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Improving healthcare decisions

Revolutionizing Regulatory Pathways: Unleashing the Power of Real-World Evidence, Adaptive Trials and Synergistic Collaboration for Expedited FDA Device Approval, Breakthrough Designation and CMS Reimbursement

ISPOR 2024 – Atlanta, Georgia USA

May 7, 2024 1:45PM – 2:45PM

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Welcome and Session Objectives

Renée JG Arnold, PharmD, RPh
--Entrepreneur-in-Residence, National Heart, Lung and Blood Institute (NHLBI)/National Institutes of Health, New York, NY, USA
--Adjunct Full Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA
--President, Arnold Consultancy & Technology, LLC, New York, NY, USA

Today's Panel

Renée JG Arnold
Entrepreneur-in-Residence, National Heart, Lung and Blood Institute (NHLBI)/National Institutes of Health, New York, NY, USA

Douglas Kelly
Deputy Center Director for Science, Chief Scientist, Center for Devices & Radiological Health (CDRH), Food and Drug Administration, Bethesda, MD, USA

Steve Farmer
Chief Strategy Officer for Coverage at Centers for Medicare & Medicaid Services, Baltimore, MD; Associate Professor of Medicine & Health Policy and Management, George Washington University, Washington, DC, USA

Peter Neumann
Director, Center for the Evaluation of Value and Risk in Health
Tufts Medical Center, Boston, MA
Professor, Tufts University School of Medicine, Boston, MA, USA

Session Objectives

- Discuss some of the patient cohort concerns of using RWE in fit-for-purpose trials to enable inferences about healthcare resource utilization in support of healthcare decision-making
- Highlight development of a technology's value proposition as a key feature of enhancing its reimbursability within the FDA Total Product Life Cycle Advisory Program
- Understand the evolution of the CMS Transitional Coverage for Emerging Technologies (TCET) pathway to reimbursement
- Opine on CMS' assumption of a more active role as a health technology assessment (HTA) agency in light of its growing role in advancing TCET, Coverage with Evidence Development (CED) approaches and Medicare drug price negotiations under the Inflation Reduction Act

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Addressing Patient Cohort Concerns in Real-World Evidence Trials for Healthcare Resource Decision Making

Renée JG Arnold, PharmD, RPh

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- Adjunct Full Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA
- President, Arnold Consultancy & Technology, New York, NY, USA

A Few Definitions

- Health economics and outcomes research (HEOR) comprises evidence development in support of a technology's value proposition and reimbursement
- Real-world data (RWD) or real-world evidence (RWE) uses pre-existing data sources to infer effectiveness, resource use, costs, etc.
- Fit-for-purpose or fit-for use evaluation of data source(s) determines if appropriate data source to answer study question
- Adaptive study design allows for prospectively planned modifications based on accumulating study data without undermining the study's integrity or validity[2]

[1] Considerations for the use of real-world data and real-world evidence to support regulatory decision-making for drug and biological products. Guidance for industry. HHS CDER/CBER. August 2023

[2] Adaptive Designs for Medical Device Clinical Studies Guidance for Industry and Food and Drug Administration Staff. CDRH. July 2016.

Importance of Adjusted Analyses

- Mimic an RCT
- RWE provides outcomes under non-ideal conditions, such as in more diverse populations with differing levels of medication adherence and over longer time frames than in typical RCTs and helps guide decision makers.*
- Statistical methods, such as propensity score matching (PSM) and inverse probability of treatment weighting (IPW), address confounding by indication due to lack of randomization in treatment assignment in these RWE databases

*Allan V, Ramagopalan SV, Mardekian J, et al. Propensity score matching and inverse probability of treatment weighting to address confounding by indication in comparative effectiveness research of oral anticoagulants. J Comp Eff Res 2020 Jun;9(9):603-614.

