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Redesigning Adult Monitors for Use in Pediatric Anesthesia

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Children's Health Medical Center at Dallas

Conflict of interests

- Masimo Corporation Scientific Advisory Board
- Research grants from
  - Masimo Corporation,
  - West-Word Pharmaceuticals
  - B. Braun Medical Inc.
  - ENDO Pharmaceutical
  - Teva Pharmaceutical Industries

- Monitoring and new technologies
- Pediatric device development and regulators
- Our experience with developing variables for use in pediatric anesthesia monitoring

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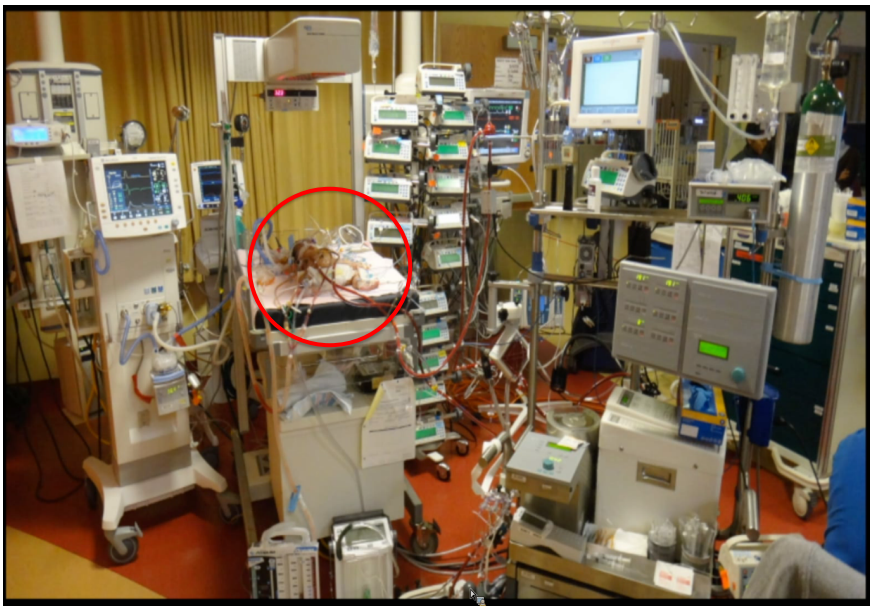
Monitoring

- "Patients who are admitted to hospital believe that they are entering a place of safety.

  They feel confident that, should their condition deteriorate, they are in the best place for prompt and effective treatment.

  Yet there is evidence to the contrary".

National Institute for Health & Care Excellence (NICE) in the UK.



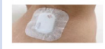
Ward monitoring 3.0

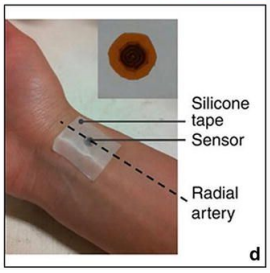
British Journal of Anaesthesia, 121 (5): 999–1001 (2018)

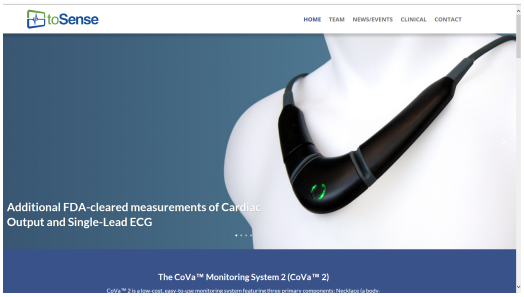
F. Michard[1,*] and D. I. Sessler[2]

- Ward monitoring 1.0 or intermittent spot checks
  - Sun Z et al.,2015 - continuous clinician-blind SpO_2 monitoring on surgical wards:
    - ✓ SpO_2 was <90% for more than 1 h in 33% of patients, and
    - ✓ SpO_2 was <90% for more than 6 h in 10% of patients.
  - Nurses who measured vital signs every 4 h missed 90% of the hypoxemic episodes lasting at least 1 h.
- Ward monitoring 2.0 or continuous bedside monitoring
  - Taenzer et al, 2010, continuously monitored HR and SpO_2 in 2841 patients recovering from orthopedic surgery, most of whom were given opioids.
  - There were fewer rescue events and critical care transfers than in parallel control wards
- Ward monitoring 3.0 or continuous (and wireless) monitoring

Table 1 Examples of medical-grade adhesive patches for physiologic monitoring. BP, blood pressure; HR, heart rate; PR, pulse rate PWTT, pulse wave transit time; SpO_2, peripheral capillary oxygen saturation; T, temperature

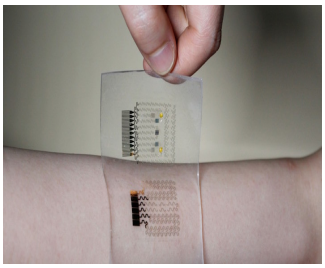
	Company website	Sensor(s)	PR/HR	ECG	Ventilatory frequency	SpO_2	BP	T
	Intelesens.com	Chest patch (x2)	+	+	+			Skin
	Irhythmtech.com	Chest patch	+	+				
	Isansys.com	Chest patch	+	+	+			
	Medicompinc.com	Chest patch	+	+				
	Medtronic.com	Chest patch	+	+				
	Pmd-solutions.com	Chest patch			+			
	Preventicesolutions.com	Chest patch	+	+	+			
	Raiing.com	Axillary patch						Axilla
	Sensium.co.uk	Chest patch, axillary thermistor	+		+			Axilla
	Smartcardia.com	Chest patch	+	+		+	PWTT	Skin
	Vitalconnect.com	Chest patch	+	+	+			Skin

