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Re: Retraction Requested of "Diaphragm Pacing" Article

Dear Editors of Medscape,

We are writing to inform you of certain incorrect and misleading statements in the article entitled "Diaphragm Pacing," written by Shabir Bhimji, MD, PhD, edited by Zab Mosenifar, MD, FACP, FCCP, and published by Medscape on December 16, 2015 (the "Pacing Article"). The Pacing Article mischaracterizes the current medical devices and surgical procedures used for diaphragm pacing and suggests that a relatively new pacing device, which has the least clinical history and about which adverse events have been reported, is the better, safer, and more effective pacing device. As a result, the Pacing Article increases the risk that providers will choose an inappropriate therapy. For the reasons detailed below, we ask Medscape to retract the article and publish this letter to correct the record.

At the outset, it must be noted that in the United States there is only one commercially available medical device for diaphragm pacing that has received full approval from the Food and Drug Administration—the Avery Breathing Pacemaker System (the "Avery System") manufactured by Avery Biomedical Device Inc. ("Avery"). In 1987, FDA first approved the Avery System "for persons who require chronic ventilator support because of upper motor neuron respiratory muscle paralysis ("RMP") or because of central alveolar hypoventilation ("CAH") and whose remaining phernic nerve, lung, and diaphragm function is sufficient to accommodate electrical stimulation."[1] This includes adult and pediatric patients who have CAH,

[1] FDA Approval Letter, PMA P860026, January 5, 1987.

decreased day or night ventilator drive, brain stem injury or disease, or spinal cord disease. The safety *and* effectiveness of the Avery System was established with clinical data and information that met FDA requirements for full marketing approval of its Premarket Approval Application ("PMA").[2] Over the years, Avery has made significant improvements to the Avery System, each of which was carefully reviewed and approved by the FDA.

Since 1971, the Avery System has been used by over 2000 patients in 40 countries. The reference in the Pacing Article to the "older method of phrenic nerve stimulation for diaphragmatic pacing" is a reference to the Avery System. Given this long clinical history, it is all the more significant that to date not one adverse event has been attributed to the Avery System.

The only other available pacing device in the United States is the NeuRx® Diaphragm Pacing System ("DPS") marketed by Synapse Biomedical Inc. under an FDA-approved Humanitarian Device Exemption ("HDE").[3] The threshold for HDE is lower than for a standard PMA approval. HDE approval is based on a showing of safety and *probable benefit.* HDEs are exempt from the requirement to demonstrate "reasonable assurance of effectiveness." In June 2008 Synapse obtained an HDE approval from FDA, without establishing reasonable assurance of effectiveness, for use in patients 18 years old and older with "stable, high spinal cord injuries with stimulatable diaphragms, but lack control of their diaphragms."[4] In September 2011 Synapse obtained HDE approval from FDA, without demonstrating reasonable assurance of effectiveness, for use of its pacer in amyotrophic lateral sclerosis ("ALS") patients 21 years and older with a stimulatable diaphragm, who are experiencing chronic hypoventilation (CH) but have

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[2] Clinical data presented in the PMA included data from 136 patients treated at four medical centers. In addition, a registry maintained by Yale University provided clinical information about approximately 500 patients who had been implanted with the Avery Pacer between 1972 and 1986. *Id.*

[3] HDE applications may only be submitted for devices that have been designated by FDA as a Humanitarian Use Device ("HUD"), which is defined to mean a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year." 21 CFR 814.3(n).

[4] FDA HDE Approval Letter for the Synapse NeuRx® DPS, H070003, June 17, 2008, available at https://www.accessdata.fda.gov/cdrh_docs/pdf7/H070003A.pdf.

not progressed to an FVC less than 45% predicted.[5] The reference in the Pacing Article to the "newest approaches to diaphragmatic pacing" is a reference to this Synapse pacing device. Because there is limited data about effectiveness, FDA requires that the Synapse, like all other HDE-approved devices, be used only in a medical facility after an Investigational Review Board ("IRB") has approved its use in that facility, except in certain emergencies.

Since 2009, Synapse's NeuRx® DPS has been the subject of at least 15 serious adverse events reported to the FDA. These serious adverse event reports include: recurring infections at the percutaneous exit site of the lead wires of the diaphragm;[6] track infection and infection at sub-xyphoid site;[7] ventricular couplets and ventricular tachycardia;[8] electrode erosion through skin;[9] artery puncture due to free floating electrode;[10] and death.[11]

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[5] FDA HDE Approval Letter for the Synapse NeuRx® DPS, H100006, Sept. 28, 2011, available at https://www.accessdata.fda.gov/cdrh_docs/pdf10/H100006A.pdf.

