Clinical trial optimization

The commercial context

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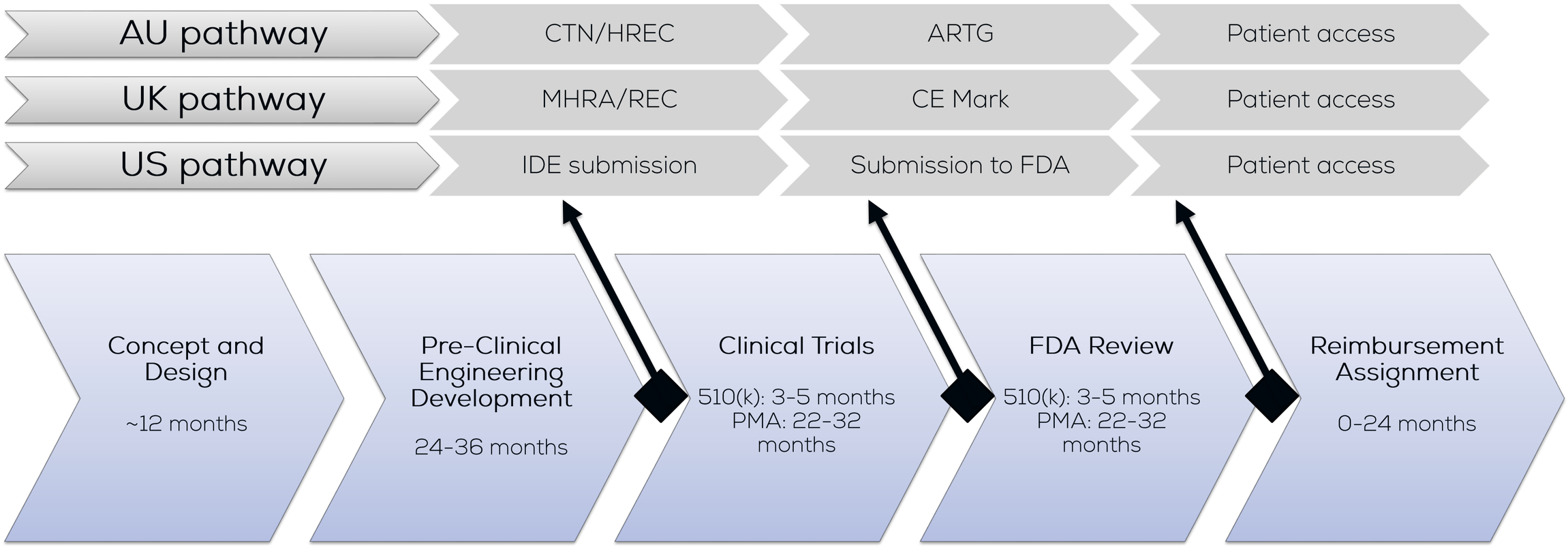
What is a clinical trial for an implantable device?

- A systematic investigation or study in human subjects, undertaken to assess the safety and/or performance/efficacy of a medical device
- Economic or marketing studies or service evaluations for commercial use

Are the risks associated with the use of the device acceptable when weighed against the benefits?

Medical device development pathway



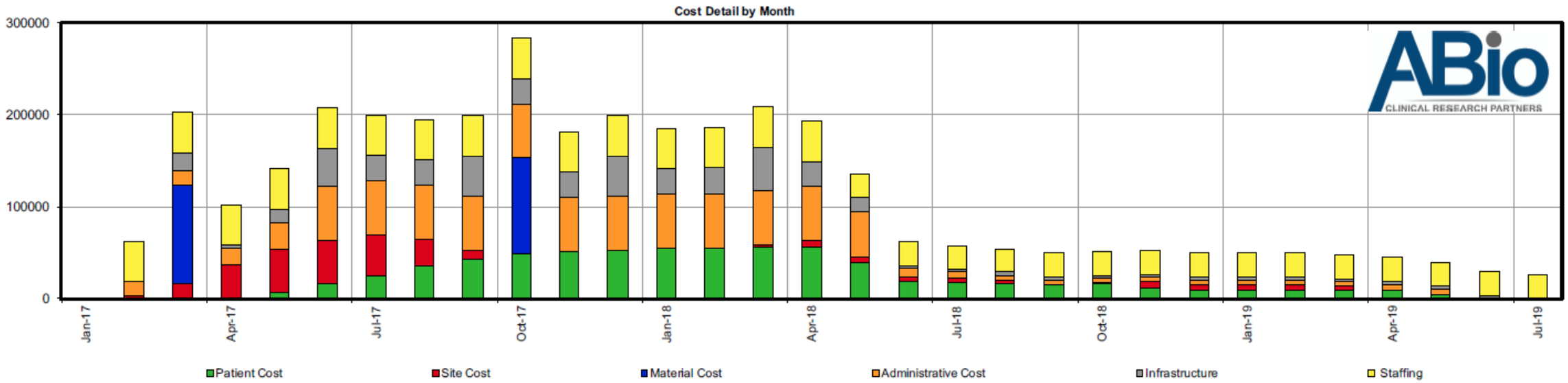
Approximately 40 Pre-Market Approvals (PMAs), and 3,000 streamlined 510(k) clearances are approved each year by the FDA.

