SIGNIFICANT RISK VS. NONSIGNIFICANT RISK DEVICES:

WHAT'S THE DIFFERENCE & WHY DOES IT MATTER?

presented by:

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Carlsbad, California

and

Adjunct Professor of Regulatory Science, Medicine and Biomedical Engineering
Cornell University Graduate Dept. of Biomedical Engineering

GreenLight.Guru (February 15, 2024)

https://www.greenlight.guru/webinar/significant-vs-nonsignificant-risk-devices

For questions or more information, call
(508) 887 – 9486 or e-mail mdrues@vascularsci.com

SIGNIFICANT RISK VS. NON-SIGNIFICANT RISK DEVICES:

What's the difference and why does it matter?

presented by: ***Michael Drues, Ph.D.***

In the US, there are three *independent* but also *interdependent* systems to categorize the risk a medical device poses. Perhaps the best known is the classification system, i.e., Class I, Class II and Class III. A second system is the Software Documentation Level, i.e., basic or enhanced system (formerly known as the Software Level of Concern, i.e., Class A, Class B or Class C system). Finally, the third important but seldom talked about risk system is the Significant Risk (SR) vs. Non-Significant Risk (NSR) system.

There is plenty of information available on the classification and software risk systems as well as SR devices, e.g., their regulatory requirements and the IDE process. However, there is much less available on how to handle an NSR device. Given that the vast majority of devices are NSR, what is a manufacturer of a NSR device to do?

Using his unique signature style, Dr. Drues will use the case study approach to take a detailed looked at the various risk systems focusing on the SR vs. NSR system including:

- What is a significant risk (SR) vs. non-significant risk (NSR) device?
- How does the SR vs. NSR system compare to the other systems of risk?
- Who determines if my device is SR or NSR and how is the determination made?
- Why does SR vs. NSR matter? What are the requirements of each?
- If my device is SR, what do I do? If my device is NSR, what do I do?
- When and how should you take my SR vs. NSR determination to the IRB(s) and/or FDA?
- Does my device need a clinical trial? How are clinical trials different for SR vs. NSR devices?
- How should I select clinical trial sites and IRB's?
- Is there a template for the SR vs. NSR determination?
- Should I do a pre-submission meeting with FDA for an NSR device even though it's *not* required?
- What are the challenges for the future?

Using the case study approach, participants will learn best practices to avoid timely and costly mistakes as well as creative ways to use the SR vs. NSR system to their advantage!

Additional Resources

- Podcast: *3 systems of Risk* (Mike on Medtech, Sept, 2021) here.
- Podcast: *3 Systems of Risk for Medical Devices from FDA* (April, 2021) here
- Presentation: *Risks that No One Wants to Talk About* here
- Webinar: *The Many Connotations of Risk and the Consequences of Getting Them Wrong* (Mar, 2017) here.
- Podcast: *Significant Risk vs. Non-Significant Risk Devices – What's the Difference?* (Feb, 2017) here
- Podcast: *Using the Bucket Method for Medical Device Risk Management* (Dec, 2016) here.
- Column: *The Many Connotations Of Risk and the Consequences of Getting Them Wrong* (Aug, 2015) here.

Additional columns, articles, podcasts and webinars can be found: Global Medical Device Podcast (GreenLight.Guru) here, Mike on MedTech (Medical Product Outsourcing) here, Medical Design and Outsourcing here, Guerilla Regulatory Strategy (MED Device Online) here and Healthcare Packaging here or LinkedIn here.

Presenter Bio

Michael Drues, Ph.D., is a regulatory strategy consultant specializing in designing novel regulatory strategies to bring new and innovative medical products to market and in developing effective communication strategies between companies and regulatory agencies to minimize time to market and avoid delays.

Dr. Drues received his B.S., M.S., and Ph.D. degrees in Biomedical Engineering from Iowa State University. He works with leading medical device, pharmaceutical and biotechnology companies ranging in size from start-ups to Fortune 100 companies. He also works on a regular basis for the U.S. Food and Drug Administration, Health Canada, the US and European Patent Offices, the Centers for Medicare and Medicaid Services and other regulatory and governmental agencies around the world.

Dr. Drues is an internationally recognized expert and featured keynote speaker on cutting-edge medical technologies and regulatory affairs. He conducts seminars and short-courses for medical device, pharmaceutical and biotechnology companies, the FDA, Health Canada, the US and European Patent Offices, CMS and other regulatory and governmental agencies around the world.

Finally, Dr. Drues is an Adjunct Professor of Regulatory Affairs, Medicine and Biomedical Engineering at several universities and medical schools. He regularly teaches graduate courses in Regulatory Affairs and Clinical Trials, Medical Device Regulatory Affairs and Product Development, Combination Products and Pathophysiology.

Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

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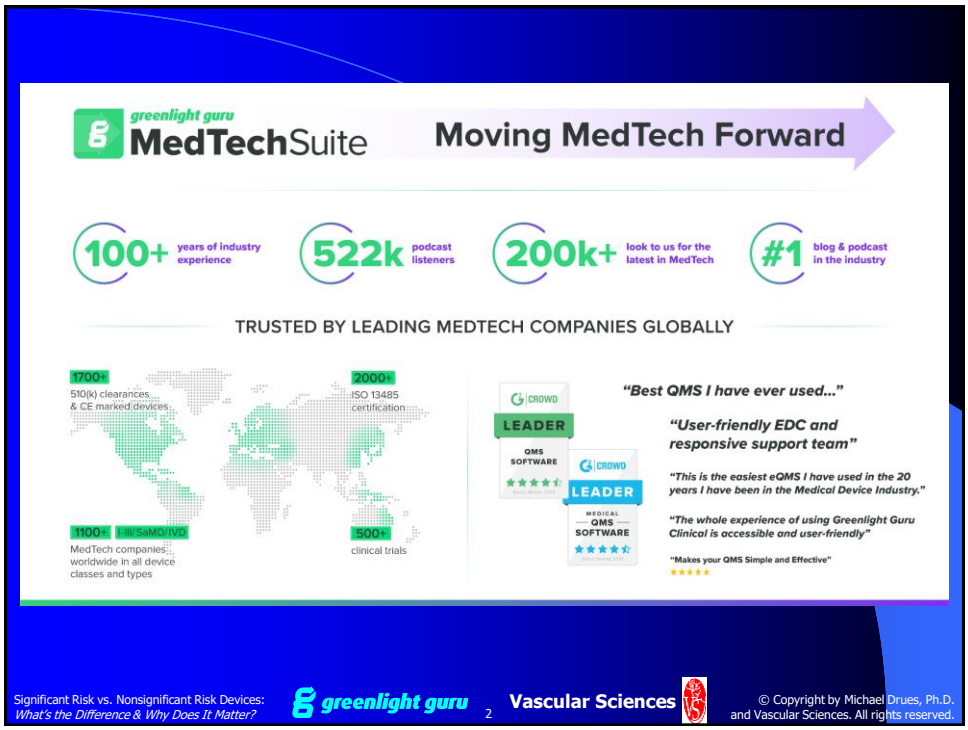

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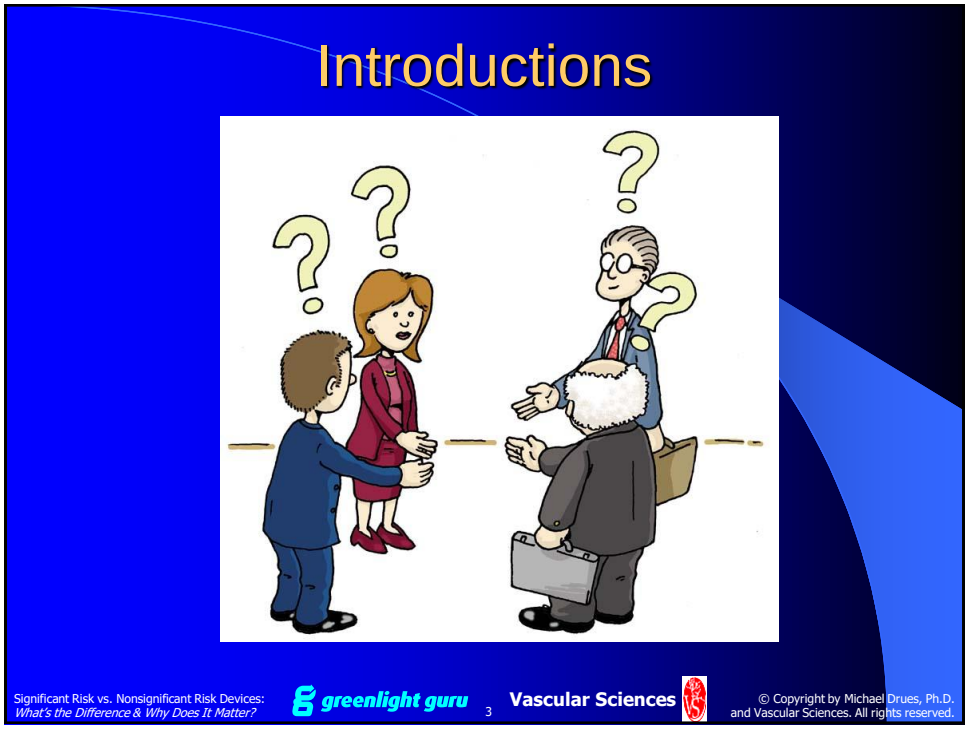

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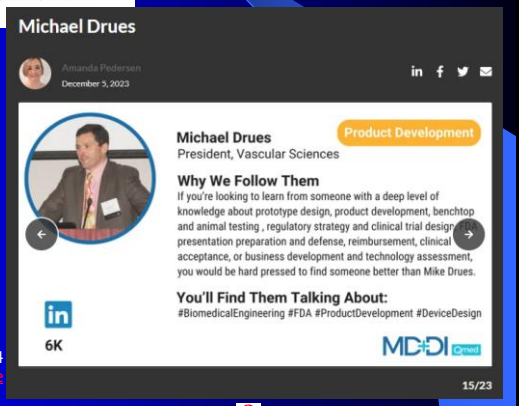
Not bragging but…



from 24 Medtech Voices to Follow in 2024 (MDDI, Dec 5, 2023) here

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First, an important disclaimer…

I can't make you an expert in a few minutes!

I'm not even going to try but…

Remember my philosophy of education:

To teach you how to think not what to think!

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Significant Risk vs. Nonsignificant Risk Devices:

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Is it possible to think regulatory?

"Science is a way of thinking much more than it is a body of knowledge."

Carl Sagan (1934–1996)
American astronomer, author and science journalist

So how about this?

"Regulatory affairs is a way of thinking much more than it is a body of rules and regulations – or at least it should be!"