[6] *See* Manufacturer and User Facility Device Experience ("MAUDE") report, December 2, 2016, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=6142010&pc=OIR; MAUDE report, December 1, 2015, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=5266874&pc=OIR; and MAUDE report, July 3, 2014, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=4058237&pc=OIR.

[7] *See* MAUDE report, December 1, 2015, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=5266870&pc=OIR.

[8] *See* MAUDE report, July 19, 2016, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=5804354&pc=OIR MAUDE report, October 8, 2013, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=3410448&pc=HCC; MAUDE report, September 7, 2012, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=2739305&pc=HCC; MAUDE report, January 21, 2011 available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=2114661&pc=HCC; and MAUDE report, December 14, 2009, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=1566417&pc=HCC.

[9] See MAUDE report, December 1, 2015, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=5266871&pc=OIR; MAUDE report, May 26, 2015, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=4797745&pc=OIR.

[10] *See* MAUDE report, November 24, 2014, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=4283602&pc=OIR.

[11] *See* MAUDE report, May 12, 2016, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=5649750&pc=OIR.

Unfortunately, the Pacing Article discusses the older and newer devices and related surgical procedures inaccurately and with misleading or incorrect graphics. The inaccuracies are found throughout the article, even in Bhimji's description of the history of diaphragm pacing.

***The History of Diaphragm Pacing***

Bhimji begins the background section of the article by stating that physicians experimented with phrenic nerve stimulation in the early 1990s to produce diaphragm contraction and used phrenic nerve stimulation in the 1950s to treat polio patients, when pacing was still crude. This is incorrect. Relying on phrenic nerve stimulation research dating as far back as 1872, physicians began experimenting with phrenic nerve stimulation in the 1960s. In the 1950s, phrenic nerve stimulation was used only once, experimentally, to treat respiratory insufficiency of a single polio patient.

The first practical application of phrenic nerve pacing was done by William W.L. Glenn, a pioneer in cardiac pacemaker research, and his colleagues at the Yale University School of Medicine. They described their work in an article titled "Radio-frequency electrophrenic respiration. Long-term application to a patient with primary hypoventilation," published March 1968 in the Journal of the American Medical Association.[12] The diaphragm pacing prototypes developed by Glenn were manufactured and marketed by Avery Laboratories, Inc. in the early 1970's and, were continuously improved leading to the Avery System marketed today.

The Avery System works by controlling the function of the diaphragm, the main breathing muscle of the body, through electrical stimulation of the phrenic nerve by an implanted electrode, which causes the diaphragm to contract and pull air into the lungs to mimic inspiratory inhalation activity seen with normal breathing. Exhalation then occurs passively when the electric pulses stop and the diaphragm relaxes. The application of repetitive stimulus patterns to the phrenic nerves causes smooth, rhythmic contractions. Such a system provides respiratory function that is physiologically similar to natural breathing through the use of negative pressure

[12] Glenn WW, Judson JP. "Radio-frequency electrophrenic respiration. Long-term application to a patient with primary hypoventilation." Journal of the American Medical Association. March 1968, 203(12), pp. 1033-1037.

that naturally pulls air into the lungs as opposed to mechanical ventilation that uses positive pressure forcing air into the airway passages and lungs.

On July 22, 1986, FDA published a regulation requiring the submission of a Premarket Approval Application ("PMA") for high risk devices, including implantables, classified as Class III, which included breathing pacemakers.[13] Based on clinical study data and information demonstrating safety and reasonable assurance of effectiveness, on January 5, 1987 the Avery Breathing Pacemaker System was one of the first medical device products to receive FDA approval of a PMA.[14] In 1995, the Avery System received CE marking privileges under the requirements of the Active Implantable Medical Device Directive (90/385/EEC) for distribution within the European Union.