Source: http://neurotechzone.com/posts/category/neurotechmarket

Implantable device trials

Stage	Subject numbers
Pre-clinical tests and animal trials	10+
First in Man/Pilot/Feasibility (safety)	5-50
Pivotal, IDE Trials (safety and efficacy)	50-100s
Marketing/health economic studies/reimbursement	1000s-10,000s

Implantable device trials: Budget models



How to inform the clinical trial plan

A clinical trial plan has clinical and commercial goals.

Where do I start?

…with the ending!

- Who will buy and pay for my device?
- Identify the stakeholders
  - Regulatory agencies, clinicians, providers (e.g. hospitals), insurance companies, payers, patients
- Engage early with
  - Regulatory agencies
  - Payers
  - Clinicians

"Begin with the end in mind."

- Stephen Covey

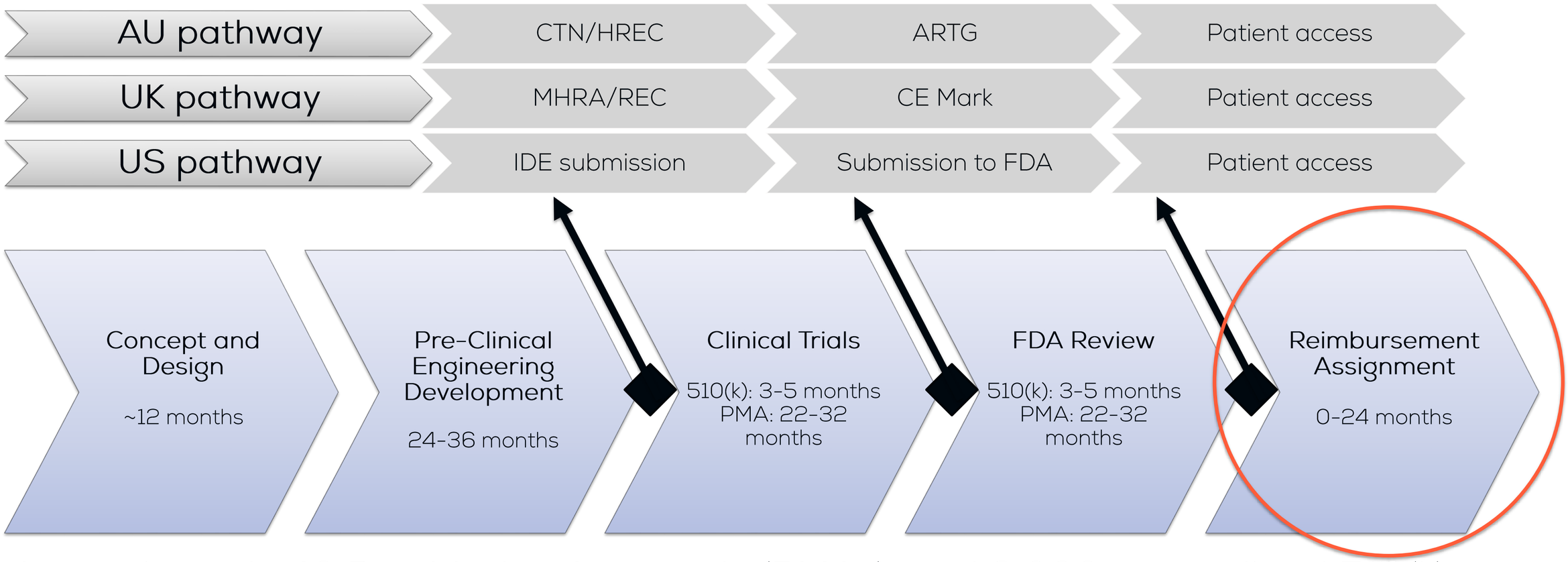
Risks are real, but it is doable

How to achieve

- Value
- Milestones
- Attract investment

….on a limited budget!