Michael Drues (1964–)
Regulatory Strategist and Amateur Philosopher ☺
www.meddeviceonline.com/author/michael-drues

Maybe Carl Sagan would be proud!

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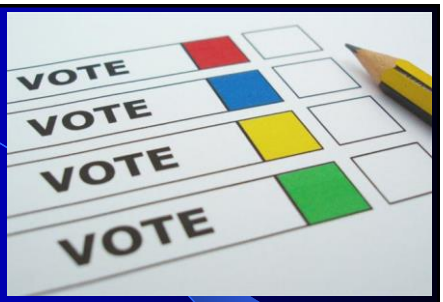
Before we begin…

Polling Questions



Are you working on a significant risk (SR) device? (y/n)

Are you working on a non-significant risk (NSR) device? (y/n)

Do you know the difference? (y/n)

Are you sure? ☺ (y/n)

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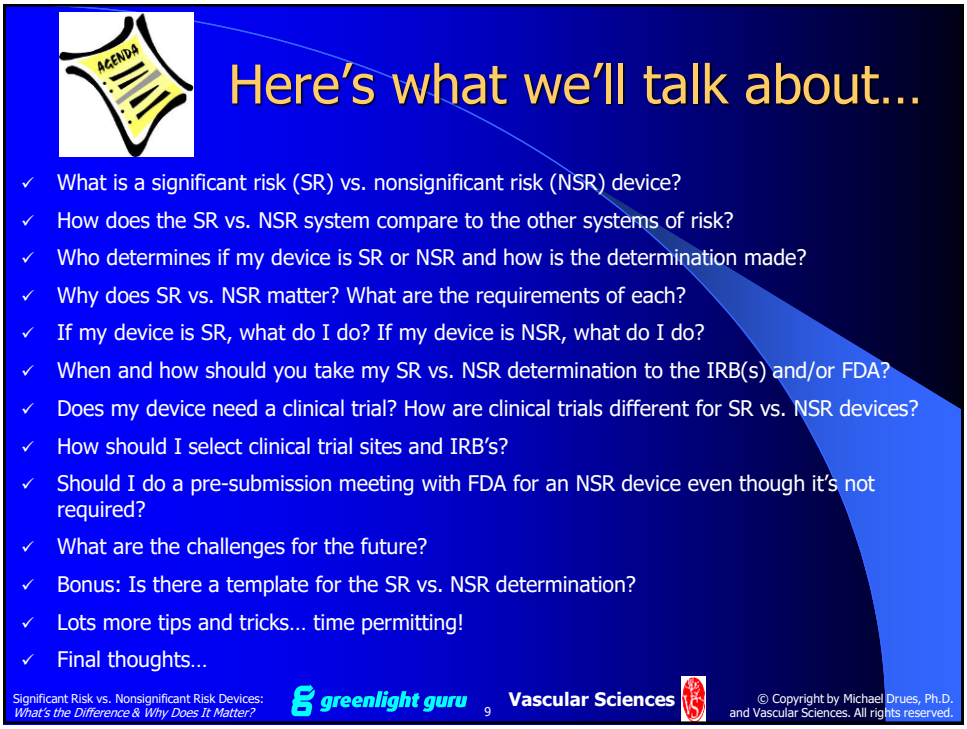

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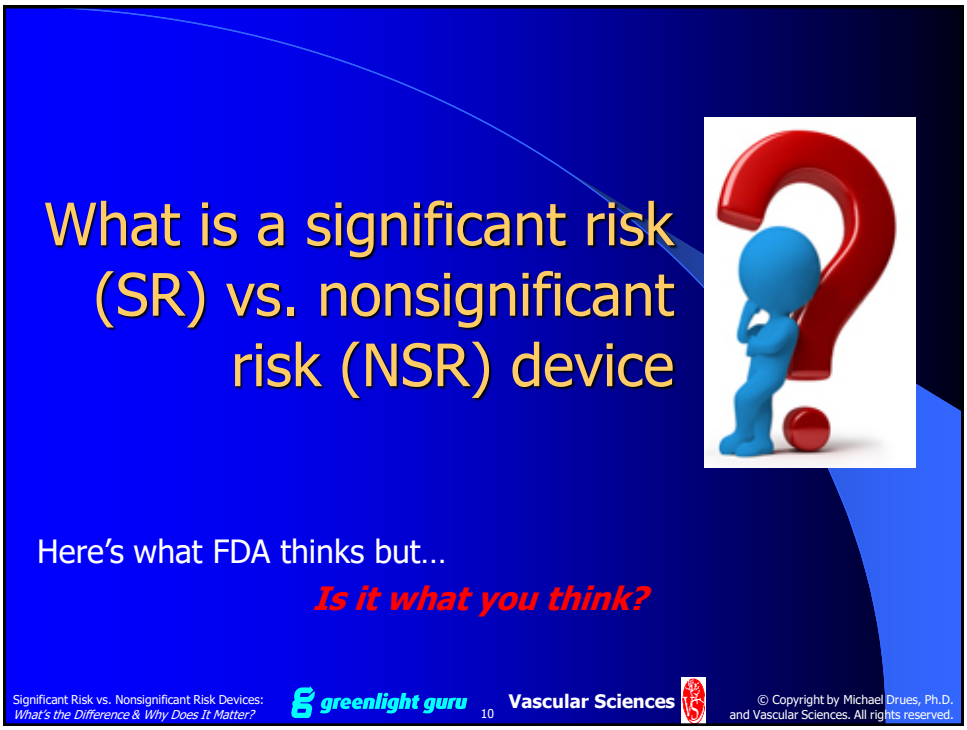

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Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

What is a Significant Risk (SR) Device?