Since the commercial introduction of the Avery System, surgical techniques substantially improved with the concurrent cervical approach and the introduction of thoracoscopic minimally invasive approaches to the implantation of diaphragm pacemakers. In 2002, Donald Shaul and colleagues at the Children's Hospital of Los Angeles reported on the first series of pediatric patients, starting in 1997, that were implanted with the Avery System using a thoracoscopic technique.[15] Also in 2002, John A. Elefteriades and his colleagues presented a long-term, multi-center analysis of a series of twelve quadriplegic patients implanted with the Avery System from 1981 to 1987.[16] Their 15 year follow-up showed that "all patients demonstrated normal tidal volumes and arterial blood gases while pacing full time. Despite theoretical concerns about long-term nerve damage, no patient lost the ability to pace the phrenic nerve."[17]

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[13] FDA Final Rule, Premarket Approval of Medical Devices, 51 Fed. Reg. 26342 (July 22, 1986).

[14] FDA Notice: Avery Laboratories, Inc.; Premarket Approval of Diaphragm Pacer, 52 Fed. Reg. 5505 (February 25, 1987).

[15] Shaul DB, Danielson PD, McComb JG, Keens TG. "Thoracoscopic Placement of Phrenic Nerve Electrodes for Diaphragm Pacing in Children." Journal of Pediatric Surgery. July 2002, 37(7), pp.974-978.

[16] Elefteriades JA, Quin JA, Hogan JF, Holcomb WG, Letsou GV, Chlosta WF, Glenn WW. "Long Term Follow-up of Pacing of the Conditioned Diaphragm in Quadriplegia." Journal of Pacing and Clinical Electrophysiology. June 2002, 25(6), pp.897-906.

[17] *Id.*

This long history showing the safety, effectiveness, and value of the Avery System is excluded from the article's background section almost entirely. Additionally, this important history plainly contradicts Bhimji's statement that clinical trials "will be required to determine whether diaphragm pacing is worth the expense and in which populations it is most useful." Over 2000 patients with upper motor neuron respiratory muscle paralysis or central alveolar hypoventilation, better known as central sleep apnea, can attest to its value.[18]

***Comparing Diaphragmatic Pacing Systems***

Bhimji proceeds to discuss the present landscape in diaphragm pacing, calling all present systems "cumbersome," however noting that "[t]he improved pacing systems now being used are more affordable and much easier to implant than earlier systems were." In this respect, Bhimji compares the "newest approach [whereby] the pacing electrodes are introduced via laparoscopy from the left chest" and the "older method of phrenic nerve stimulation for diaphragmatic pacing [the cervical approach]." This comparison suggests that the older pacing device, the Avery System, has not been improved and that introducing pacing electrodes through laparoscopy from the left chest is better. The facts, however, do not support this conclusion.

The "newest approach," which refers to the Synapse pacing device, uses four electrodes implanted on the underside of the diaphragm – two for each side – using a laparoscopy procedure through the abdominal cavity with percutaneous lead wires connected to the pacemaker. The stimulus amplitude for each electrode reaches up to 25 mA. In contrast, consider that the Avery System uses only two electrodes – one for each side – and the maximum current allowed is 10 mA, with typical stimulus values ranging between 3 and 5 mA. In addition, the Avery System has a bi-lateral redundant design to ensure a single-point failure does not result in a complete loss of life support. Whereas, the Synapse pacing device has only one control, one microprocessor, and one battery. If one fails to work, the patient has no ventilatory support, leading obviously to potentially fatal consequences.

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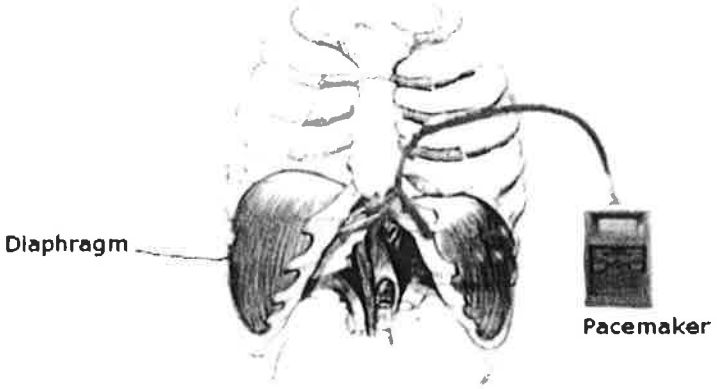
[18] FDA Approval Letter, PMA P860026, January 5, 1987.

The discussion of the "newer" or "newest" Synapse approach and its related graphic obscures the medical challenges of maintaining a connection to implanted electrodes via lead wires that exit the body through an incision. See graphic from the Pacing Article below.