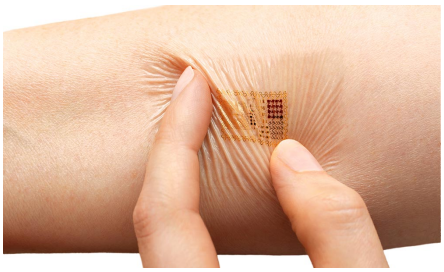




BioStamp

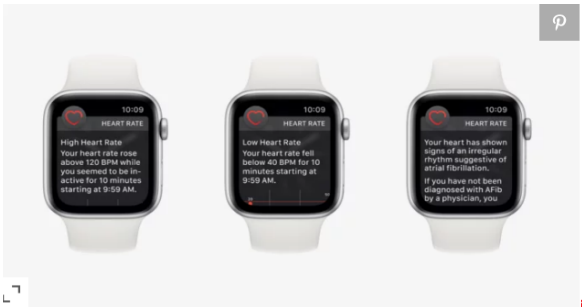
- Collect medical grade, clinical quality bio-metric, physiological data which offers a new way to quantify treatment efficacy.





Apple Watch, Series 4

- Series 4, → a personal ECG,
- In collaboration with Stanford - Apple Heart Study for arrhythmia in more than 400,000 volunteers, all wearing an Apple Watch for periodical checks
- Tim Cook: “Apple’s largest contribution to mankind will be in improving people’s health and well-being,”



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Ward monitoring 3.0

British Journal of Anaesthesia, 121 (5): 999–1001 (2018)

F. Michard[1,*] and D. I. Sessler[2]

- Avoidable deaths on hospital wards remain all too common.
- Many should be prevented by continuous vital sign monitoring.
- Venture capitalists invested a record $10.8 billion last year in startups working in health-related fields like biotech and genetics
- Wireless and wearable sensors can help as patients poorly tolerate tethered monitors.
- Although many technical solutions already exist to monitor vital signs wirelessly, validation studies remain scarce.
- Major trials are needed to determine whether wireless and wearable sensors accurately monitor vital signs, avoid excessive false alarms, detect clinical deterioration sufficiently early to allow effective intervention, and reduce serious adverse outcomes
- Pediatric patients will highly benefit from wireless monitoring

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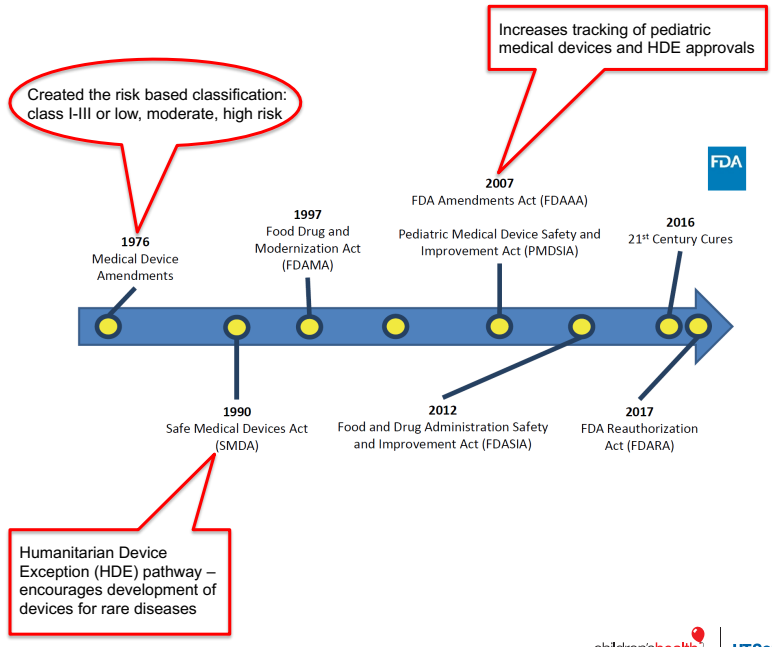
- Monitoring and new technologies
- **Pediatric device development and regulators**
- Our experience with developing variables for use in pediatric anesthesia monitoring



H.R.2430 - FDA Reauthorization Act of 2017
TITLE V--PEDIATRIC DRUGS AND DEVICES

- The bill
  - revises requirements for the FDA to report on pediatric use of medical devices.
  - extended and revised the authorization for certain medical devices for pediatric patients to be sold above cost under the humanitarian device exemption.
  - extended and revised grants for consortia to facilitate development of pediatric medical devices.
- The FDA had to convene a meeting on the development, approval, and labeling of pediatric medical devices.

FDA convened a public meeting and workshop August 13–14, 2018

- Reason:
  - the scarcity of medical devices that are designed specifically for the pediatric population,
  - to delve into the financial, regulatory, and design constraints associated with this challenging endeavor
- While there are many barriers to the development of pediatric-specific devices, FDA and industry is committed to developing innovative pathways and solutions to promote bringing pediatric devices to market.