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- ✓ Is **intended as an implant and presents a potential for serious risk to the health, safety, or welfare** of a subject;

Hmmm… what is an implant? Note does not specify permanent implant.

- ✓ Is purported or represented [i.e., intended] **to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare** of a subject;

Hmmm… what does "supporting or sustaining human life" mean?

- ✓ Is **for a use of** [i.e., intended for] **substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject**; or

Hmmm… what does "substantial importance" mean? what does "impairment of human health" mean?

- ✓ Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Note redundancy… why limit to "subject" i.e., patient?

Examples of SR Devices

Surgical Lasers, Tissue Adhesives, Cardiac Bypass Devices, Intravascular Stents, etc.

Note: *SR not limited to Class III devices!*

FDA Website SR Devices here.

Guidance: *Significant Risk and Nonsignificant Risk Medical Device Studies: Guidance For IRBs, Clinical Investigators, and Sponsors* (Jan, 2006) here.

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What is a Non-Significant Risk (NSR) Device?

Under 21 CFR 812.3(m), an NSR device means an investigational device that:

"…does not meet the definition for an SR device." – *nothing else said!*

Does this help?

Examples of NSR Devices

Contact Lens Solutions, Dental Filling Materials, Digital Mammography, Ureteral Stents, etc.

Mike's Recommendation:

Start by assuming your device is SR… then prove its not!

FDA Website NSR Devices here

Guidance: *Significant Risk and Nonsignificant Risk Medical Device Studies: Guidance For IRBs, Clinical Investigators, and Sponsors* (Jan, 2006) here..

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Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

How does the SR vs. NSR system compare to the other systems of risk

Short answer:

They do NOT compare!

…other than by categorizing risk of course.

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Podcast: Three Systems of Risk

Podcast here.

Highlights:

- Three systems for risk: classification, SR vs. NSR, Basic/Enhanced Documentation (formerly sLOC)
- Classification system stratifies risk in layers (i.e., classes), e.g., Class I, II, or III
  - The higher the class, the higher the risk. The lower the class, the lower the risk
  - Gross oversimplification *and* there are a ton of exceptions
- Classification in US does not translate linearly to class in EU and elsewhere
  - Similar systems but are philosophically different, i.e., NSE (pun intended!)
- SR vs. NSR system important in clinical trials
  - Does device require an investigational device exemption (IDE) or is it IDE Exempt?
  - Determination of SR vs. NSR is not made by FDA or IRB but the medical device company.
    - Is this the fox in charge of the henhouse? Absolutely… but that's what the reg says!
- Basic/Enhanced Documentation (formerly sLOC, i.e., class a, b, and c) determines level of documentation required for software
- Reminder: Default classification for any new medical device is Class III.
- Reminder: When it comes to labeling, say anything you want… so long as you can support it. However, if same technology but different labeling, risk also changes (usually).

Three systems are independent and interdependent!

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Why does SR vs. NSR matter? What are the requirements of each

For SR Devices:

- ✓submit IDE to FDA and obtain FDA approval (§812.20) AND
- ✓submit investigational plan including prior investigations (§812.25 and §812.27) to each IRB

For NSR Devices:

- ✓submit investigational plan including prior investigations (§812.25 and §812.27) to each IRB
- ✓No IDE required (i.e. IDE Exempt)

…but take your NSR device to FDA anyway even though its not required! Why?

Reminders:

- ➢FDA considers a NSR device to have an "approved IDE" when IRB agrees with NSR determination and approves study – *how do you show this?*
- ➢If IRB disagrees with NSR determination, sponsor must notify FDA within five working days [§812.150(b)(9)] – *this is to be avoided! Why?*

IDE Approval Process here

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If my device is SR, what do I do? If my device is NSR, what do I do

In a nutshell…

- ✓ If device is SR, notify FDA (via IDE) *and* all IRB's
- ✓ If device is NSR, not required to notify FDA (IDE Exempt) but still notify all IRB's

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When and how should you take my SR vs. NSR determination to the IRB(s) and/or FDA

Just like pre-subs…

It's never to early but no earlier than when you are ready!

At the very least…

Identify clinical trial site(s), traditional vs. commercial IRB options, etc.

i.e., get your ducks in a row!

More specifically…

Anticipated Start Date – Average IRB Approval Time X Safety Factor

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Does my device need a clinical trial

Unlike many believe…

This is not a regulatory decision… at least not completely!

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Substantial Equivalence and Regulatory Burdon

Question: When is clinical data required?

Clinical data is never required!

A 510(k) requires demonstration of "substantial equivalence" to another legally U.S. marketed device (i.e., a predicate device). ***Substantial equivalence means that the new device is at least as safe and effective as the predicate.***

A device is substantially equivalent if, in comparison to a predicate it:

- has the ***same intended use*** as the predicate; and
- has the ***same technological characteristics*** as the predicate;

↓ regulatory burden → ↓ reliant on clinical data

or

- has the ***same intended use*** as the predicate; and
- has ***different technological characteristics*** and the information submitted to FDA;
- ***does not raise new questions of safety and effectiveness***; and
- demonstrates the device ***is at least as safe and effective*** as legally marketed device.

↑ regulatory burden → ↑ reliant on clinical data

In other words,

The more similar you are, the less you have to do… but is this a good thing?