Percutaneous wires require constant wound care to prevent infection. Percutaneous wires also raise the risk of capnothorax, that is, air tracking into the pleural cavity, which could lead to tension pneumothorax, a life-threatening condition that requires immediate decompression. Capnothorax, caused by $CO_2$ used to inflate the abdomen during surgery related to the electrode implantation procedure, was the most commonly occurring adverse event (42%) in the clinical study conducted by Synapse in support of its 2008 HDE approval.[19] Percutaneous wires are also awkward and preclude a patient from bathing, swimming, or any activity with exposure to excessive moisture. Without information about these risks, the Pacing Article fails to provide a balanced description of this approach.

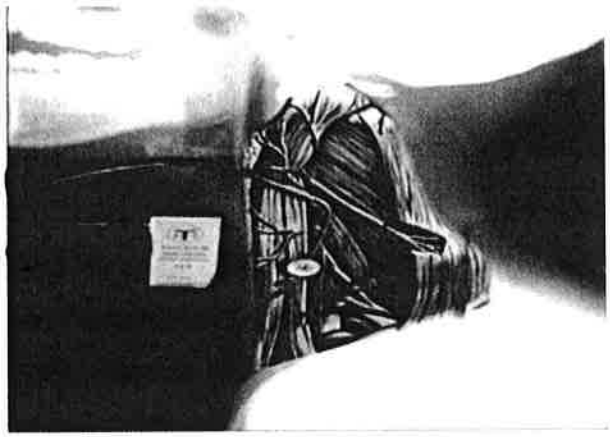
It is also important to note that, in addition to requiring that Synapse obtain IRB approval prior to the use of its pacing device, FDA conditioned the 2011 HDE-approval on Synapse's agreement to conduct a postapproval clinical study to evaluate adverse events ("AEs"). The FDA letter stated:

> . . . Occurrence and timing of major device-related AEs will be evaluated as well as death and permanent tracheostomy with mechanical ventilation. In

[19] *See* HDE H070003: FDA Summary of Safety and Probable Benefit for NeuRx® DPSTM, RA/4 Respiratory Stimulation System by Synapse Biomedical Inc., pp. 3-4, available at https://www.accessdata.fda.gov/cdrh_docs/pdf7/h070003b.pdf.

> addition, evaluation will include capnothorax, mechanical ventilation for 24 hours or longer post-procedure, periopeirative complications delaying initiation of therapy, severe discomfort, device malfunction. electrode dislodgement, wire infection and any other device- or procedure-related serious AE.[20]

The graphic depicting the "older method" is also misleading. First, it is not a depiction of the Avery System or its function. Rather, it shows an external stimulator connected to a small round device to be placed on the skin. See graphic from the Pacing Article below.



The blue arrow points to what is labeled as the "electrode on phrenic nerve," which is not accurate.

The picture does not show the implanted side, where one would see the receiver (about the size of a quarter) implanted in a subcutaneous pocket just under the skin with a lead wire connected to an electrode placed under or near the phrenic nerve. Moreover, when the surgical procedure is cervical, the best location to implant an electrode on the phrenic nerve would be on the base of the neck, but above the clavicle, which is also not shown.

For example, the photograph below shows the proper electrode placement under the phrenic nerve, which is in contrast with the graphic portrayed in the Pacing Article[21]

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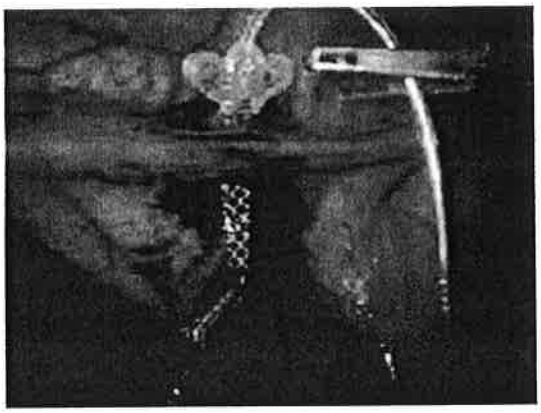
[20] FDA HDE Approval Letter for the Synapse NeuRx® DPS, H100006, Sept. 28, 2011, available at https://www.accessdata.fda.gov/cdrh_docs/pdf10/H100006A.pdf.

[21] Image reproduced with permission from Avery Biomedical Devices, Inc.