FDA reports to Congress for the last decade

- 380 approved medical device applications
- 56 (15%) were approved to treat, diagnose or cure disease in pediatrics
- 21% approved with an indication for pediatric population
- 2% of the applications approved were solely for use in pediatrics

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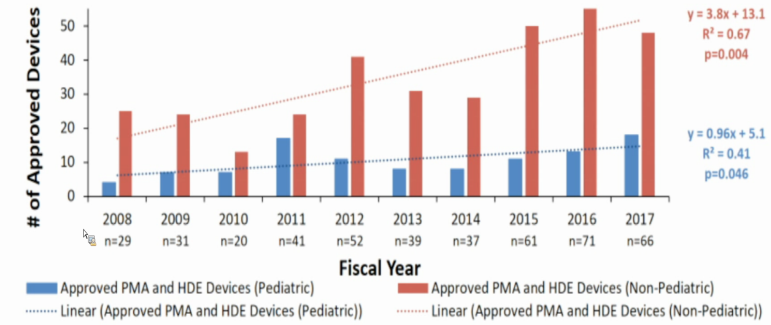
Adult Devices Increasing Faster than Pediatric



Upward trajectory in the total number of PMA and HDE applications
Adult approvals significantly greater than pediatric approvals

www.fda.gov

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- Development of pediatric medical devices lags behind adult devices by 5-10 years.

What are the hurdles in developing innovative products for children?

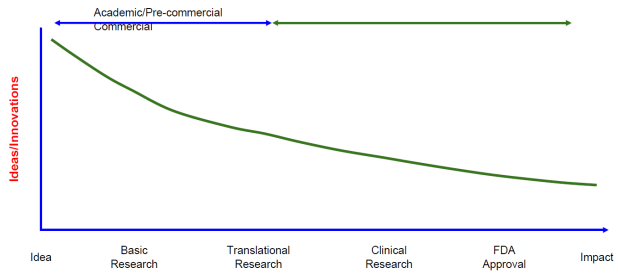
- The main challenge - small market size, which makes it unattractive
- There is need for:
  - Creative incentives and the availability of non-dilutive funding for early- and mid-stage pediatric device development
  - Specific regulatory process used to evaluate pediatric devices
- An exclusive regulatory path that incorporates data extrapolation and alternative statistics models for safe and effective pediatric medical device development could provide the right incentives.

How can regulators help?

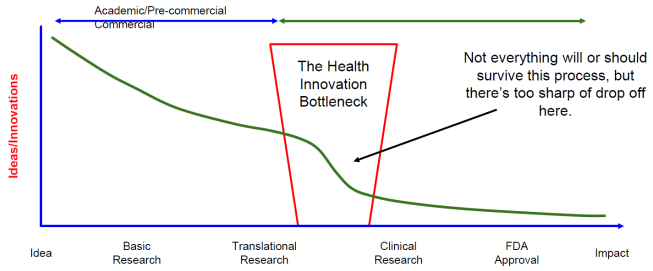
- Incentives and regulations have worked in the drug development world.
- "There are far fewer incentives available as either carrots or sticks to prod investment in devices" for the pediatric population.- *FDA Commissioner Margaret Hamburg, MD,*
- Incentives applied to pediatric drugs can serve as a model,
- There are differences between pharmaceutical and device development:
  - The 6-month period of pediatric exclusivity drug makers to encourage development of products for children do not work with medical devices.
  - There are multiple modifications throughout the development lifecycle.
  - Once a medical device makes it to the market, it may become obsolete and replaced by an improved product in as little as 18 months.
- There are startups and small businesses that are specifically focused on pediatric device development, and the FDA wants to work with them.

Early stage investor in pediatric devices

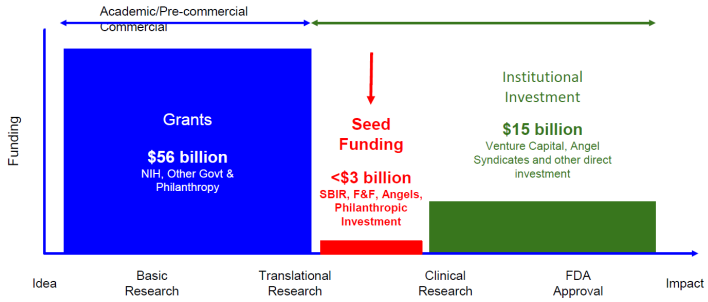
What's the problem? We expect this:



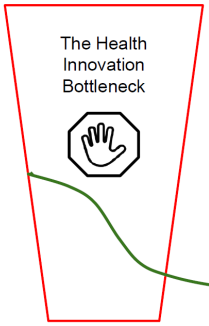
What's the problem? We have this:



Why the bottleneck?

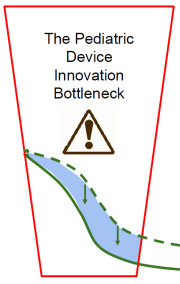


All new health technologies have risk



- Scientific Risk
- Pathway Risk
- Management Risk
- Time risk
- Valuation

And it's even tougher with pediatric devices



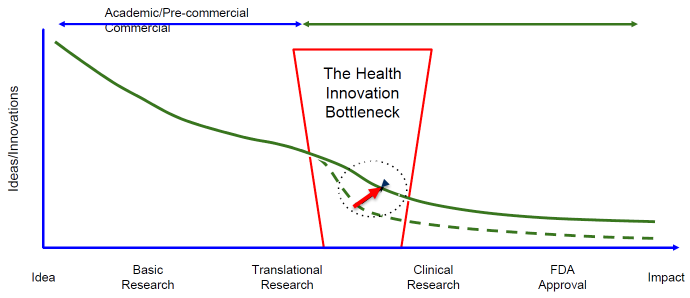
- Harder to scale
- Fewer and smaller exits
- Fewer economic incentives
- Greater lack of investor Interest
  - No home runs
  - No "curb appeal"