Question: *do you want to swing for a single or swing for a home run?*

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How are clinical trials different for SR vs. NSR devices

Regardless of SR/NSR determination…

- ✓ Labeling - device must be labeled in accordance with IDE regulations (§812.5) and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."
- ✓ Distribution - Investigational devices can only be distributed to qualified investigators §812.43(b).
- ✓ Informed Consent - Each subject must be provided with and sign an informed consent form before being enrolled in the study (21 CFR 50, Protection of Human Subjects)
- ✓ Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols (§812.46)
- ✓ Prohibitions - Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited (§812.7).
- ✓ Records and Reports - Sponsors and investigators are required to maintain specified records and make reports to investigators, IRBs, and FDA (§812.140 and §812.150).

IDE Approval Process here

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Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

How should I select clinical trial sites and IRB's

That's really the subject of another webinar but here's a start… consider:

- ✓ Investigator/cite experience with same/similar devices
- ✓ Patient enrollment
- ✓ Average IRB approval time for your clinical area
- ✓ How often does IRB meet? How responsive (i.e., cooperative) are they?
- ✓ Traditional vs. Commercial IRB options?
- ✓ Economics, i.e., "indirect" costs
- ✓ PR Value of investigator and/or cite and/or key opinion leaders
- ✓ Many other factors to consider…

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Should I do a pre-submission meeting with FDA for an NSR device *even though it's not required*

Short answer:

Almost ALWAYS!

Why? Mitigate/eliminate two common problems:

- ✓ Confirm FDA agreement on SR vs. NSR determination
- ✓ Confirm FDA agreement on clinical trial design

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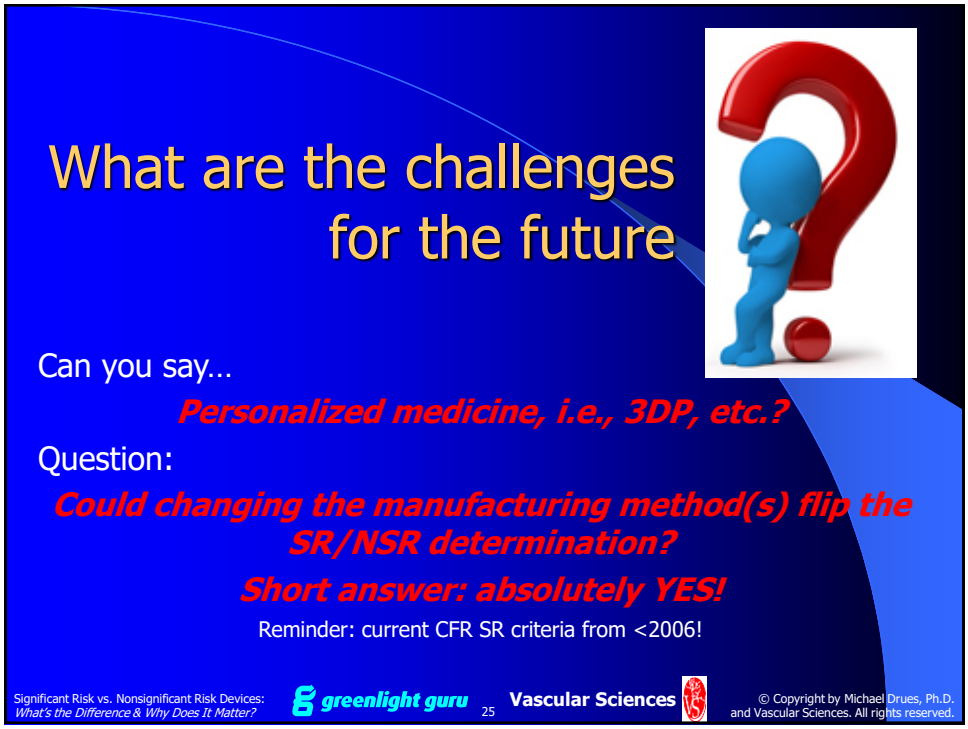

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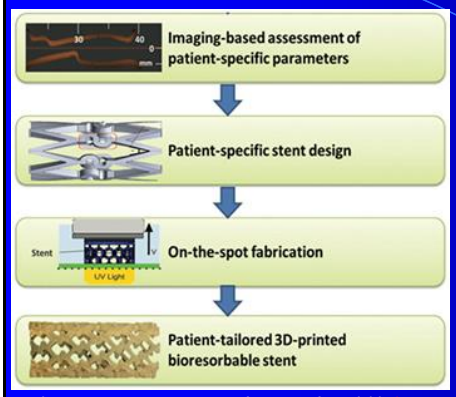
Can we 3DP a 'customized' vascular stent?



Northwestern Engineering News (Oct, 2016) available here.

Video: 3DP Vascular Stent (1 min)

Absolutely! Watch this…

Method:

micro continuous liquid interface production (microCLIP)

↓

liquid photo-curable resin to print objects with light

↓

fabricate stent precisely matching patient anatomy

Advantages:

- Extremely high res (print features small as 7μm)
- Print up to 100 stents at a time → faster/cheaper than traditional manufacturing
- Speed: print 4-cm stent in minutes

What's next?

How about a personalized (i.e., 3-D printed) *DES? – wicked cool!* ☺

Advantages: choose drug (drugs), dosage, release rates, location, etc.

Should FDA regulate this? If so, how?

