Clinical Research STRATEGIES

Tips & Tricks for Customizing a Clinical Trials Program for your Medical Device, IVD, or Digital Therapeutic that Satisfies Regulators, Investors & Patients

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President and Founder | October 7, 2021

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About

- Contract research organization (CRO) and executive management consultancy for life sciences executives
- Founders have 60+ years of life sciences expertise
- Represent start-ups, mid-size, and Fortune 100 life sciences companies
- Solutions range from trial conduct, QMS-building, regulatory strategy and submissions, and many services to respond to clients' unmet needs
- Instill fiscal discipline to prioritize quality, regulatory, clinical, and market access
- Particular focus in medical devices: IVDs, SaMD, first-in-class De Novos, NSRs, wellness, combination products….
- International regulations << US + latest EU MDR >>
- Top-10 Compliance Solution Provider – *Life Sciences Review 2021*

Today's Objectives

- Understanding the BIG picture
- Formulate the best Intended Use, Indication(s) for Use, MOA and Device Description
- Meeting with Regulators (US and EU strategies)
- Considerations for clinical evidence generation
- Generating substantive evidence that satisfies
  - Regulators and payers
  - Investors
  - Patients
- Review case studies for comparativeness

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The BIG picture and defining my device

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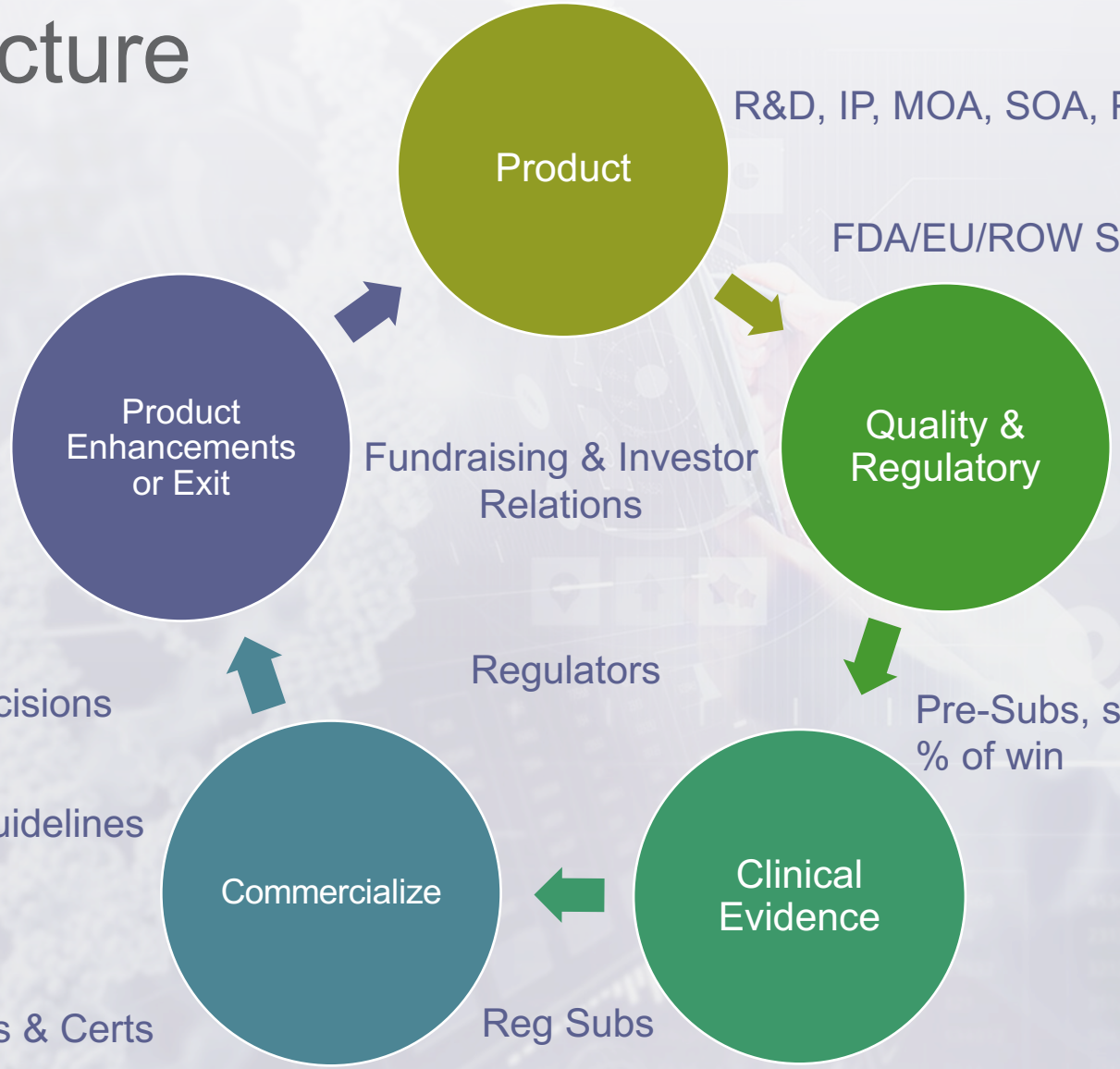
The BIG picture