No wonder it's hard to attract investors

- There are simply
  - Easier
  - More profitable
  - Less risky, and
  - More exiciting

…ways to make money than to invest in pediatric devices

Multiple pieces needed to make a difference



VIEWPOINT

The Emerging Market of Smartphone-Integrated Infant Physiologic Monitors

JAMA January 24/31, 2017

- In the past 2 years, - a new class of infant physiologic monitors marketed to parents for use in the home
- Smartphone apps integrated with sensors built into socks, buttons, leg bands, and diaper clips have the capability to display infants' respirations, pulse rate, and blood oxygen saturation, and to generate alarms for apnea,

Table. Features of Consumer Infant Physiologic Monitors With Smartphone Integration

	Monitor Brand Name				
	Baby Vida	MonBaby	Owlet	Snuza Pico	Sproutling
Location of device	Sock	Button	Sock	Diaper clip	Leg band
Pulse rate	Yes	No	Yes	No	Yes
Respiratory motion	No	Yes	No	Yes	No
Pulse oximetry	Yes	No	Yes	No	No
Cost, $	150	170	250	Not announced	300

- The makers of consumer infant physiologic monitors have avoided FDA medical device regulation by not making claims that the devices prevent SIDS.
- One company reportedly intended to sell its products as medical devices and was planning to pursue FDA approval but later changed its mind reportedly because of the time and expense required.

VIEWPOINT

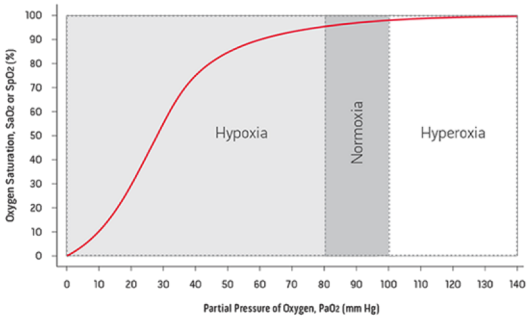
The Emerging Market of Smartphone-Integrated Infant Physiologic Monitors

JAMA January 24/31, 2017

- Smartphone apps integrated with sensor that monitor infants' vital signs are innovative and have potential to improve care.
- Unknown performance characteristics
- There are no current medical indications for their use.
- There is no evidence that consumer infant physiologic monitors are life-saving, and there is potential for harm if parents choose to use them.
- Child and family advocates should make it clear to the FDA and policy makers that regulatory guidance and research evaluating the safety, accuracy, and effectiveness of these products are needed.

- Monitoring and new technologies
- Pediatric device development and regulators
- Our experience with developing variables for use in pediatric anesthesia monitoring

Limitations of pulse oximetry



Pulse oximetry – no evidence of improving outcome but increases safety and decreased the number of claims. Pedersen T, Cochrane Database Syst Rev. 2014;3:CD002013

What is Oxygen Reserve Index - ORI?

- ORI non-dimensional index that ranges from 0.0 to 1.0 as the PaO_2 increases from 80 to 200 mmHg.
- Measured with a multiple wavelength pulse co-oximeter sensor (R1 25L) connected to a Radical-7 pulse oximeter Masimo Rainbow SET technology
- Arterial & venous pulsatile signals are extracted, enabling optical detection of changes in PaO_2 relative to changes in SvO_2 at the measurement site.

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Dallas, Texas

ORI - Principles of measurement

- ORI algorithm combines the Fick formula* with oxygen content equation* & absorption properties of arterial & venous hemoglobin

$$\text{Fick - } VO_2 = CO \times (CaO_2 - CvO_2)$$

$$\text{Oxygen content – } VO = CO \times (SaO_2 \times tHb \times 1.34) + 0.003 \times (PaO_2)$$

- With extra O_2 supply, as PaO_2 increases >100, SvO_2 continues to increase, even though SaO_2 has saturated at 100%, if **O_2 consumption, hemoglobin & cardiac output are stable.**
- This modest increase in **SvO_2 > 75% will eventually stop at 80%** as PaO_2 reaches significantly higher values (>200 mmHg).

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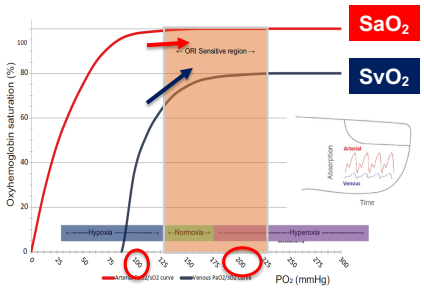
Dallas, Texas

ORI - Principles of measurement - summary



As PaO_2 increases to ~ 100 mmHg SaO_2 maximizes (~100%) while SvO_2 at the measurement site continues to increase (from ~75% to ~80%) until it stabilizes at a PaO_2 of ~200mmHg.

The resulting change in light absorption over this PaO_2 range is the basis for the ORI calculation

From T.W.L Scheeren et al. 2017

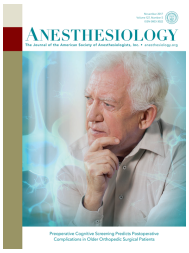
Oxygen Reserve Index

A Novel Noninvasive Measure of Oxygen Reserve—A Pilot Study

Peter Szmuk, M.D., Jeffrey W. Steiner, D.O., Patrick N. Olomu, M.D., Roxana P. Ploski, B.S., Daniel I. Sessler, M.D., Tiberiu Ezri, M.D.