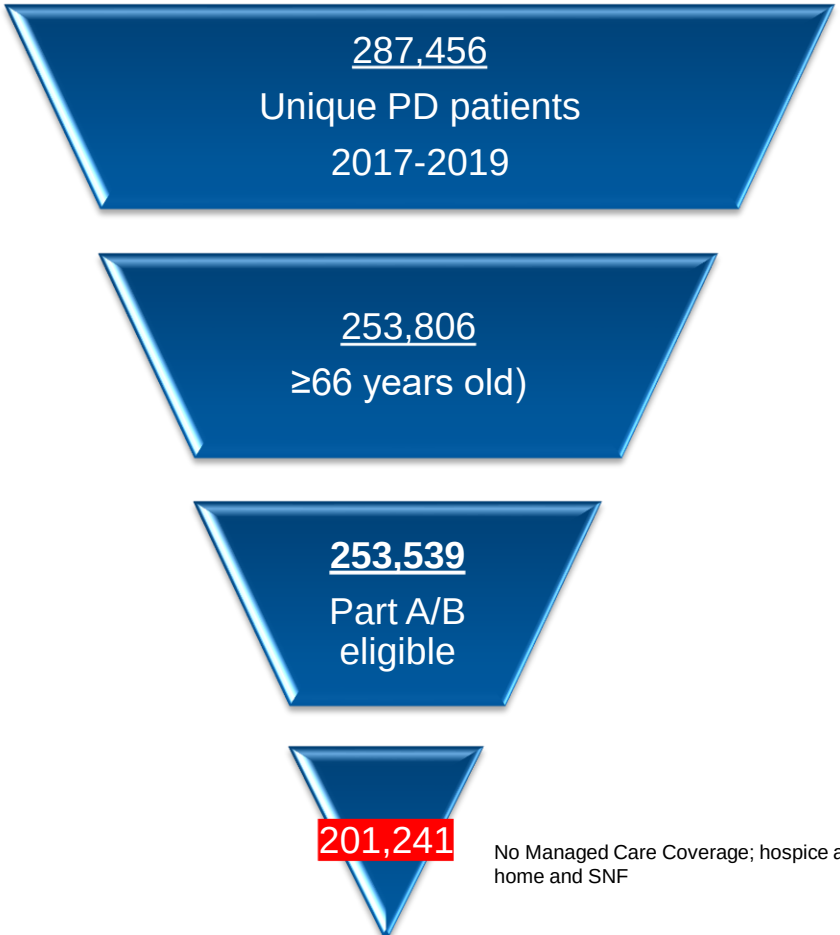
Decision to Use Medicare Research Identifiable Files (RIFs)

- Large enough patient group to be able to segment into major PD medications
- Medications (RIFs vs Limited Data Sets (LDS))

Parkinson's Disease Resource Use and Cost of Illness Using RWD: A Case Study in Developing a Technology's Value Proposition Through Resource Use

CONSORT DIAGRAM: Creation of the Initial Data Set

- **Collaboration with Arnold Consultancy & Technology LLC and Icahn School of Medicine at Mount Sinai.**
- **RESDAC required data use agreement with research institutions for access to Medicare research identifiable files (RIFs).**
  - **RIFs are the only Medicare files with Part D data associated with other claims data**
- **Inclusion criteria included:**
  - **Patients had any International Classification of Disease (ICD)-10 code "G20.X (Parkinson's disease“) for all three years of study (2017-2019);**
  - **Patients had to have an Rx for at least one levodopa-containing medication, to be found during at least one year (2017 OR 2018 OR 2019) in the Part D Event File**



Problem with Balancing Treatment Groups

- **Disease severity was an important consideration**
- To account for this lack of randomization of assigned treatments, we needed to “balance” the treatment groups. Normally we can use readily available, e.g., age, sex, race, or calculable, data (e.g., Charlson Comorbidity Score), to help to “balance” the groups.
- Statistical methods such as propensity score matching (PSM) and inverse probability of treatment weighting (IPW) address confounding by indication due to a lack of randomization in treatment assignment in these RWE databases

2020 FDA RWE statistics workshop https://ww2.amstat.org/meetings/biop/2020/onlineprogram/handouts/SC4-Handouts.pdf

Use of LEDD and IPTW

- **Two innovative approaches allowed for balancing the treatment groups:**
- Levodopa Equivalent Daily Dose (LEDD) used as proxy measure for disease severity
- Populations balanced using inverse probability of treatment weighting (IPTW)[1]

