AND JUSTIFICATION

Adult patients, males or females suffering from dysphagia who are scheduled for PEG (Newly PEG insertion and PEG replacement involving endoscopy procedure) with protocol local anesthetic. There will be minimum of 10 Newly PEG inserted patients enrolled to the study from the overall sample size.

The enrollment of patients to be studied in the clinical trial will respect a gender criterion in order to involve a similar number of male and female patients in the study and highlight any specific differences observed that might refer to biological characteristics and social/cultural factors.

9.2 ELIGIBILITY CRITERIA

9.2.1 Inclusion Criteria

1. Male or female patient 18 up to 90 years.
2. Consecutive adult patients suffering from oropharyngeal dysphagia impairing or anticipated to impair the patients' nutritional status with need for enteral feeding (PEG).
3. Ability to give informed consent for the study by patient or legal guardian.

4. Willingness to undergo 4 follow up visits 1, 3 and 4 months following PEG insertion/replacement, as well as unscheduled sick visits.

9.2.2 Exclusion Criteria

1. Pregnancy (all women of child-bearing age would be questioned and told by the consenting physician regarding that criteria).
2. All current practice PEG contraindication
3. Acute gastrointestinal bleeding
4. Extreme obesity patients (BMI>40)
5. Emergency endoscopy
6. Infectious disease local or systemic (e.g.- sepsis, pancreatitis)
7. Known esophageal pathology (e.g.- stenosis, eosinophilic esophagitis, varices, achalasia, reflux)
8. In case of PEG replacement: lack of a well healed gastrostomy or Infection around the insertion site.
9. Known gastric pathology that may prevent safe device insertion, feeding, removal and Bumper flanges expulsion according to the investigator discretion.
10. Any history of bowel obstruction, pseudo-obstruction.
11. Crohn's disease
12. Severe GERD, recurrent vomiting
13. Inability to tolerate sedated upper endoscopy due to cardio-pulmonary instability or other contraindication to endoscopy
14. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study.

9.2.3 Reasons for Withdrawal or Termination (Early Discontinuation):

Patients will be removed from study when any of the criteria listed below applies. The reason/s for study removal and the date in which the patient was removed will be documented in the Case Report Form (CRF):

9.2.3.1 Patients not complying with the protocol requirements.

9.2.3.2 AE resulting in discontinuation of the study.

9.2.3.3 Patient decides to withdraw from the study.

9.2.3.4 IRB request to discontinue the study.

9.2.3.5 Lack of adherence of stomach to abdominal wall.

9.2.3.6 Inability to complete Fidmi device gastrostomy placement

9.2.4 Handling of Participant Withdrawals or termination

The participation in the study, as in any clinical study, is voluntary and participants are allowed to withdraw from the study at any time.

Participants who leave the study prematurely will be replaced. A patient discontinuing the study before Fidmi PEG placement can be replaced, at the discretion of the investigator, by another consenting patient. The discontinuing patient will be followed for safety.

We anticipate from previous reports (9) that about 20% will not complete the 4 months study due to death and addition of 20% will withdraw from the study due the above listed reasons.

Each case of premature withdrawal will be properly recorded. As deemed necessary.

9.3 9.3 SUBJECT ENROLLMENT

9.3.1 SCREENING

The study will be conducted both in the Gastrology Institute at Shaare Zedek Medical Center, Jerusalem, Israel and in the Gastrology Institute at Hadassah Medical Center, Jerusalem, Israel. Prior to any study-related screening procedure, delegated study team members (investigators and nurses) will approach potentially eligible adults subjects suffering from oropharyngeal dysphagia impairing or anticipated to impair the patients' nutritional status, who are waiting to be scheduled for PEG insertion or replacement, involving endoscopy procedure. Those who may be eligible will be offered the choice of undergoing screening to potentially enroll in the study or receiving free treatment for their current illness without participating in the study. Subjects who do not meet inclusion criteria or who are for any other reason determined to be too ill for inclusion in the study, or who decline to participate in the study, will be considered and recorded as "screen failure" and receive standard and appropriate treatment.

9.3.2 CONSENTING

Consenting will be performed at the Gastrology Institute at Shaare Zedek Medical Center. In case of 'special population consenting' (demented patients) a designated consenting form (3A) as deemed by the Israeli MOH (HANOHAL) will be signed by the patient guardian and a copy of the signed Apotropos authorization documents would be collected and documented in the patient binder . Any use of study samples that is outside the scope of the objectives of this protocol will be submitted for prior review and approval by the appropriate IRBs. The informed consent document will be signed and dated for screening and enrollment and each subject consenting will be documented in the subject medical binder. The patient will be given a copy of the consent form together with the study doctor's letter at the time of enrollment. The clinician will ask the patient about his plans and his willingness to attend all scheduled and unscheduled follow-up visits.