Anesthesiology 2016; 124:779-84

- 25 healthy patients
- Age 7.6 ± 4.6 years



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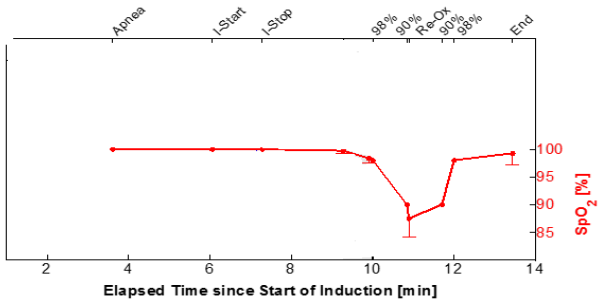

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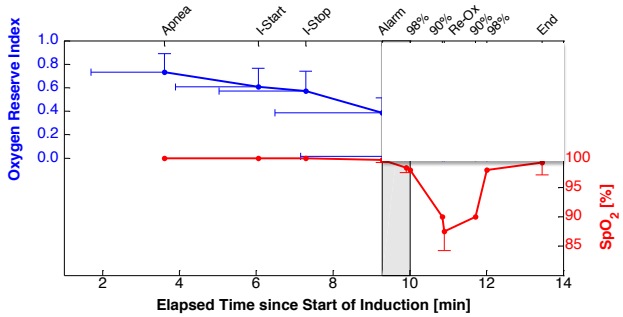
- ORI slowly and progressively decreased over a mean of 5.9 ± 3.1 min from 0.73 ± 0.2 at the beginning of apnea to 0.4 ± 0.1 when the ORI began to decrease rapidly. Spo2 remained 100% throughout this initial period



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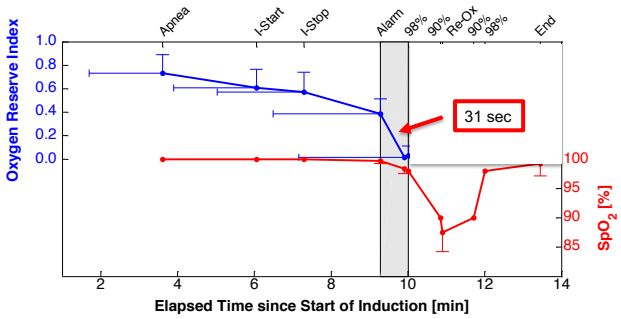
ORI began to decrease rapidly, and in median of 31.5 s (IQR, 19 to 34.3 s), saturation decreased to 98%.



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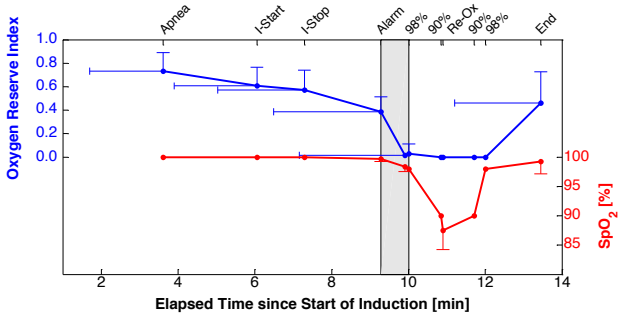
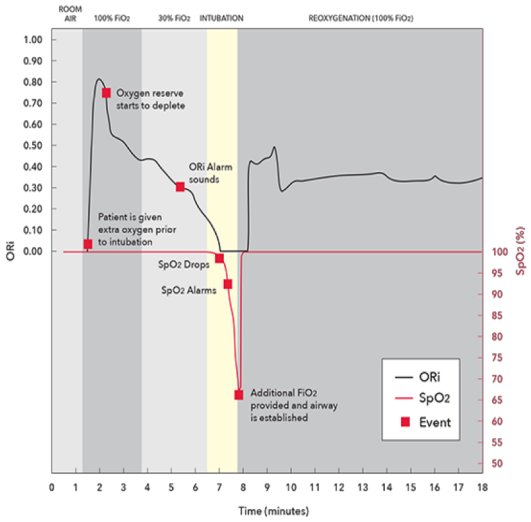


ORI detected impending desaturation in median of 31.5 s (interquartile range, 19–34.3s) before noticeable changes in SpO_2 occurred.



Challenges with re-designing monitoring devices from adults to pediatric patients

- Inability to get a stable reading as children tend to move their hands and feet more often than not.
- Movement introduces noise into the system and the pleth signals get corrupted.
- Dynamic parameters like pleth variability index (Pvi) cannot be used as is on peds as their hemodynamic response is different from that of adults and correlating the same pleth amplitude changes to fluid volume status might result in inaccurate measurements

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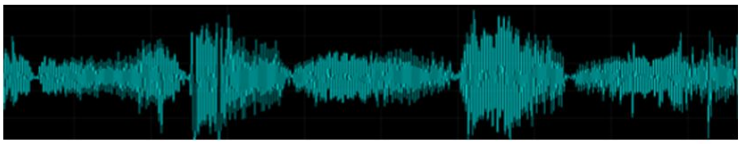
Acoustic Respiratory Monitor (RAM)



Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

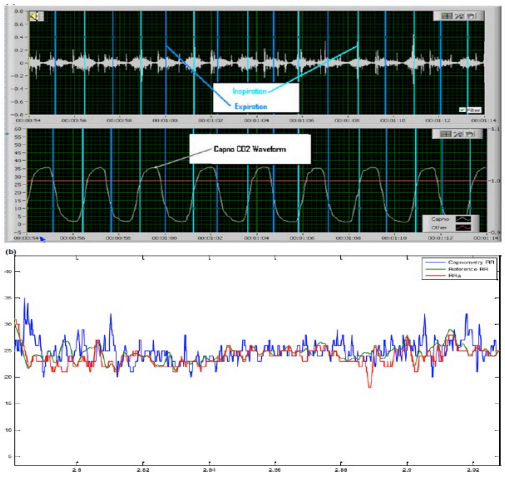
2013 Dec;23(12):1166-73.

ORIGINAL ARTICLE

Accuracy of acoustic respiration rate monitoring in pediatric patients

Mario Patino[1], Daniel T. Redford[2], Thomas W. Quigley[2], Mohamed Mahmoud[1], C. Dean Kurth[1] & Peter Szmuk[3]

- 57 patients, 1,2-15 y.o.
- When compared to nasal capnography, RRa showed good agreement and similar accuracy and precision but was better tolerated in postsurgical pediatric patients.



Comparison of Postoperative Respiratory Monitoring by Acoustic and Transthoracic Impedance Technologies in Pediatric Patients at Risk of Respiratory Depression

(Anesth Analg 2017;124:1937–42)

Mario Patino, MD,* Megan Kalin, MS, CCRP, * Allison Griffin, MS,† Abu Minhajuddin, PhD,‡ Lili Ding, PhD,§ Timothy Williams, MS,‖ Stacey Ishman, MD, MPH,¶ Mohamed Mahmoud, MD,* C. Dean Kurth, MD,*# and Peter Szmuk, MD**††

- 58 children, 6.5 ± 3.4 y.o. post T&A,
- Had preoperative severe OSA - at risk of postoperative respiratory depression,
- RR assessment by RAM was not different to manual counting.
- RAM was well tolerated, had a lower incidence of false alarms, and had better specificity and positive predictive value than TI.

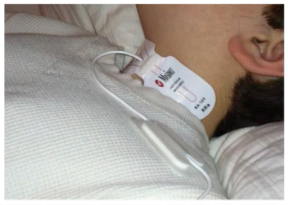


Figure 2. Respiratory acoustic sensor placed in a patient's neck.

Respiratory Acoustic Monitor (RAM)

	Accuracy (A_{RMS}	Range Respiration per minute	Sensor Design	Sensor Placement
Adult/Pediatric	1	4 to 70	Rectangular	Neck
Infant/Neonatal	1	1 to 120	Circular	Chest

SedLine Brain Function Monitoring

EEG in infants

- In infants <6 m. o., neural network regulation by anesthesia is weak due to insufficient early development of the CNS, as reflected in:
  - the unique burst suppression pattern of neonatal EEG
  - low sensitivity of EEG to anesthesia .

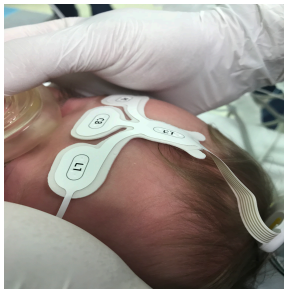
Hayashi K et al, 2012

- any EEG-derived anesthesia depth monitor that uses adult algorithms is very unlikely to provide equivalent information in infants <6 m. of age
- any EEG-derived index developed in infants will need to use fundamentally different EEG parameters.

Davidson AJ et al, 2008

Incidence of isoelectric EEG events during routine pediatric anesthesia.
Clark N, Gonzalez A, Zhong J, Griffin A, Rivera K, Szmuk P
SPA, 2017

- 44 patients, age 11.1±4
- Isoelectric EEG
  - 71% at least one episode
  - 64% - 2 episodes
  - 59% - 3 episodes
  - 16%- >10 episodes



- 85.3% occurred during induction or between induction and the start of the procedure.
- This deep level of anesthesia is due to the high Sevoflurane concentrations used for induction, often supplemented by IV anesthetics and scarce use of muscle relaxants

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Conclusions

- Few medical devices have pediatric specific indications and labeling
- There is little change in the pediatric devices approval/ 10 years
- The chief challenge - small market size
- For pediatric device development, there is need for:
  - exclusive regulatory pathways
  - specific incentives and regulations
- Off-label pediatric devices use is necessary and will continue until sufficient pediatric specific devices are available.
- Challenges in using adult monitors in pediatric patients:
  - Anatomical differences requiring sensor size change or new design
  - Instability due to movement