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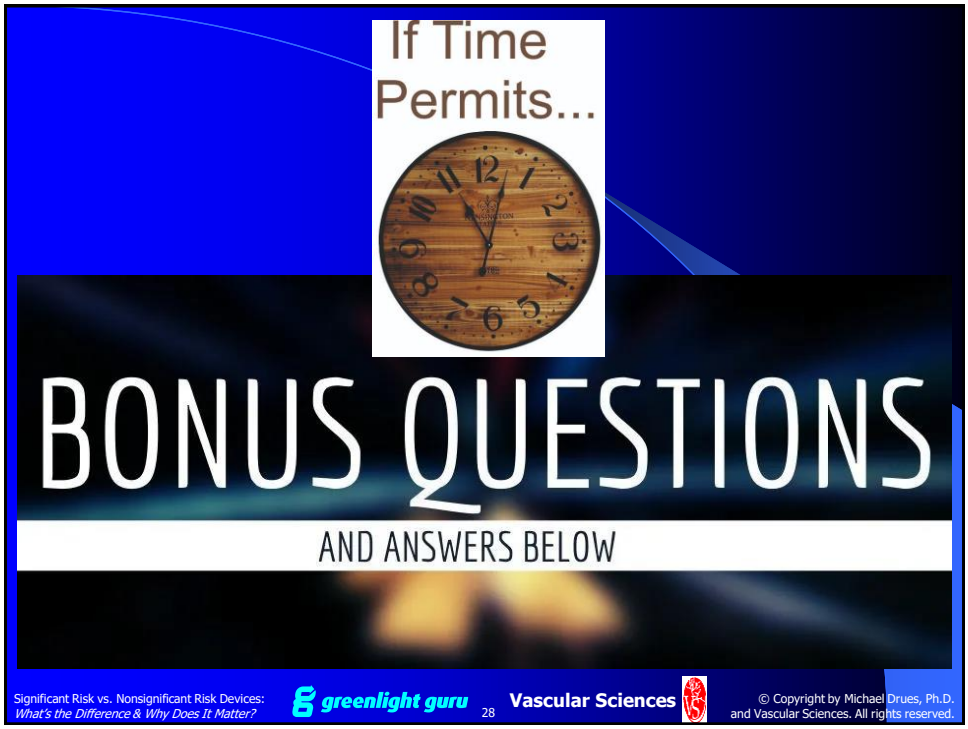

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Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

Is there a template for the SR vs. NSR determination

There are many…

Google "significant risk vs. non-significant risk template" here

But would you sue any of these? I would not!

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For those who like templates…

Can you say *thinking inside the box?* No *creativity?* No *imagination?*

But if you really want one, I have one…

NSR Justification Example Template here (not publicly available…sorry)

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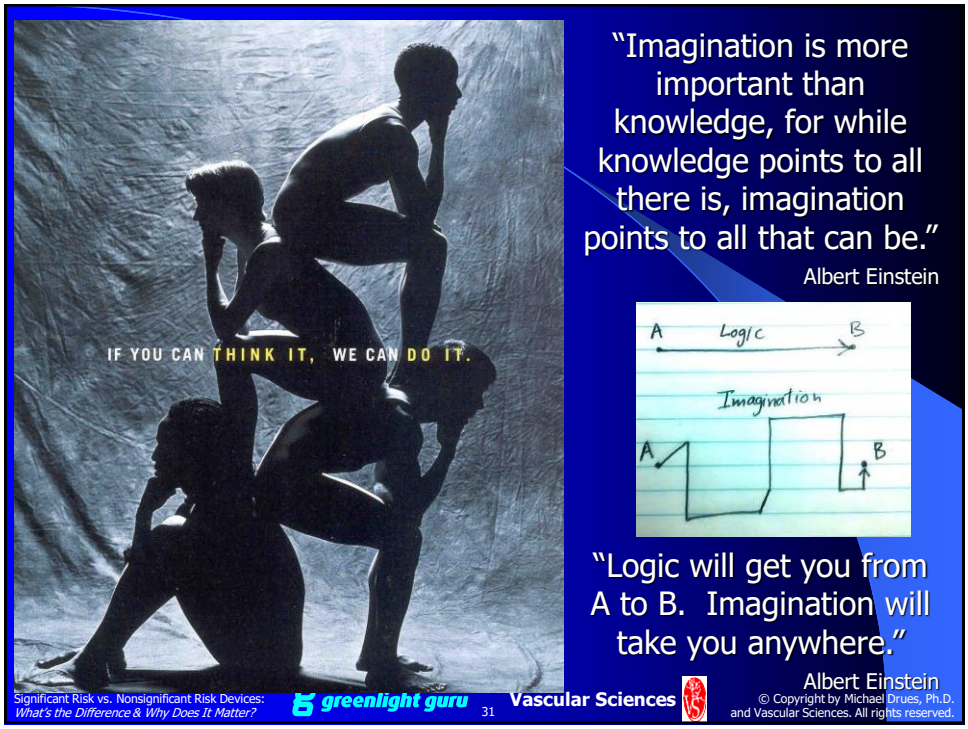

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Want more?

Have you seen the musical Oliver?

Oliver Video here (20 sec).

Additional Resources

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"Current" Guidance

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Significant Risk and Nonsignificant Risk Medical Device Studies

Additional copies are available from:

Office of Good Clinical Practice
Office of Special Medical Programs, Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave., WO32-5129
Silver Spring, MD 20993-5129
(Tel) (301)-796-8340
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

or

Division of Small Manufacturers, International, and Consumer Assistance
Office of Communication, Education and Radiation Programs
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., WO66-4521
Silver Spring, MD 20993
Tel: 1-800-638-2041 or 301-796-7100
dsmica@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)

January 2006

Significant Risk and Nonsignificant Risk Medical Device Studies: Guidance For IRBs, Clinical Investigators, and Sponsors (Jan, 2006) here.