9.4 SUBJECT IDENTIFICATION

Patients will be identified by a serial number and will be numbered according to the site number (first digit) and their recruitment (2nd and 3rd digits): e.g. 101, 203 etc.

9.5 SCREENING FAILURE

Patients who have not fulfilled all the inclusion criteria, or have fulfilled one of the exclusion criteria will not be included in this study. Patient who have screen failure will be replaced.

9.6 SUBJECT ACCOUNTABILITY

Once subject is screened and enrolled into the study the following study logs will be documented:

Enrollment Log - Indicates all eligible subjects who signed the informed consent and were enrolled to the study. This log includes for each subject his/her subject identification number and the dates of signing the informed consent and of enrollment.

Subject Consenting Log – documents all subjects enrolled and details their ICF consenting details: date, ICF version, consenting investigator, re-consenting if required etc.

Patient Identification Log - Correlates the name and details of every subject with the relevant subject identification number. This log should be kept only at the investigational site.

Subject Visit log – list all planned visits (1-7) for each enrolled subject. This log can be filled further on the study conduct.

10 TRIAL PROCEDURES

For study Schedule of Assessment, refer to

Table 3 **- Visit procedure chart.** No procedure or evaluation will be done prior to obtaining study consent.

After informed consent is obtained, a case record form (CRF) including all listed below will be recorded. Eligible patients will be enrolled into the study and be treated according to standard treatment protocols with PEG device insertion procedure with protocol local anesthetic.

10.1 STUDY SPECIFIC PROCEDURES

10.1.1 PATIENT ENROLLMENT TO DISCHARGE

Visit 1: Screening and Enrollment, as part of PEG pre-operative visit (can be performed up until 2 weeks before insertion procedure - visit 2)
Following signing of informed consent, patients scheduled and amenable for PEG insertion/replacement, will be screened for study enrollment by assessment of inclusion and exclusion criteria. The following assessments will be performed:

- Demographics (gender, age, race, ethnicity).
- Medical history (principal diagnosis requiring enteral nutrition, or hospitalization in the last 12 months).
- Vital signs
- Current medications.
- Physical examination.

Eligible patients will be enrolled into the study and be treated according to standard treatment protocols with PEG insertion/replacement.

The procedure for the PEG insertion/removal (Visit 2, see below) may be performed at the day of enrollment

Visit 2: Insertion/replacement of Fidmi device in the Endoscopy suite

If the procedure is taken on a different day than the inclusion day then the following assessments will be completed prior the procedure conducted:

a) Eligibility criteria

b) Physical examination
c) Vital signs

All patients will be operated by study delegated Gastroenterologist by the same method (see Investigator Brochure). Antibiotics will be administrated to patients on trial according to the investigator discretion.

The insertion procedure is performed by the investigator physician in a dimmed lighted room while the device is placed on a bedside tray under a protocol of local anesthetic.
Fidmi device method of insertion is detailed and illustrated in the Investigator Brochure.
An anonymous endoscopy recording of the procedure will be obtained for each patient.

Patients' charts will be reviewed and the following assessments will be completed following the procedure:

d) Illuminated clear photos of the insertion/replacement site taken:
    - Frontal to the insertion site/ external bumper
    - Perpendicular (from the profile) to the insertion site/ external bumper
    - In close perspective if outstanding issues (medical or technical) are observed
e) An anonymous endoscopy recording of the procedure
f) PEG Physician usability Form

Study PEG insertion Form:

insertion needed number of needle Re-puncture (sheath kink, loss of visualization), PEG insertion characteristics and duration, PEG placement location, Stoma Insertion/Removal site, Residual Tube above skin evaluation, heart rate at the end of the operation, time to resume typical enteric diet, amount and type of analgesia consumed, postoperative bleeding, use of anti-bleeding agents (such as tranexemic acid (hexakapron)).

Endoscopist feedback Form: Endoscopist 10-point Visual Analogue Scale for placement/removal procedure difficulty.

g) Study Patient Discharge form.

A study qualified personnel will instruct the patient before discharge with specific home instructions for use (IFU), maintenance, and instructions on how to periodically replace the Fidmi Disposable Feeding Tube when needed (see appendix in the IB). Together with the IFU leaflet the patient would be provided with his home Fidmi Disposable Feeding Tube pack. Instructions about the patient diet and medication should be given separately to the study.

The patient will be asked for his most convenient day for the Visit 3 follow up (see below) – this day will be recorded by the study nurse at the **Patient Visits Log**.

10.1.2 PATIENT FOLLOW UPS AND PEG REMOVAL

Patients will be monitored for follow-up after 2, 30, 60 and 90 and 120 days following their PEG insertion/replacement procedure and will be evaluated by the study nurse for their medical conditions. PEG device removal will be conducted 3 months following its placement.