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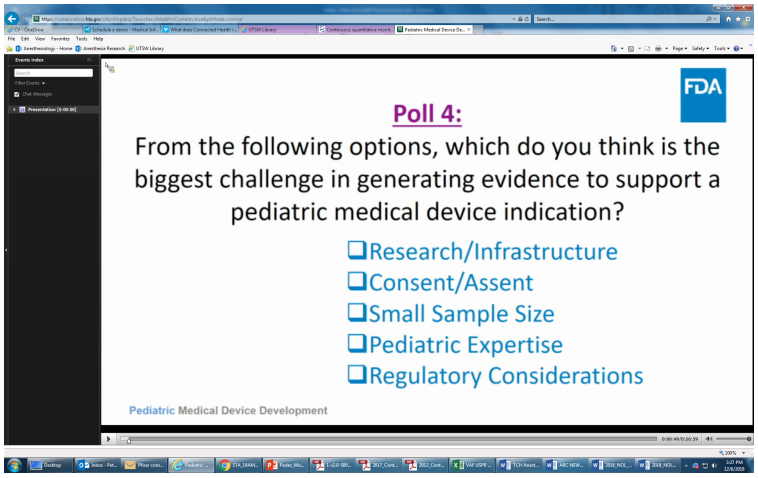
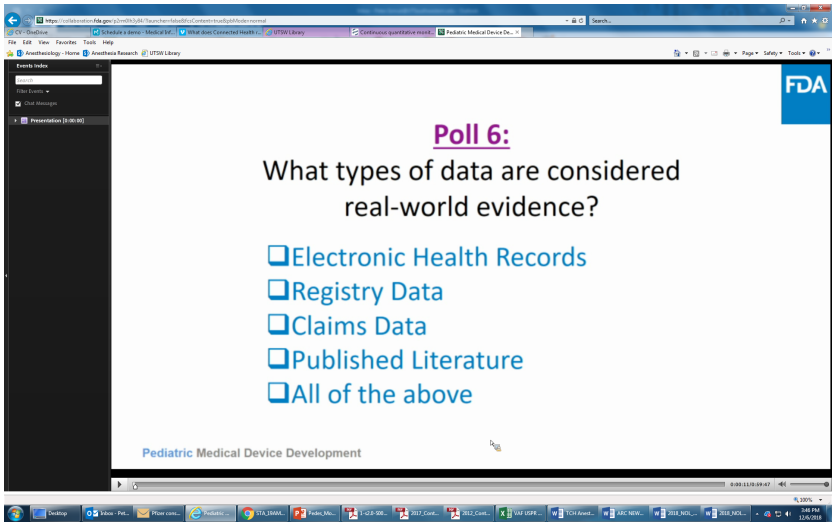
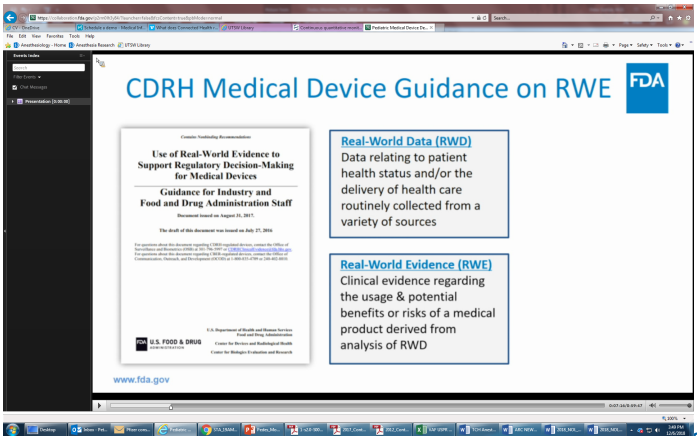
There can be no keener revelation of a society's soul than the way in which it treats its children.