Medical device development pathway



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Clinical trials value generation

- Hard to extract value out of a trial retrospectively
- Factor in the regulatory and health economic environment

- USA
  - For-profit healthcare systems
  - Device company share margins in a complex supply chain
  - Clinical trial data needs to generate real value beyond first and second degree endpoints

Small budget? Test the market

Fire small bullets to test the market

- Leverage international network to gain knowledge and then test the response
- Use local knowledge, European, USA, Asia, EMs
- Competition analysis predicates
- Payer insights
- Clinician insights
- Provider insights

Validate knowledge

Develop the clinical plan

Strategy perception

- Investors respect forward thinking
- Look bigger than what you are
- Show diligence in understanding market forces **even if you don’t have all the answers**
- Upside, minimize equity dilution

Regulatory landscape for devices

The regulatory pathway and therefore the clinical trial plan is determined by the device classification.

It is critical to establish the applicable regulations for each device early on.

ADAPT YOUR STRATEGY

Changes to EU medical device regulations will see EU and FDA regulatory strategies more convergent.

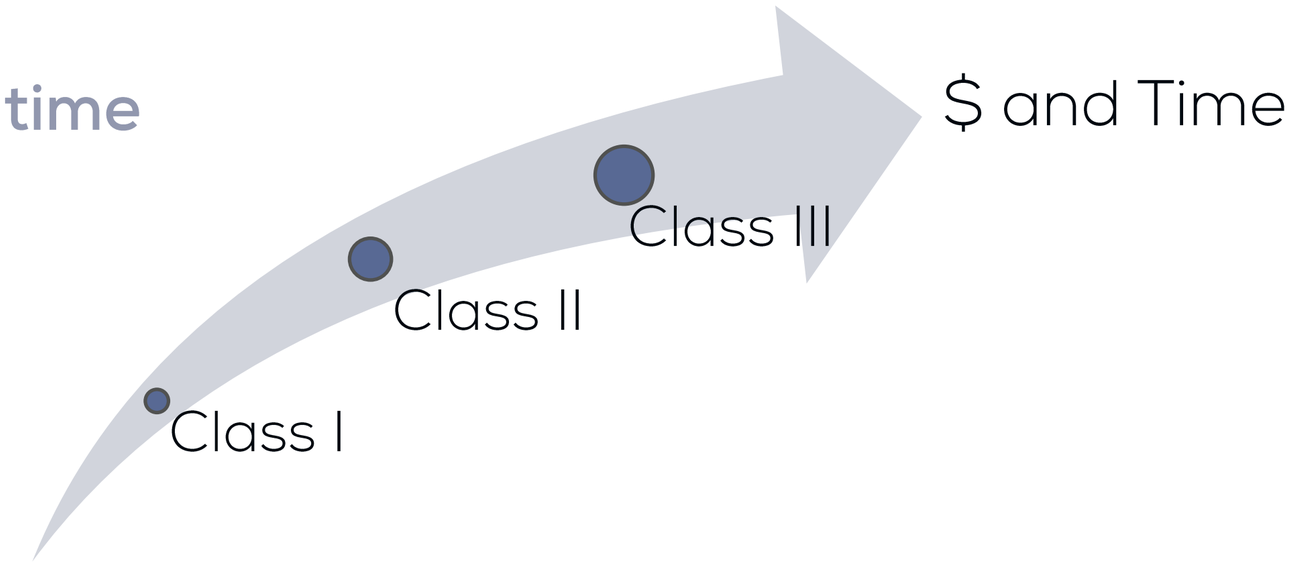
e.g. Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

USA trends

- Pre-submissions
- De Novo clearances for devices with no predicate to avoid Class III
- Cybersecurity

Classifications

Higher class, higher costs, more time



FDA, EU, AU (similar)*

- Class I, II, III

EU/AU*

- Additional Active Implantable Medical Devices Directive (AIMDD) 90/385/EEC (high risk, similar to Class III)

ROW, Emerging Markets

- Territory specific classifications, fractured system

*Territory specific variations exist

Implantable medical device

What is the definition? It varies.

Most government agencies have a risk-based approach to device regulations.