Visit 3: Follow up 2 days (+/- 1 day) following procedure (sub-investigator visit in patient facility)

In compliance with the Centric Patient Approach, study delegated sub-investigator will visit the patient facility at the specific day scheduled together. The patient will be asked to report his nutritional status (malnutrition defined as a body mass index [BMI] <19 kg/m^2) and any stomal complication (wound infection, peristomal leakage, hypergranulation, pressure ulcer, any skin lesion adjacent to external bumper) – all will be investigated by the study **sub-investigator** using **Visit 3 safety Follow Up Form**.

In addition patient will be asked regarding his postoperative morbidity, any other Adverse Events and Concomitant medications.

Illuminated clear photos of the insertion site will be taken:

- Frontal to the insertion site/ external bumper
- Perpendicular (from the profile) to the insertion site/ external bumper
- In close perspective if outstanding issues (medical or technical) are observed

The study **sub-investigator** will also investigate tube performance: accidental dislodgement, buried bumper, gastric outlet obstruction, tube leakage, Residual Tube above skin evaluation, number of scheduled tube replacement, method of feeding (bolus, continues gravity, mechanical pump etc.), Scale 1-10 – ease of connecting the extension tube, ease of feeding, any replacements of disposable tubes other than scheduled (and reason) using **Visit 3 Tube Utilization Form.**

The following assessments will be conducted:

a) Physical examination
b) Vital signs

The patient will be asked for his most convenient day for his 30 days follow-up (Visit 4 follow up, see below) – this day will be recorded by the study nurse at the **Patient Visits Log**.

Visit 4: Follow up after 1 month +/- 10 days (sub-investigator visit in patient facility)
In compliance with the Centric Patient Approach, delegated study sub-investigator will visit the patient facility at the specific day scheduled together. The patient will be asked to report his nutritional status (malnutrition defined as a body mass index [BMI] <19 kg/m^2) and any stomal complication (wound infection, peristomal leakage, hypergranulation, pressure ulcer, any skin lesion adjacent to external bumper) – all will be investigated by the study **sub-investigator** using **Visit 4 safety Follow Up Form**.

In addition patient will be asked regarding his postoperative morbidity, any other Adverse Events and Concomitant medications.

Illuminated clear photos of the insertion site will be taken:

- Frontal to the insertion site/ external bumper
- Perpendicular (from the profile) to the insertion site/ external bumper
- In close perspective if outstanding issues (medical or technical) are observed

The study **sub-investigator** will also investigate tube performance: accidental dislodgement, buried bumper, gastric outlet obstruction, tube leakage, Residual Tube above skin evaluation, number of scheduled tube replacement, method of feeding (bolus, continues gravity, mechanical pump etc.), Scale 1-10 – ease of connecting the extension tube, ease of feeding, any replacements of disposable tubes other than scheduled (and reason) using **Visit 4 Tube Utilization Form**.

The following assessments will be conducted:

a) Physical examination
b) Vital signs

The patient will be asked for his most convenient day for the PEG removal hospital visit (Visit 6 follow up, see below) – this day will be recorded by the study nurse at the **Patient Visits Log**.

Visit 5: Follow up after 2 months +/- 10 days (phone call follow up)

In compliance with the Centric Patient Approach, delegated study member will call the patient facility at the specific day scheduled together. The patient will be asked to report his nutritional status (malnutrition defined as a body mass index [BMI] <19 kg/m^2) and any stomal complication (wound infection, peristomal leakage, hypergranulation, pressure ulcer, any skin lesion adjacent to external bumper) – all will be investigated by the study nurse using **Visit 5 safety Follow Up Form**. In addition

patient will be asked regarding his postoperative morbidity, any other Adverse Events and Concomitant medications.

The study personnel will also investigate tube performance: accidental dislodgement, buried bumper, gastric outlet obstruction, tube leakage, Residual Tube above skin evaluation, number of scheduled tube replacement, method of feeding (bolus, continues gravity, mechanical pump etc.), Scale 1-10 – ease of connecting the extension tube, ease of feeding, any replacements of disposable tubes other than scheduled (and reason) using **Visit 5 Tube Utilization Form**.

The patient will also be reminded for already scheduled day for the PEG removal hospital visit (Visit 6 follow up, see Patient Visits Log).

<u>Visit 6</u>: Follow up after 3 months +/- 10 and Fidmi device removal/replacement by balloon gastrostomy.

Prior to the procedure the patient will be asked to report his nutritional status (malnutrition defined as a body mass index [BMI] <19 kg/m^2) and any stomal complication (wound infection, peristomal leakage, hypergranulation, pressure ulcer, any skin lesion adjacent to external bumper) – all will be investigated by the study nurse using **Visit 6 safety Follow Up Form**. In addition patient will be asked regarding his postoperative morbidity, any other Adverse Events, Concomitant medications.