To confuse matters more, the graphic in the Pacing Article shows a pacemaker that is labeled "Tulgar", which is a neurostimulater that has been used for vagus nerve stimulation. Even more misleading is the failure of the author to reveal that this device is not approved for *any* use by the FDA or by any other regulatory authority in the world. There appears to be only one publication, in a non-peer-reviewed journal, discussing the Tulgar implant. In that article, Dr. Metin Tulgar describes using the Tulgar implant for vagus nerve stimulation in the management of refractory treatment of epilepsy, not for phrenic nerve stimulation or pacing.[22]

***Improvements to the Avery System***

Since its initial introduction in 1971, the Avery System has benefited from continuous and significant improvements and from advances in surgical techniques for implantation that are absent in the Pacing Article. The Avery System consists of electrodes, a coin-sized radio receiver, and an external transmitter/antenna using 9-volt batteries.[23] The implanted receiver,

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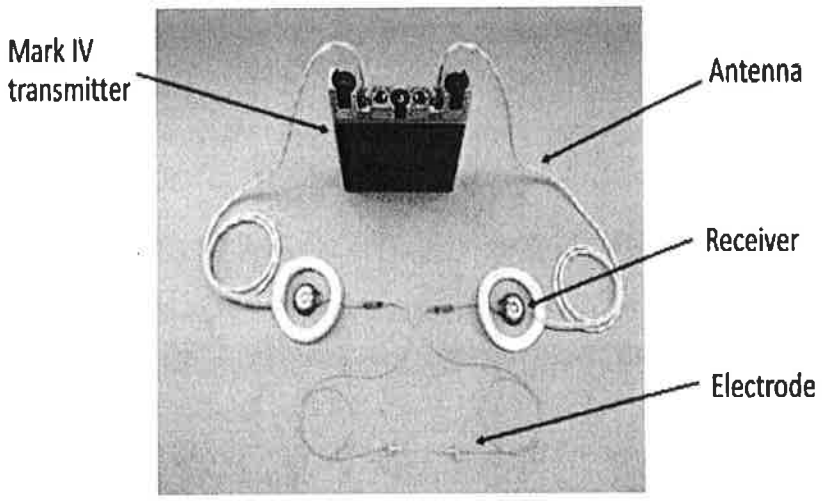
[22] *See* Tulgar, M., Bilgin, S. & Yildirim, A., "The Human Body's Own Language to be Considered for Safe and Effective Neurostimulation," Neurol Ther. December 2012, 1(2), doi:10.1007/s40120-012-0002-x, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4389039/. The Tulgar is advertised on Alibaba, the Chinese online e-commerce company, https://www.alibaba.com/trade/search?fsb=y&IndexArea=product_en&CatId=&SearchText=tulgar, from which one is invited merely to contact the manufacturer, Dr. Metin Tulgar, Professor Tulgar Neurotechnology Center, https://message.alibaba.com/msgsend/contact.htm?spm=a2700.details.0.0.tGjFjo&action=contact_action&domain=1&id=12210941&id_f=IDX11Vu5I4q64csiuXJjhB4775ALTfOLbKNoSsZoPXlqNrhijb2kwOnCZAPAjEhthJ18&mloca=main_en_detail&tracelog=tracedetailfeedback&umidToken=B1d7c02ccb59a81ed74972d7d573ae3d8. No information has been found that indicates this device is being manufactured, sold, or is approved by any competent regulatory authority for any human use.

[23] *See* Avery Biomedical Devices, Inc., Instruction Manual for the Avery Breathing Pacemaker System, pg. 6, available at http://www.averybiomedical.com/wp-content/uploads/2015/10/EN-6025-AB-SYSTEM-INSTRUCTION-MANUAL.pdf (hereinafter "User manual").

which is currently about the size of a quarter and approximately 1/4" thick, see image below;[24] is mischaracterized by Bhimji as being the size of a pack of cigarettes.




The receiver contains no batteries, which would require periodic replacement. It receives radiofrequency energy from the external transmitter and converts the radio waves into stimulating pulses. These pulses are then sent through the implanted electrodes to the phrenic nerves causing the diaphragm (or hemidiaphragms) to contract. The electrode is a highly flexible stainless steel wire, insulated by silicone rubber, with a platinum nerve contact on one end, and a connector that mates with the receiver at the other.

The external antenna, available in one to two meter lengths, is worn over each implanted receiver. The antenna is a durable disposable item that sends power and radio signals from the transmitter to the receiver transcutaneously; there are no wires or plugs protruding from the skin. It is recommended that the antennas be replaced every six months.