Defining my device

- What is my medical product?
  - Regulatory Pathway Assessments (RPAs) often elucidate state of the art, product codes, predicates or novelty
- Risk-level and risk-benefit (low, moderate, high)
  - Class I
  - Class II
  - Class III
- Getting this right is tantamount to your business
- Critical questions to raise
  - Achieve market clearance with “good enough” vs change the game

Defining my device

- Intended Use
  - *"Intended for the treatment of Type 2 diabetes and the stabilization of blood glucose levels"*
- Indication(s) for Use
  - *Indicated for adults <<21 and older>> with Type 2 diabetes*
- Mechanism of Action (MOA)
  - How it interacts with the patient (treat, diagnose)
- Device Description
  - All the components, accessories, way it is used

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Meeting with the Regulators

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Meeting with the Regulators

Regulators are not adversaries

- Federal and international regulators must protect patients first
- Bad actors, post-market problems have led to higher scrutiny and policy reform
- Safety and efficacy must be scientifically proven
- Quality and integrity of documentation and data collected must be proven
- Risk-benefit of device must be well-defined and substantiated per the regulations
- Embrace the challenges that lie ahead
- EU is no longer the cheaper and faster location to launch vs US

Meeting with the Regulators

US vs EU vs ROW

- Careful RPA and market access requirements
- Understanding and anticipating contemporary regulatory reform
- Preparing regulatory submissions
- Quality of documentation for submittals, conformance with regulator expectations

Meeting with the Regulators

US strategy

- Define your strategy in preparation of your submission
- Read relevant guidance docs for meeting requirements and timing
- View early discussions as a way to de-risk your product and your trial(s) program
- Example questions that are most important to exchange…
  - Pilot trial data protocol
  - Wellness Device vs Medical Device
  - Confirmation of equivalence to marketed product before attempting a 510(k) submission
  - Breakthrough Designation Request requirements

Meeting with the Regulators

US submission documentation

- Preparing your submission documentation per the type of meeting and pathway
  - Cover letter
  - Check whether an FDA Form is required
- 513(g) Request for Information – used when no predicate is found and device is novel
- Direct De Novo when there is NSE device, with potential for Class I or II
- 510(k) when SE device(s) are obvious
- Q-Sub program
- Breakthrough Designation

Meeting with the Regulators

US meeting planning

- Once the meeting is planned, prepare brief slide deck
- Assess the personnel who should attend (TC or F2F)
- Rehearse and script out the 1 hour
- Important to be ready unless if written feedback is agreed upon
- The time flies while in the actual meeting
- Sponsor is responsible for meeting minutes
  - Appoint 1-2 team members who are very good at note-taking and not a key participate in the discussion
  - Permanent record

Meeting with the Regulators

EU – Notified Body

- MDR has changed access to the EU
- Strategy should include EU, timing and potential use of US/ROW data
- Risk-benefit profile is still the top consideration
  - Risk management file
  - Early evidence
  - Literature (state of the art - SOA), objective clinical evaluation
- All bets are off – too difficult to predict ease of market access
  - Only several dozen NBs are MDR-certified
  - Deficit of talent in NBs to understand the new regulations

Meeting with the Regulators

EU – Notified Body

Strategy for Technical File or Design Dossier Preparation

- GAP Analysis to MDR 2017/745
  - Route to Conformity
  - Classification Justification
  - General Safety Performance Requirements (GSPR) Risk Evaluation
  - Quality Management System (Sponsor and Economic Operators)
    - Certification ISO 13485
- Technical File Mitigation and Completion
- Notified Body Selection/Engagement
  - **Application Submission: trial data or trial proposal for EU**
- MDR Quality Management System Audit Support
- Technical File Submission/Review/Approval
- Distribution Channels (Possible connection with Authorized Representative to cover all EU countries)
- In going Post Market Surveillance Support (reporting, complaint handling, Post-Market Clinical Follow-up, etc.)