Any device which is intended:

- To be totally introduced into the human body or,
- To replace an epithelial surface or the surface of the eye, by surgical intervention which is intended to remain in place after the procedure
- Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device

EU/AU – Medical device regulations are similar

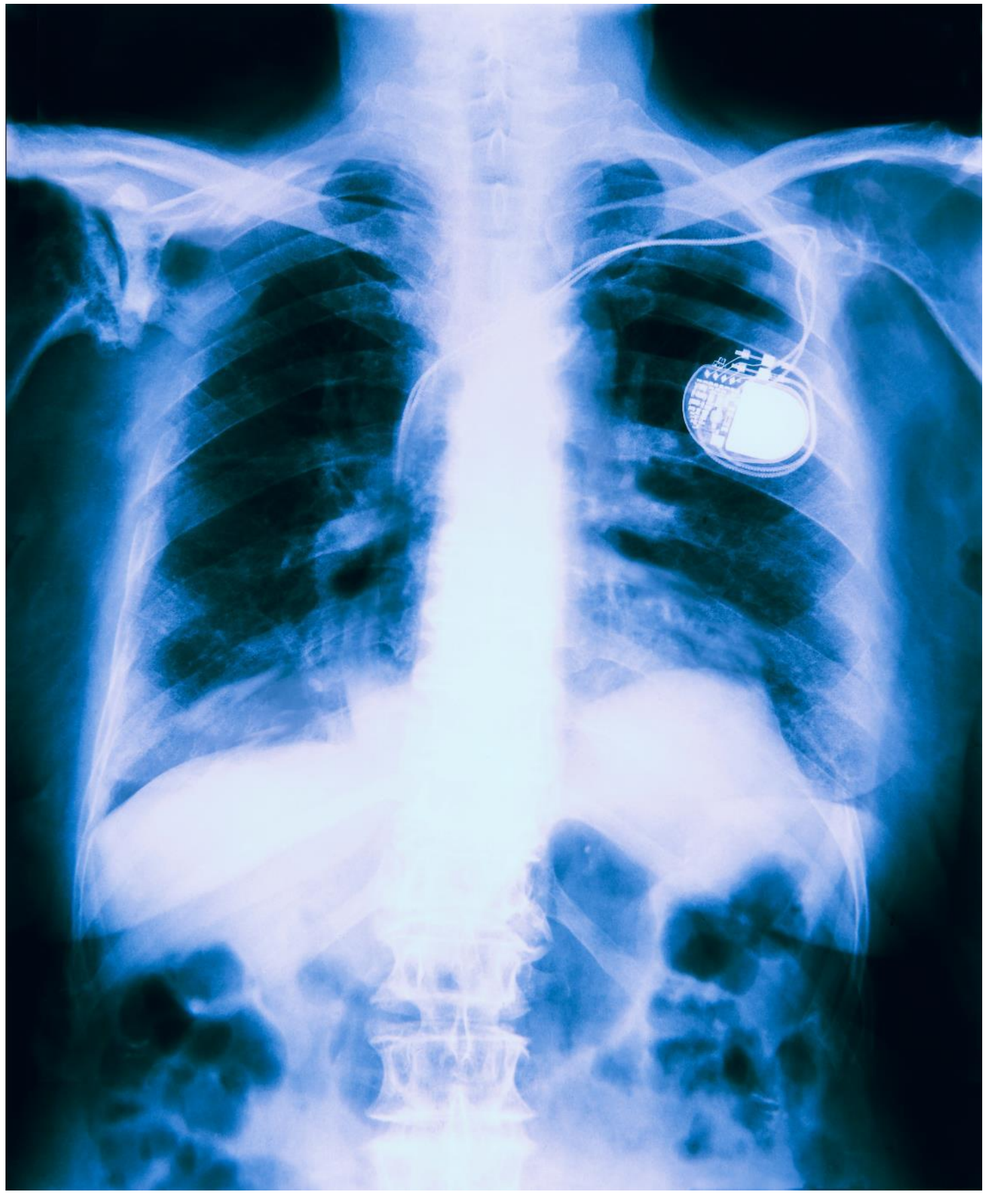
- Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease,
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- Investigation, replacement or modification of the anatomy or of a physiological process,
- Control of conception,
- And which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted by such means.