The current external transmitter, called the Mark IV, is battery powered to generate stimulus patterns and deliver them to the phrenic nerve via the external antennas, implanted receiver, and electrodes. The design employs two independent output stimulus generators, each with its own battery power source, external indicators, and respiratory rate control, which allows

[24] Image reproduced with permission from Avery Biomedical Devices, Inc.

for synchronous or asynchronous stimulation (e.g., different pulse widths, pulse intervals) to meet every patient's specific needs.[25]

Since the early 1970's and 1998 (FDA approval of Mark IV transmitter) there have been considerable advances in phrenic nerve stimulation. For example, bilateral redundancy with individual controls and a battery for each side ensures the transmitter will provide ventilatory support to one side if the other one fails; monopolar electrode instead of bipolar electrode and strain relief on both ends of the electrode lead helps prevent possible damage to the nerve. No adverse events have been reported to Avery, to the FDA MAUDE database,[26] or in the scientific literature pertaining to this Avery phrenic nerve stimulator.

Phrenic nerve stimulation can be used continuously for 24 hours a day, seven days a week. Indeed, of the Avery System users who require 24/7 ventilatory support, a majority rely solely on the Avery System.

A surgical procedure averaging two to four hours in length is required to place the implanted electrode under the phrenic nerve and the implanted receiver just under the surface of the skin in the subcutaneous region. This procedure can take place cervically or thoracically.[27] The thoracic approach can be performed in a minimally invasive manner by using VATS (video-assisted thoracic surgery) techniques using both standard endoscopic instruments or use of a surgical robot. Meanwhile, the cervical approach is minimally invasive as it does not require a thoracotomy or chest procedures. These discussions of the various surgical techniques currently being used with the Avery System, in addition to the improvements of the device, are absent in the Pacing Article.

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[25] User manual at 9, 11.

[26] MAUDE refers to the Manufacturer and User Facility Device Experience database administered by FDA. The MAUDE database is a repository of reports from device manufacturers, importers, and user facilities that are required to submit reports of adverse events and malfunctions related to medical devices. The MAUDE database also accepts voluntary reports from healthcare professionals, patients, and consumers.

[27] The patient is typically discharged from the hospital within one or two days, although sometimes the procedure can be performed on an outpatient basis. *See* Avery Biomedical Devices, Inc., Surgical Information, available at http://www.averybiomedical.com/breathing-pacemakers/surgical-information/.

***Diaphragm Pacing and Quality of Life***

We do agree with several points made by Bhimji regarding the medical and quality of life advantages of pacing over mechanical ventilation. Indeed, independence, the ability to speak, and the decrease in complications previously resulting from tracheotomies are noteworthy. However, diaphragm pacing with the Avery System provides many more important advantages over mechanical ventilation not noted in the Pacing Article, such as:

- Negative pressure respiration that is similar to the physiological function
- Improved venous return
- Lower production of secretions
- Lower risk of respiratory infections (thus fewer hospital stays)
- Improved quality of speech
- Ease of eating and drinking
- Regained sense of smell
- Improved mobility
- Inconspicuousness from silent operation due to absence of moving parts and small size
- Overall improved quality of life including better integration in society
- Simplified equipment, including the use of two inexpensive, 9-Volt alkaline batteries, available anywhere in the world
- Limited disposables (2 antennas and 2 batteries)
- No periodic maintenance
- No restriction on age (the youngest implanted was 57 days, the oldest 80+ years old)
- Patient may opt to be decanulated
- Cost effectiveness, e.g., the annual cost of batteries and antennas is less than $1,000 / year.

Bhimji, however, fails to note the improvement in survival rates. Instead, he incorrectly claimed "there is, as yet, little evidence to indicate that it improves survival in these patients."

The Avery System has been shown to extend survival rate by 13.09 years over patients on mechanical ventilators.[28]

***Request for Action***

The "Diaphragm Pacing" article is riddled with errors, misstatements, and misleading graphics. This letter is intended to correct the most egregious of these and elucidate the benefits, advantages, and demonstrated effectiveness of the oldest diaphragm pacing device, the Avery System. We respectfully request that Medscape retract "Diaphragm Pacing" and correct the record by publishing this letter.

Sincerely,

Areta Kupchyk

Areta L. Kupchyk

[28] Long-Term Evaluation of Phrenic Nerve Pacing for Respiratory Failure Due to High Cervical Spinal Cord Injury. Romero FJ, et.al. Spinal Cord, 2012 50, 895-898.