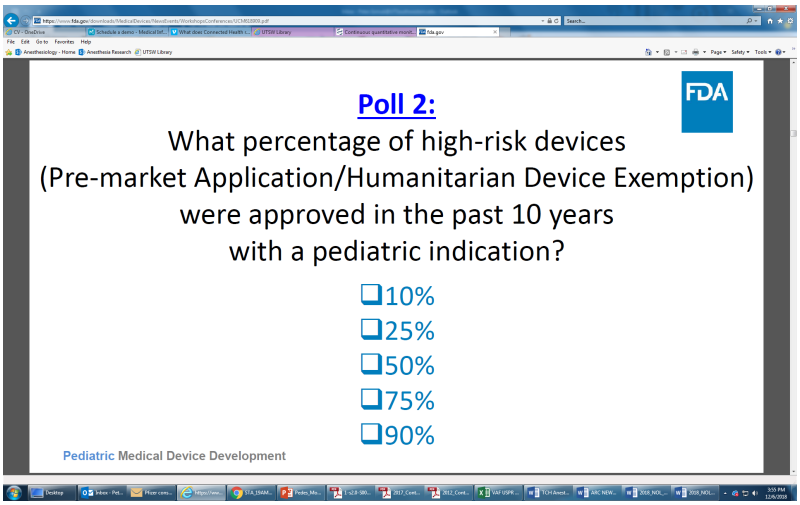
Nelson Mandela

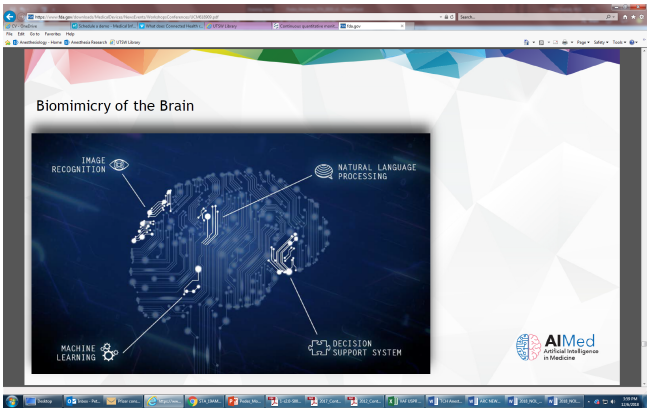


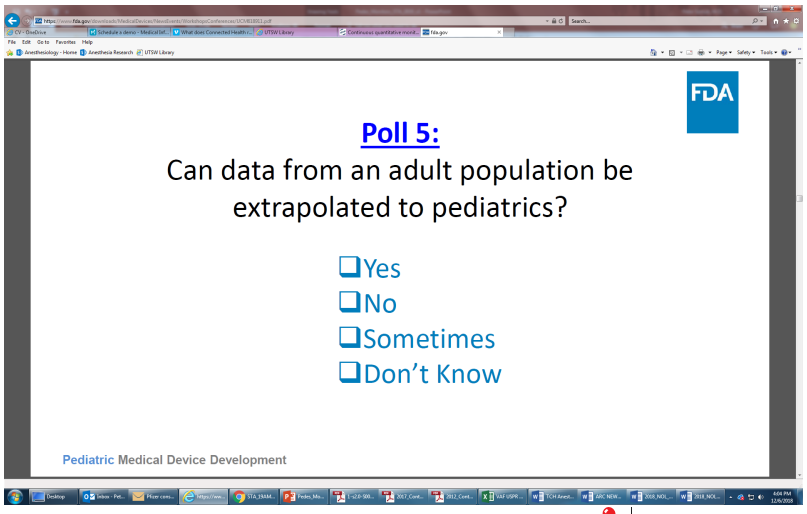


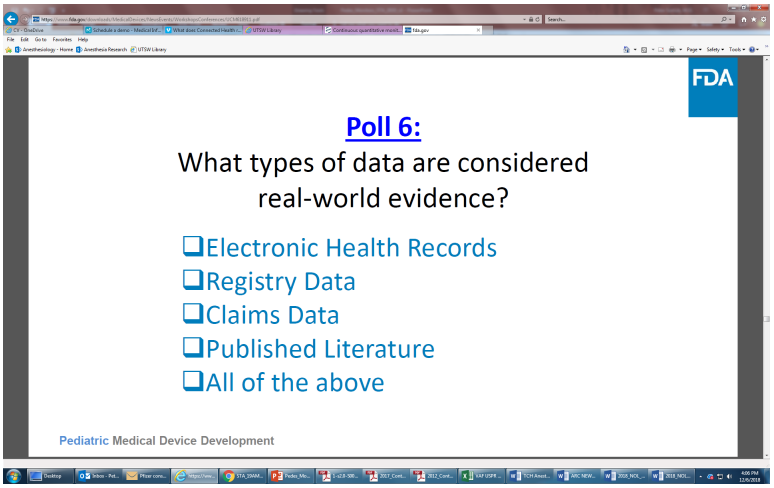
The Center for Devices and Radiological Health (**CDRH**) is the branch of the United States Food and Drug Administration (FDA) responsible for the premarket approval of all medical devices, as well as overseeing the manufacturing, performance and safety of these devices.

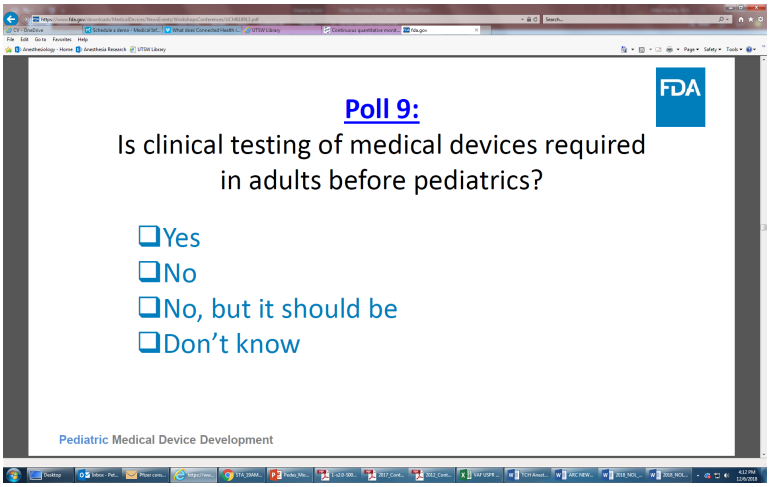



Poll 2:
What percentage of high-risk devices
(Pre-market Application/Humanitarian Device Exemption)
were approved in the past 10 years
with a pediatric indication?
❑10%
❑25%
❑50%
❑75%
❑90%
Pediatric Medical Device Development


Biomimicry of the Brain
IMAGE RECOGNITION
NATURAL LANGUAGE PROCESSING
MACHINE LEARNING
DECISION SUPPORT SYSTEM
AIMed


FDA
Poll 5:
Can data from an adult population be extrapolated to pediatrics?
❑Yes
❑No
❑Sometimes
❑Don't Know
Pediatric Medical Device Development


FDA
Poll 6:
What types of data are considered real-world evidence?
❑Electronic Health Records
❑Registry Data
❑Claims Data
❑Published Literature
❑All of the above
Pediatric Medical Device Development



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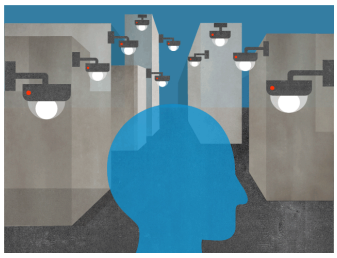

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