Illuminated clear photos of the insertion site will be taken:

- Frontal to the insertion site/ external bumper
- Perpendicular (from the profile) to the insertion site/ external bumper
- In close perspective if outstanding issues (medical or technical) are observed

Study nurse will also investigate tube performance: accidental dislodgement, buried bumper, gastric outlet obstruction, tube leakage, Residual Tube above skin evaluation, number of scheduled tube replacement, method of feeding (bolus, continues gravity, mechanical pump etc.), Scale 1-10 – ease of connecting the extension tube, ease of feeding, any replacements of disposable tubes other than scheduled (and reason) using **Visit 6 Tube Utilization Form**

The following assessments will be conducted prior to device removal/ replacement by balloon gastrostomy:

a) Physical examination
b) Vital signs

*An endoscopic examination is not required but may be performed on a need base, and following the investigator discretion.

In case a Gastrostom replacement is required, the study investigator will advise the patient from various types of technologically equivalent or similar devices including 'low profile' types. The replacement procedure will be performed routinely as specified in the Instruction for Use.

The following assessments will be conducted following the device removal/ replacement by balloon gastrostomy:

c) PEG Physician usability Form

Study PEG removal Form:

Procedure duration, heart rate at the end of the operation, amount and type of analgesia consumed, postoperative bleeding, use of anti-bleeding agents (such as tranexemic acid (hexakapron)).

Endoscopist feedback Form: Endoscopist 10-point Visual Analogue Scale for removal procedure difficulty.

d) Patient PEG removal/ replacement Feedback Form
e) Study Patient Discharge form.

The discharging study investigator will instruct the patient (or his care giver) to immediately call the site in case of: vomiting, swollen belly, repeated abdominal aches and general deterioration (for demented patients). In case there is a suspicious of GI perforation or hemorrhage bowel obstruction the study investigator will schedule an un-scheduled visit.

The patient will be asked for his most convenient day for the termination visit (Visit 7 study termination, see below) – this day will be recorded by the study nurse at the **Patient Visits Log.**

Visit 7: Follow up after 4 months +/- 10, X-ray and termination visit

In compliance with the Centric Patient Approach, a home X-ray examination will be offered to the patient and his family. If chosen, a certified technician (Medix at Home, FDA and MOH approved) will visit the patient facility at the specific day scheduled together, in order to conveniently perform abdominal X-ray examination (required to verify Bumper flanges expulsion). A copy of the imaging will be provided to delegated sub-investigator for evaluation.

Following the X-ray examination, a delegated study member will call the patient facility to verify no technical issues occurred. The patient will be asked to report his nutritional status (malnutrition defined as a body mass index [BMI] <19 kg/m^2) and any stomal complication (wound infection, peristomal leakage, hypergranulation, pressure ulcer, any skin lesion adjacent to external bumper) – all will be investigated by the study nurse using **Visit 7 safety Follow Up Form**. In addition, patient will be asked regarding his postoperative morbidity, any other Adverse Events and Concomitant medications.

Alternatively, the patient will be admitted to the Gastrology Institute at Shaare Zedek Medical Center, Jerusalem an hour before the planned X-ray examination scheduled time accompanied by the study nurse. Prior to the examination he will be asked to report his nutritional status (malnutrition defined as a body mass index [BMI] <19 kg/m^2 and any stomal complication (wound infection, peristomal leakage, hypergranulation, pressure ulcer, any skin lesion adjacent to external bumper) – all will be investigated by the study nurse using **Visit 7 safety Follow Up Form**. In addition,

patient will be asked regarding his postoperative morbidity, any other Adverse Events, Concomitant medications.

The following forms will be completed:

a) Post PEG removal imaging Form
b) Termination visit

*An endoscopic examination is not required but may be performed on a need base, and following the investigator discretion.

Un-scheduled visit:

In case particle/s from the bumper can be seen in the imaging the discharging study investigator will instruct the patient (or his care giver) to immediately refer his caring doctor in case of: vomiting, swollen belly, repeated abdominal aches and general deterioration (for demented patients). The patient must call the study nurse to schedule an un-scheduled visit only under his caring doctor discretion of: GI perforation or hemorrhage or bowel obstruction. In such case Un-scheduled visit form will be recorded. In that kind of visit the patient will be clinically managed by the study team in the Institute of Gastroenterology and Liver Diseases until. An additional X-ray imaging will be performed to illustrate and determine the localization of the retained particles. In case of colon localization the PI will consider removing those particles by colonoscopy procedure.