Active implantable medical device (AIMD)

Defined in AIMDD Directive (90/383/EEC) as:
"Any medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure…"

Examples:

- implantable cardiac pacemakers
- implantable defibrillators
- leads, electrodes, adaptors for the above
- cochlear implants



Regulatory approval ≠ sales or adoption

- Regulatory approval does not mean sales or adoption
- Endorsement of value proposition, now need to validate it with more studies and additional economic outcome data
- Consider how additional data from the early trials can be obtained to support market acceptance

The payer’s role

- Clinical trial needs to resonate with what the Payer and Clinician
- Payers are diverse in metrics and objectives
  - Hybrid payer systems
    - USA: Medicare, Medicaid, insurance carriers, other third-party payers, or health plan sponsors(employers or unions).
    - UK: NHS and private insurance
  - Single payer systems
    - Canada and Taiwan
- Flexible, creative, multi-pronged approach as payers can be fickle and change the parameters
- Do not go big, focus on smaller payers in USA
  - e.g. Small third party payer, one state, 500K – 3M population, motivated to improve outcomes, impact on bottom line.

The fun starts after approval

Case Study: Qiagen, HPV test

- $100M spent for regulatory approval
- $300M spent for reimbursement!
- Addressed requirements of multiple Payers
- Not a strategy for small pockets

Source: ADVAMED, 2017, Peer Shatz, CEO, Qiagen

Commercial considerations upfront: decision makers and adoption

1. Why would they use your device and what will cause its adoption?

   Value proposition for clinician:
   - What would they want to use your device for?
   - What evidence do they need to change practice?
   - Are you solving a problem, i.e. is there an unmet need for your device?
   - Clinician hip pocket impact?
   - Procedural impact

2. What is the competition landscape?

3. Clinical setting: private, public, etc. caseload to match complexity

Share price plunge

CMS change

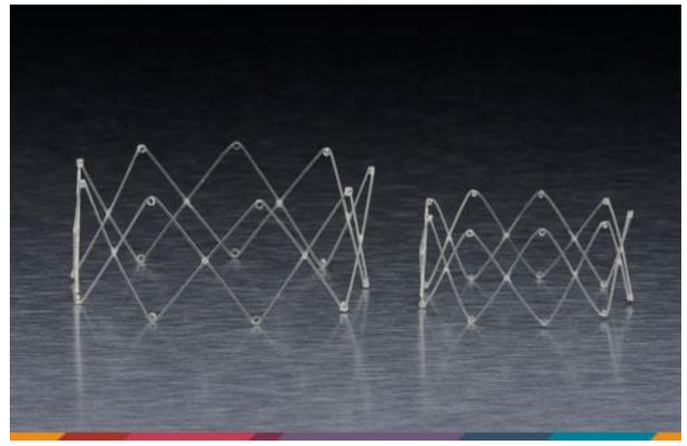
15.45 +0.05 (0.32%)
After Hours: 15.45 0.00 (0.00%)
Mar 13, 4:31pm GMT-4
NASDAQ real-time data - Disclaimer
Currency in USD

Range	15.23 - 15.70	Div/yield	-
52 week	7.65 - 20.64	EPS	-0.89
Open	15.30	Shares	28.68M
Vol / Avg.	0.00/238,074.00	Beta	-
Mkt cap	459.48M	Inst. own	81%
P/E	-		

Source: Google Finance: Accessed 14 March 2017

Consider payer risk; change in procedure coverage

Case Study: Intersect ENT Nasal stent



On November 1 2016, the Centres for Medicare & Medicaid Services (CMS) released the 2017 Medicare Hospital Outpatient Final Rule, implementing comprehensive ambulatory payment classification (APC) for upper airway procedures, including sinus surgery. The ruling for upper airway procedures, including sinus surgery, includes reimbursement at a fixed amount that is 40% to 50% below the current average amount. The ruling went into effect on January 1, 2017.

The ruling led to J.P. Morgan downgrading Intersect ENT shares from overweight to neutral.

J.P. Morgan also reduced its price target to $16 from $25. Between the ruling and J.P. Morgan's downgrade, Intersect ENT's shares tumbled by more than 40% the following day.

Why? The new procedure coverage means the device cost is approx. 1/3 of the procedure cost.