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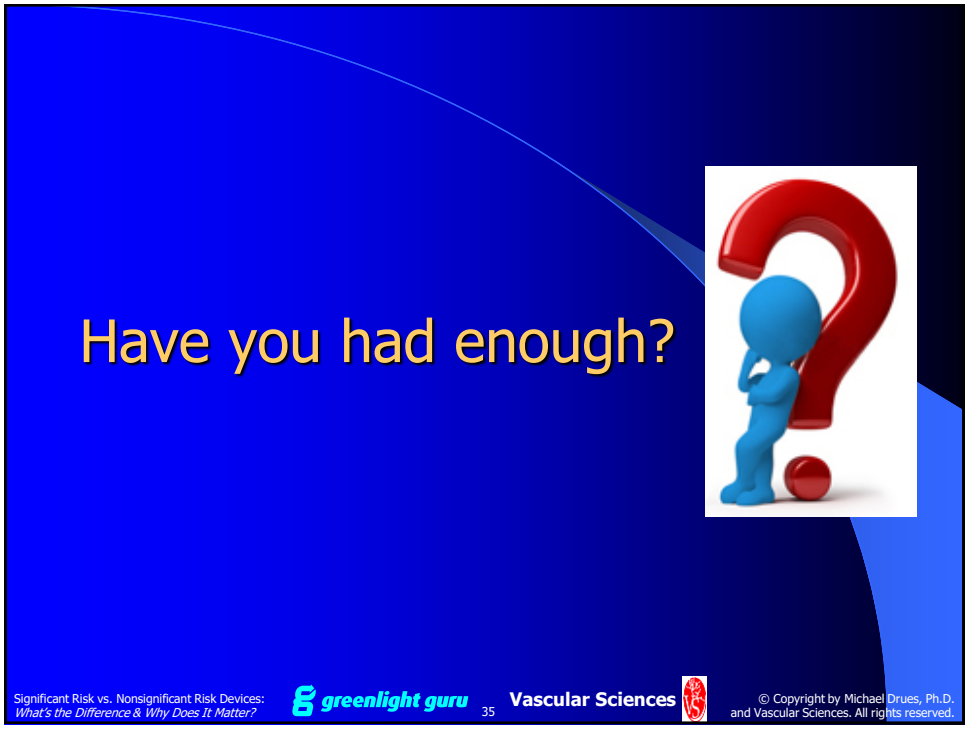

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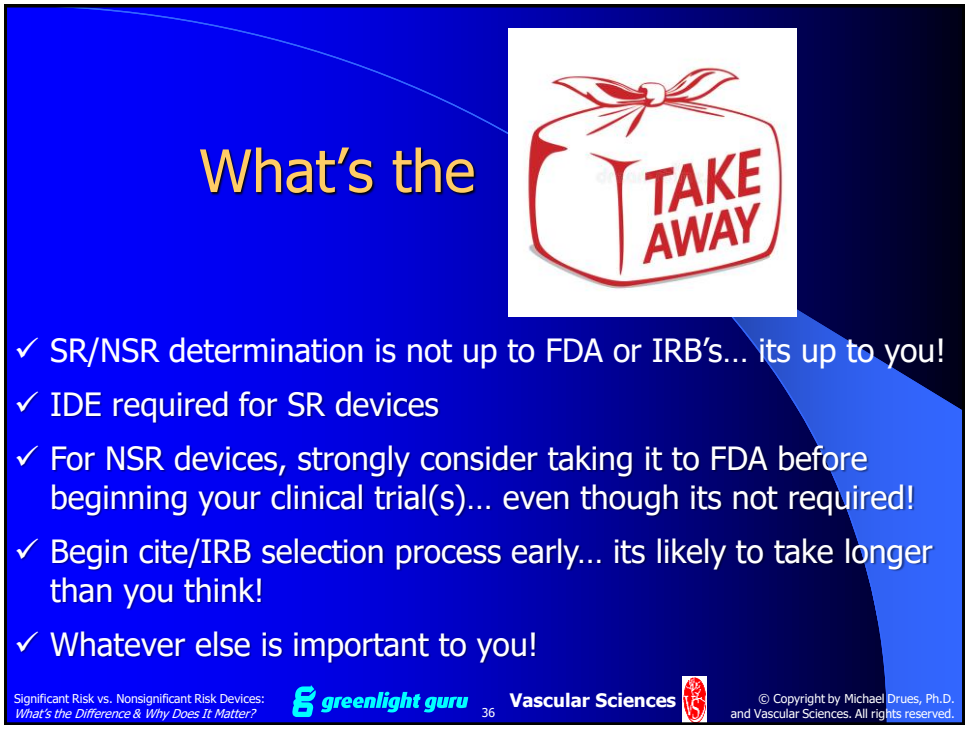