Table 3 - ***Visit procedure chart***

	Enrollment and device placement		**Follow Up Period**				
Procedure	Screening & Enrollment	Fidmi device insertion	**Sub-I** visit in patient facility	**Sub-I** visit in patient facility	Follow up call with the patient	Fidmi device removal	X-ray and termination visit
Visits	V1	V2	V3	V4	V5	V6	V7
Time Schedule (Days)	-7	0	2	30	60	90	120
Time Window (+/- Days)	7		1	10	10	10	14
Informed consent	X						
Demographics+ Med. history	X						
Concomitant medications	X	x ----------					
Physical exam	X	x	x	x		x	
Vital signs	X	x	x	x		x	
Adverse event evaluation		x ----------					
Endoscopy recording		x					
Photos of the insertion site		x	x	x		x	
PEG usability Form (physician)		x				x	
Patient Discharge form		x				x	
Safety Follow Up Form			X	X	X	x	x
Tube Utilization Form (patient/care giver)			X	X	X	x	
Patient feedback Form						x	
Patient Bumper flanges expulsion Form							x
X-ray imaging (home/clinic)							x
Post PEG removal imaging Form							x
Termination Visit							x
Subject Visit log		X	X	X	X	x	
Un-scheduled visit Form (if needed)							

10.2 SCALES AND EVALUATIONS

Physical examination

A standard physical examination will be conducted on participating patients in all study visits. These will be conducted by the investigator or by any other authorized member of the study team.

Physical examination will include weight measurements, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, and central nervous system and, where appropriate, other body systems per discretion of investigator (see CRF).

Vital signs

Vital signs (temperature, blood pressure, pulse rate, respiratory rate, and blood oxygen saturation) will be collected at all study visits.

Illuminated photos of the insertion site

All photos taken must be performed exactly like the previous visits- same shape and distance

*If the patient has any lesion such as an ischemic area, gangrene, ulcer, rush, edema etc. – take at least one close photograph demonstrating the lesion. Take a new photo of every new lesion that appears through the visits.

11 SAFETY ASSESSMENT

11.1 Anticipated Adverse Events

Placement complication: excessive stoma wound bleeding, over tightened external bumper, gastric and/or esophageal laceration, aspiration, device unintended disassembly, need for more than one needle puncture

Post placement complication; [Time Frame: 1week-4 months]: Fever, gastric distention, infection, blockage/ occlusion, tissue necrosis, migration, erosion/embedding into the gastric wall ("Buried Bumper Syndrome"), aspiration, bleeding, fistula, GE reflux, pain, perforation, ulceration, pressure sores, skin lesion (tissue granulation) adjacent to external bumper, dumping syndrome, tube clogging, malposition, leakage, kinking, inadvertent removal, small bowel obstruction, and granulation tissue.

Post removal complication: Bowel obstruction, Bowel peroration, GI bleeding, painful defecation.

Death after PEG procedure

The average survival time of patients undergoing PEG insertion is 720 days (9). At Day-30 following PEG insertion, 6.5% - 19% of the patients dies from complications Predictive factors of increased 30-day mortality were higher age, lower body mass index (BMI), and the presence of diabetes mellitus. (10)

97% of death occurred following PEG insertion (30 days' time window) patients have coexistent neurologic disease. Main death causes are: cardiovascular disease, respiratory disease and central nervous system disease. (11). Most patients demonstrate multiple co-morbidities and a poor functional baseline level pre-procedure.

Significant higher mortality rates (7 times higher) were observed in PEG inserted patients that were hospitalized during that time (first 30 days) compared to patients from nursing homes (12)

11.2 Precaution to Minimize Risk

The abovementioned risks will be minimized by having trained and qualified clinicians perform the procedure. Clinicians will be available for evaluation if there is any untoward effect.

In addition, sterile unused needles and lancets will always be used and pressure will be held at the insertion site after placing the PEG device. Further mitigations:

- Antibiotics as prescribed by the investigator
- Study nurse will provide the patient with Home instruction including emergency call (24 hours).
- Tactile Fidmi device placement/replacement and removal performed only by trained and qualified physicians.
- X-ray imaging to ensure bumper flanges expulsion
- Readiness and patient guidance for "un-scheduled visits"

11.3 ADVERSE EVENTS REPORTING

Adverse Events (AE) will be done according to National Cancer Institute (NCI) Terminology Criteria for Adverse Events v4.0 common terminology criteria for AE (CTCAE). See link for CTCAE v4.0 - (13).

AE will be collected throughout the study and recorded on the CRF. Pre-existing conditions will not be considered AEs only if they worsen beyond what would be expected. In all cases, the etiology should, as much as possible, be identified, recorded, and the Sponsor notified.

11.3.1 ADVERSE EVENT SEVERITTY

The severity of the AE will be evaluated by the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for toxicity and adverse event reporting. A copy of the CTC Version 4.0 should be accessed from the CTEP site (13)- containing all NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files and related documents. All treatment personnel should have access to a copy of the CTC version 4.0.