United Kingdom – MDR Compliance

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Considerations for Clinical Evidence Generation

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Building a Compendium of Evidence

- Evidence generation is costly
- Stakeholders must see clear proof device does what it's claims say
- Start small: proof-in-concept, early feasibility, training sets, NSR studies
  - Not statistically meaningful
  - Used to attract more investment for larger trials
  - Not enough for reimbursement
  - Goal is to start publishing
- Obtain regulator buy-in before spending for larger pivotal trials

Building a Compendium of Evidence

Study types – each provide variable evidence generation

- Human factors
- Training set
- FIM, POC, EFS, Investigator-initiated
- Equivalence (Class I, 510k)
- Pilot-to-pivotal, adaptive
- Pivotal
- In silico
- Post-market: safety surveillance, registry, observational, RWE, cost analysis

Building a Compendium of Evidence

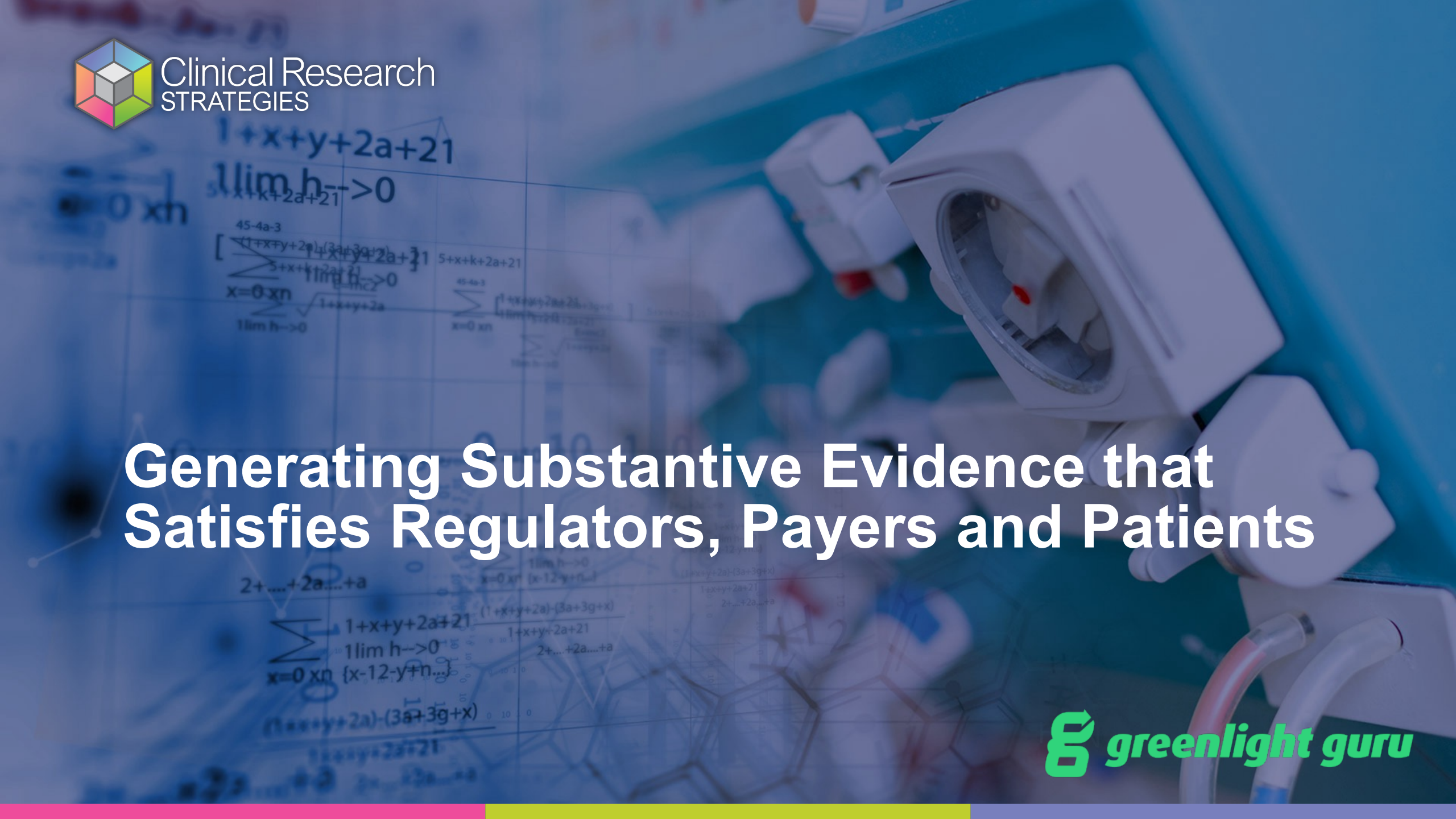
Weighted scale toward gold standard

- Pivotal, RCTs to prove
  - Superiority to other treatments or SOC
  - Non-inferiority to SOC
- Pilot, investigator-initiated
- Increasing use of in silico and RWE studies, *some* for potential regulatory decision-making

Building a Compendium of Evidence

Publications program

- High impact journals – long road
- Lower impact, quick online publications
- White papers
- Voice of customer / testimonials
- Feeds into continuous clinical evaluation and risk-benefit narrative
- Competitor's literature may also prove beneficial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Generating Substantive Evidence that Satisfies Regulators, Payers and Patients
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Satisfying Regulators, Payers, Patients

- Long road
- Leverage meetings with FDA-CMS, category B for IDE studies
- Quality and quantity of evidence matters
- Pocketbook can't always pay for gold standard RCT
- Focus on clearance or approval
- Billing studies can be add-ons to pre-approval or post-market trials
- New indications could be explored
- Bottom line: reduce costs of care, patient disease burden, QOL
- **If you designed a clinical trial to meet everyone's needs it would not be affordable or realistic to conduct**

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Review of Case Studies

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Case Study 1

CE Mark approach with insufficient data

- De novo, first-in-class device in ER setting
- US start-up device company management hired unskilled and unqualified friends
- Suspect QMS and pilot trial data
- Decided to try for CE Mark with limited clinical dataset