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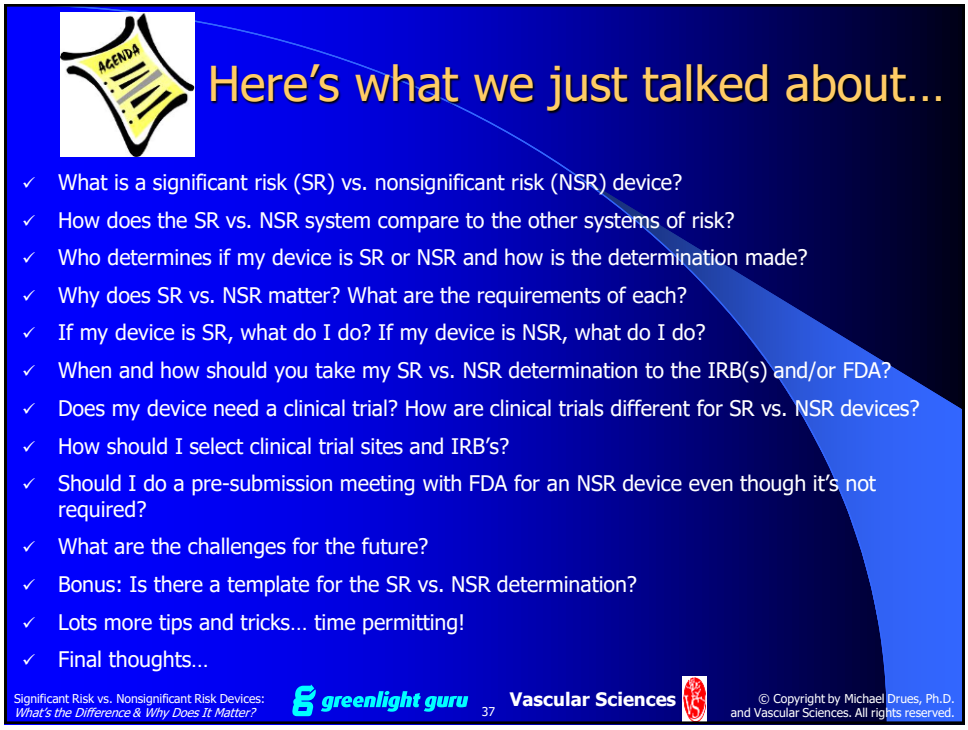

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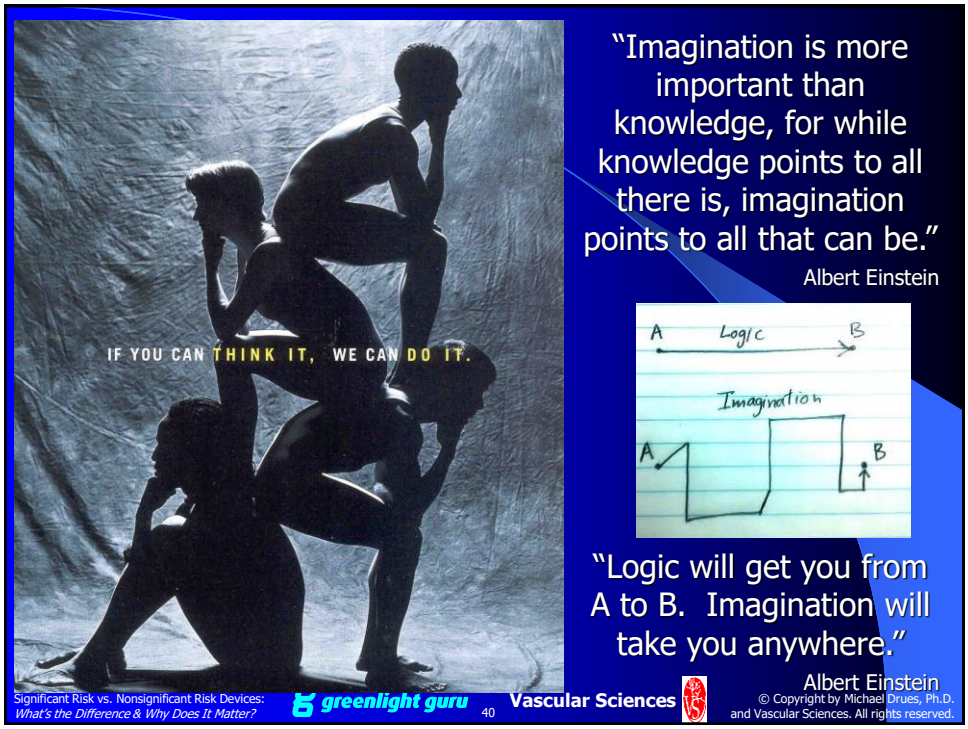

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Significant Risk vs. Nonsignificant Risk Devices:

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Taking inspiration from one of best…

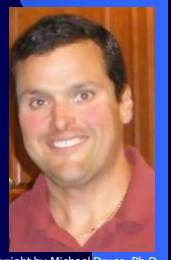
"Here's to the crazy ones. The misfits. The rebels. The troublemakers. The round pegs in the square holes. The ones who see things differently. They're not fond of rules. And they have no respect for the status quo. You can quote them, disagree with them, glorify or vilify them. About the only thing you can't do is ignore them. Because they change things. They push the human race forward. And while some may see them as the crazy ones, we see genius. Because the people who are crazy enough to think they can change the world, are the ones who do."

Steve Jobs (1955 – 2011), entrepreneur, marketer and inventor, the co-founder of Apple Inc. and widely recognized as a pioneer of the personal computer revolution.

More importantly…

"Imagine where we could be if discontent for the status quo was the norm rather than the exception."

Can you guess who said this?



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Questions?
Comments?
Suggestions?
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GreenLight.Guru Webinar (February 15, 2024)

https://www.greenlight.guru/webinar/significant-vs-nonsignificant-risk-devices