Each CTCAE term is a representation of a specific event and corresponds to a single MedDRA Lowest Level Term (LLT). Grade relates to severity for the purposes of regulatory reporting and is defined as follows:

0. No AE (or within normal limits).

1. Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2. Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).

3. Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

4. Life-threatening consequences; urgent intervention indicated.

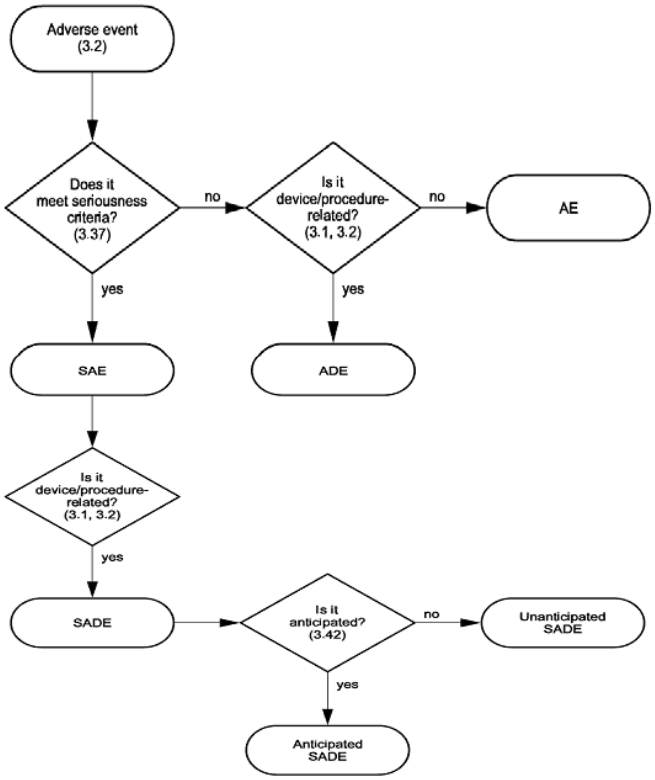
5. Death related to AE.

The investigator shall appoint a safety monitor who will assess the relationship of the observed symptoms to the investigational treatment. AEs will be collected

from subject enrollment through follow-up period. In all cases, the etiology should, as much as possible, be identified and the Sponsor notified.

AE will be assessed by the investigator for severity, causality and outcome.

Figure4 - AE definition (ADE- Adverse drug event, SADE-serious adverse device event)



11.3.2 ADVERSE EVENT OUTCOME

The outcome of an AE will be assessed as:

- **Recovered/resolved -** recovered or resolved without medical sequelae. "Stop date" of the event should be the date the event is no longer present or stabilizes. If there are lingering effects after a patient is discharged then the event will not resolve until all symptoms have ceased or stabilized.

- **Not recovered/not resolved -** for an ongoing AE - for AEs that did not cause the death and were not resolved prior to the death, the outcomes for these events will be entered as "Ongoing."
- **Recovering/resolving -** in the process of writing of the report
- **Recovered with sequelae/resolved with sequelae-** the nature of the sequelae will be reported

Fatal (SAEs only) - the date of dead will be reported, the autopsy report will be given, if one will be done.

11.3.3 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- 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,
- Required Intervention to Prevent Permanent Impairment or Damage (Devices)
- Medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect (not applicable to this study).

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical 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 also usually be considered serious.

11.3.4 REPORTING SERIOUS ADVERSE EVENT

Medical judgment will be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not 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, may also be considered serious .

In order to satisfy regulatory requirements, any Serious and Unanticipated Events, whether investigational product deemed related or not, must be reported to the Sponsor/ Designated CRO as soon as possible after the investigator or coordinator has become aware of its occurrence. The SAE form completion and reporting must not be delayed even if not all of the information is available at the time of the initial contact.

The Serious Adverse Event (SAE) form should be submitted within 24 hours of becoming aware of the event to the Sponsor/ Designated CRO .

Additional information (follow-up) regarding any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available to the Sponsor or designee .

Serious adverse events should be reported by the site to their EC/IRB as dictated by their hospital policies and procedures using Matarot clinical study designated software.

Subjects who have had an SAE during the treatment period may be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained. The investigator is responsible for the ongoing safety assessment of the investigational products. The Sponsor shall inform all the parties involved in the conduct and approval of the trial, i.e. the Investigators, IRBs and the Ministry of Health, of findings that may affect the safety of trial participants, or findings which have implications on the method of trial conduct, or findings that may affect the decision of the parties that approved the trial. The investigator is responsible for the ongoing safety assessment of the investigational products. The Sponsor shall inform all the parties involved in the conduct and approval of the trial, i.e. the Investigators, IRBs and the Ministry of Health, of findings that may affect the safety of trial participants, or findings which have implications on the method of trial conduct, or findings that may affect the decision of the parties that approved the trial.