Source: https://www.fool.com/investing/general/2016/11/03/why-intersect-ent-shares-are-rallying-back-12-toda.aspx

Consolidation: value analysis process

Case Study: Mayo Clinic, USA

- Network of 24 hospitals
- What is the product value?
- Drill down to the data about the impact of the device on outcomes
- Needs of the patient and the value equation

$$\frac{\text{Quality + Outcome + Safety}}{\text{Cost}}$$

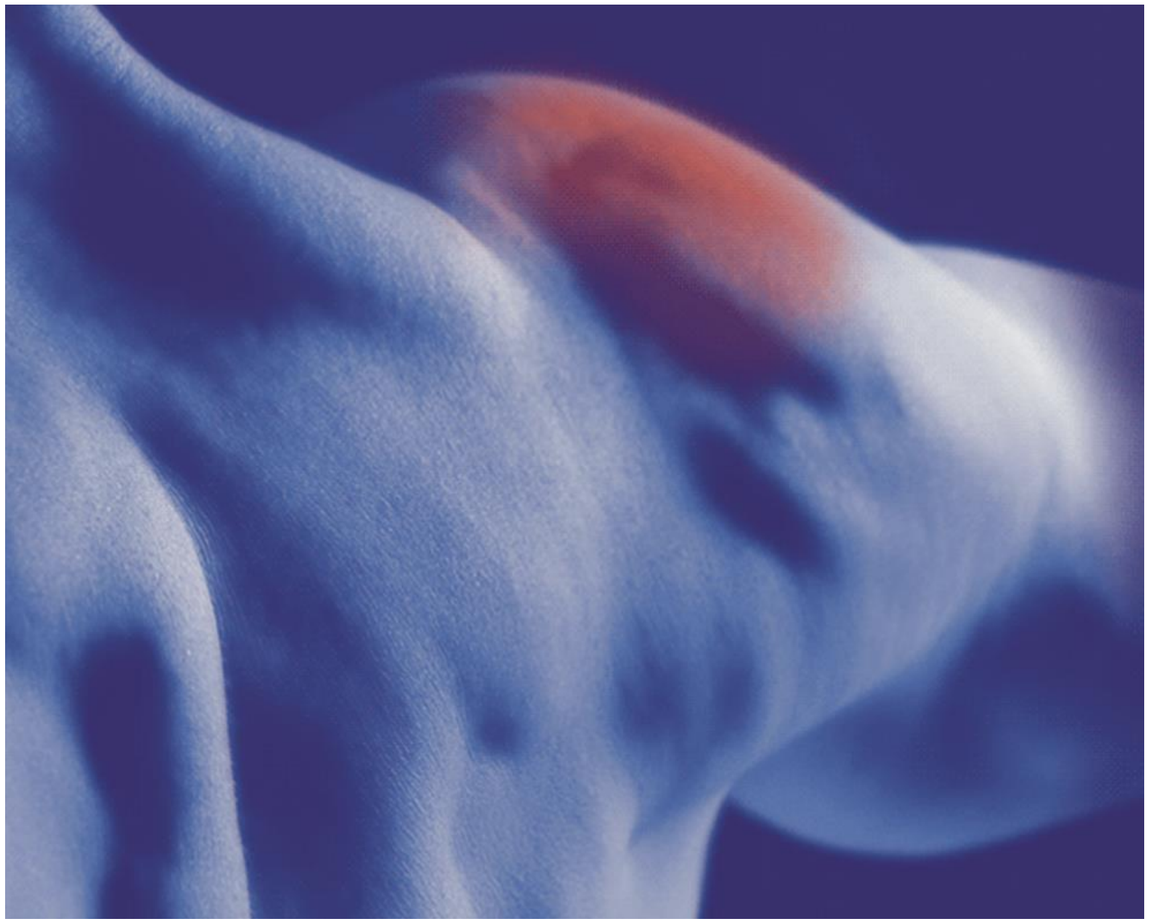
- A handful of distributors only
- GPO consolidation
- Few companies sell direct
- If a high touch device and technical support is needed, direct selling may be acceptable.
- Hospitals have standardised purchasing across all sites: want all hospitals to use the same products

Source: ADVAMED, Oct 2017, USA Market Access Seminar

Australia as a destination for clinical trials?

Case Study: Rotation Medical

- Rotation Medical conducted a multi-site, multinational trial collecting health economic data for a reimbursement application in the USA.
- 43.5% tax credit
- Supplemented data in USA trials
- Australian data is accepted globally
- Need to strike an acceptable ratio of US/OUS patients. 60/40 acceptable.
- USA Payers want to see USA data



Source: Rotation Medical ,Martha Shaden, CEO, Plymouth, MN 55447

Creating your value proposition

- Develop your value proposition for clinicians, payers and the patient
- Clinical trial data value creation, prospective data collection to avoid duplication of effort and resources

This is achievable

- The risks are real, but manageable
- Choose partners that can leverage extensive global networks and are forward thinkers that will create value
- Seek out ‘free advice’
- You don’t need all the answers
- Demonstrate vision and diligence

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