- Evaluation of device history file, design lock, and quality clinical data was suspect
- Notified Body rejected technical file
- Serious trouble after fundraise, CEO was fired

Case Study 2

Pre-IDE Strategy that went wrong

- Class III device company
- Had faulty animal data
- Never quite satisfied FDA's inflammatory response questions, biocompatibility
- Company repackaged the data in multiple pre-IDE submissions
- Company wasted 18 months, and had to repeat animal study prior to IDE approval
- Consider burn of staff over 18 months to only hear the same FDA answer again and again

Case Study 3

In Silico Trial for Regulatory Decision Making

- Large device manufacture with Class III cardiovascular device
- Worked directly with FDA on in silico trials
- Included strong animal studies and bench testing
- Proved next generation device equal to its own predecessor
- Regulatory decision-making without human clinical trials

Case Study 4

Wellness device company

- 513(g) to receive wellness device
- Self-registration
- Prepared protocol for NSR device to explore new indications with modest risk level
- Registry that collects data in paying consumers who agree to participate
- RWE generation, may only be able to substantiate the reason to conduct larger trials

Case Study 5

Software as a Medical Device (SaMD) Company

- Brain mapping software used to provide for surgeon decision making tool
- Considerations for intended use:
  - Aid in the surgical decision planning (coupled with other tools and clinical data)
  - Definitive surgical decision planning (new SOC)
- Considering what we learned today, what do you think they chose for their pathway to the FDA?

Case Study 6

IVD

- COVID diagnostic with great potential to test in other infectious diseases
- Aptamer (saliva) test, very inexpensive
- Early V&V testing demonstrated that the reliability was questionable
- FDA has outlined approach for proving specificity and sensitivity levels against PCR test
- Literature has similar success stories; not large enough datasets
- New funding infused for improving the test kit and reliability

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Summary

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Summary

Lessons

- Know your intended use, indications for use, device description and MOA
- Meet with regulators for key agreement and understanding ahead of trials
- Establish strategy for clinical evidence generation
- Reflect clinical evidence in publications program
- Consider different stakeholders in order of importance

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Questions and Answers

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