11.3.5 SERIOUS ADVERSE DEVICE EVENT

Any serious adverse event somehow related to treatment with the investigational product.

11.3.6 POST-TRIAL EVALUATIONS

Patients who have moderate or severe on-going adverse events at the completion of the study will be advised to consult their personal physician if the event is not considered to be related to the index hospitalization. An un-scheduled visit will be arranged to manage the problem and to determine the severity and duration of the event, if it is considered to be related to the investigational device. If appropriate, specialist review within the MOH will be arranged.

12 STATISTICAL ANALYSIS

This study is an early feasibility research to primarily test the safety and usability of the investigated device.

All data obtained in this study and documented in the Case Report Forms will be listed and tabulated with descriptive group statistics (mean, standard deviation, minimum, maximum, number of valid cases), as appropriate.

For continuous variables such as age, body weight, vital signs, etc. descriptive group statistics (n, mean, standard deviation, minimum, maximum and number of valid cases), will be used as appropriate. For categorical discrete variables data, such as sex, number of Adverse Events (occurrence, severity, relationship with), etc., frequency and percentage will be computed.

Incidences of AEs will be presented by MedDRA system class, intensity, seriousness, and relation to study investigational product.

13 INVESTIGATION ADMINISTRATION

13.1 IRB/EC APPROVAL

This study including protocol, the informed consent document, relevant supporting information and all types of patient recruitment information will be presented for approval to the Helsinki Committee of the Shaare Zedek Hebrew University Medical Center, Jerusalem prior to any study initiation. An update of the addition of medical site will be notofied to the Israeli ministry of health (MOH)

The study will be conducted according to the rules and regulations of the state of Israel, those of the Shaare Zedek Hebrew University Medical Center, and will follow the IRB approved protocol. Written informed consent would be obtained from all patients and/or their guardian before enrollment in the study and a copy of the signed Apotropos authorization documents would be collected and documented in the patient binder. The study will be monitored annually by the IRB. The trial will be registered with http://www.clinicaltrials.gov and the Israeli MOH clinical trials registry.

This trial will be conducted in accordance with the Declaration of Helsinki (see 10.9) as agreed by the World Medical Association General Assembly (Seoul 2008), ICH Good Clinical Practice and local regulatory requirements.

The investigator will be responsible for keeping their local IRB informed of the progress with study renewal at least once a year. The investigator will also keep the local IRB informed of any significant adverse events, per local institutional guidelines. Adverse event reporting guidelines can be found in Section 11.3, Reporting Adverse Events.

13.2 DATA MONITORING AND QUALITY CONTROL

The investigator, through an appointed Clinical Research Associate (CRA), will be responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s) .

The investigator will be responsible for ensuring direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the hospital, and inspection by Israeli regulatory authorities .

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

The study CRA will verify that (a) The rights and well-being of human patients are protected, (b) The reported trial data are accurate, complete, and verifiable from source documents and (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s). The full responsibilities of the trial monitor appear in full in the ICH-GCP.

The monitor(s) should follow Fidmi (or their CRO representative) written for monitoring the specific trial.

The monitor will submit a written report after each trial-site visit or trial-related communication. A report should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted. A report should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

To ensure compliance of this investigator initiated trial with current national regulations and the ICH guidelines, data generated by this study will be available for inspection upon request by representatives of the local health authorities- IRB or the national authorities - MOH, or any entity providing support for this trial. Routine monitoring or audit activities for this study will be conducted by authorized representatives. The general scope of such visits would be to inspect study data (regulatory requirements), source documentation and CRF completion in accordance with current Good Clinical Practices (GCP), the ICH guidelines and the respective local and national government regulations and guidelines.

The IRB will supervise the clinical trial and shall receive periodic reports from the investigators. The IRB shall receive an interim report on safety on an annually base. The committee shall also receive regular reports of adverse events occurring during the trial and shall discuss these events with the investigator.

13.3 SUBJECT CONFIDENTIALITY

The original data collection forms will be stored in secured cabinets at the originating institution. Institutional policy and guidance on requirements for managing clinical research data will be followed, including the appropriate levels of safeguard to ensure the confidentiality, integrity and availability of clinical research data.

The patients' confidentiality will be maintained and will only be accessible to study staff and to CRA designated by the investigator. The only non-hospital personnel notified as to participation of the patient in the study will be the family physician.

Patient will be de-identified using a systematic number (see above).

13.4 PROTOCOL MODIFICATIONS

13.4.1 Protocol Deviations

The instructions and procedures specified in this protocol require diligent attention to their execution. No alterations or changes to this protocol will be permitted. However, should there be question or consideration of deviation from the protocol, clarification must be sought from the sponsor's clinical monitor. Any subject treated in a manner that deviates from the protocol, or who is admitted into the study but is not qualified according to the protocol, may be ineligible for analysis and thereby compromises the study. The investigator and research team must comply with all applicable, state and local laws.

All Protocol Deviations would be reported to the local IRB via MATAROT specific form signed by the PI together with occurrence date, detailed deviation and justification cause. Accordingly all protocol deviations would be documented in a specific study Protocol Deviation log.

13.4.2 Protocol Amendments

The protocol cannot be amended by the investigators or study personnel without first obtaining IRB review and the concurrence of the investigator and the sponsor. Medically significant amendments to the protocol (e.g., affect the rights, safety, or welfare of the human subjects involved in the investigation, the scientific soundness

of the investigational plan, the validity of data or information resulting from the completion of an approved protocol, or the relationship of likely subject risk to benefit relied upon to approve a protocol or if they are otherwise significant inclusion of new categories of subjects, etc.) may not be instituted prior to regulatory approval by relevant IRB and MOH.

13.5 STUDY DOCUMENTATION

13.5.1 Patient File

The investigator will ensure the completeness of patient files, which will include the following documents:

- Signed ICF
- Letter to family physician
- Completed and signed CRF
- An anonymous endoscopy recording of the procedure
- Illuminated clear photos of the insertion/replacement site
- Study Patient Discharge form.
- Source documents (with the patient's identifying information crossed-out)

13.5.2 Source Documents

Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, x-rays, and laboratory results, printouts, pharmacy records, care records, completed scales for each study participant. Source documents should be kept in a secure and limited access area. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc etc). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes). Source documents that

are computer generated and stored electronically must be printed (for review by the study monitor), signed and dated by the investigator .

Source documents for this trial will include the following:

- Informed Consent Forms.
- Apotropos signed authorization documents (when applicable)
- Completed CRF.
- Patient medical file including Surgery and Discharge Reports
- Physical examination results.
- X-Ray imaging and evaluation

Source data for subjects should indicate participation in clinical protocol number and title, treatment number, evidence that inclusion/exclusion criteria have been met.

13.5.3 CRFs

Study data will be collected using paper case report forms (CRF). The PI will be responsible for the timeliness, completeness, and accuracy of the information on the CRF. All entries must be legibly recorded in black or blue ink. The entry to be corrected is to be crossed out with a single line so that the original entry remains legible. The correction then has to be made right next to the entry and confirmed by date and initials of the person making the correction. Corrections that cannot be made in this fashion have to be explained in a detailed statement (e.g. Data Clarification Form), reference to which must be documented on the relevant CRF page(s). Do not erase, overwrite, or use correction fluid on the original. All data printouts should be attached to the pertinent CRF pages.

The CRF for each subject must be reviewed and signed by the principal investigator. This should be done as soon as possible after each subject completes the study (Subject Data Lock). The Principal Investigator will make the CRF pages available for review and collection by the study monitor at each scheduled monitoring visit. A Fidmi (or CRO representative) study monitor will review the CRFs and compare the content

versus the source data. All CRFs and other pertinent records will be kept during and/or upon completion of the study for the number of years indicated by the Israeli law .

The Investigator or designated colleague will provide access to the Monitor or other designated monitor for the periodic review of source documents (e.g., hospital and clinic records) to assure accuracy and completeness of the CRFs. The investigator also must maintain and submit, if required, all incomplete CRFs that reflect subject experience with the PEG insertion procedure, including retrievable data on subjects who withdraw before completion of the study.

13.5.4 Document Retention

The investigator or the sponsor shall retain copies of the approved protocol, completed CRFs, informed consent documents, relevant source documents, the investigator site file, investigators CV, all documents signed by the Shaare Zedek University Medical Center and all other supporting documentation related to the project for a minimum of seven years.

Other information to be retained includes:

- List of committee members who reviewed the application for approval of the clinical trial.
- Documents submitted for review such as all the application documents, including the documents submitted to the Ethics Committee for approval

Investigator/Institution/Sponsor will take measures to prevent accidental or premature destruction of study documents. If the investigator is unable to retain the study documents for the required amount of time, the Galilee Medical Center or designee must be informed of the individual who will be assuming this responsibility.

13.5.5 DEVICE ACCOUNTABILITY

Accountability records must be maintained at the site at all times. The identification number of the subject, the supply/shipment date, lot number, expiry date, usage and disposal date of the Fidmi device and the date and quantity of devices returned will be recorded and maintained by the PI.

At study conclusion, all devices (used and unused) must be returned to the sponsor or sponsor's designee for destruction and documented evidence of destruction should be available. Ancillary supplies may not have to be returned.

Upon Fidmi/Fidmi designee visit at the site, accountability of the returned devices should be performed and recorded.

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