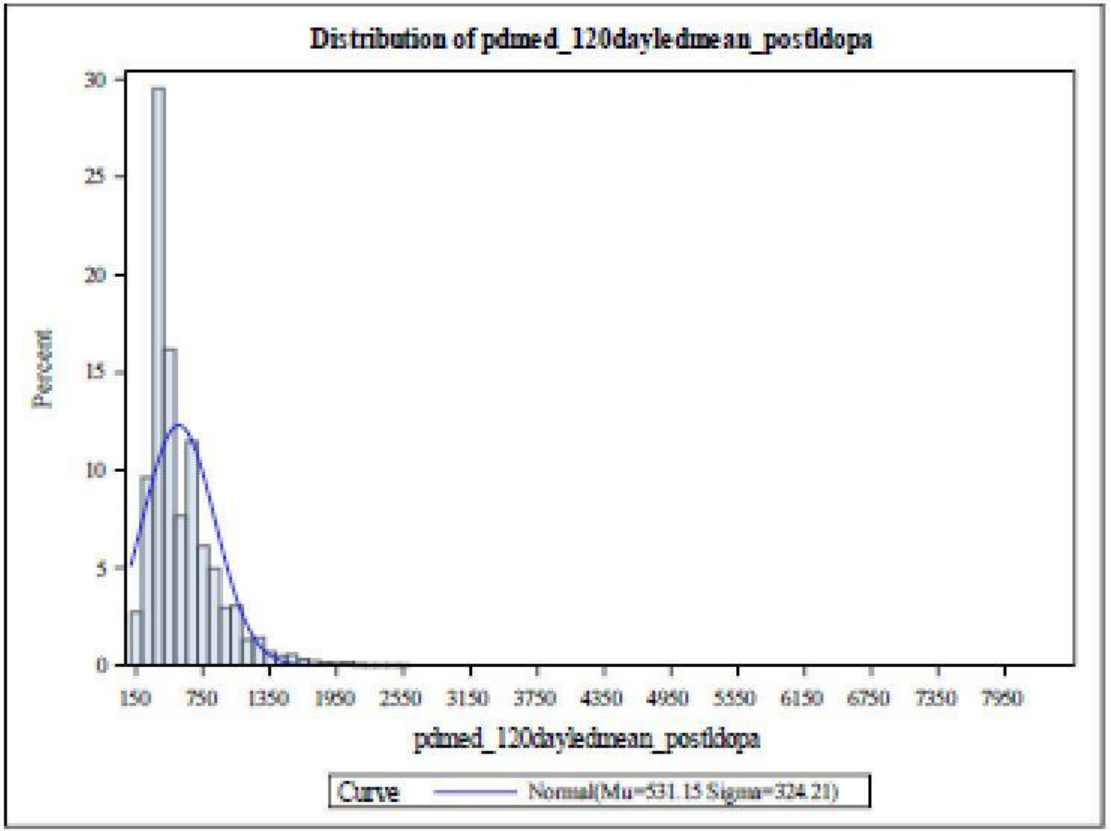
2020 FDA RWE statistics workshop https://ww2.amstat.org/meetings/biop/2020/onlineprogram/handouts/SC4-Handouts.pdf

Use of LEDD as Disease Severity Proxy

- More advanced patients have greater dopaminergic neuronal loss and therefore require greater dopamine supplementation.
- Levodopa equivalent daily dose (LEDD) estimates dopamine replacement combining various Parkinson's medications.*
- Used frequency analysis to understand the datasets and patient distributions.

*Julien C, Hache G, Dulac M, Dubrou C, et al. The clinical meaning of levodopa equivalent daily dose in Parkinson's disease. *Fundamental & clinical pharmacology*. 2021;35(3):620-630.
Nyholm D, Jost WH. An updated calculator for determining levodopa-equivalent dose. *Neurological Research and Practice*. 2021;3(1):58.
Schade S, Mollenhauer B, Trenkwalder C. Levodopa Equivalent Dose Conversion Factors: An Updated Proposal Including Opicapone and Safinamide. *Mov Disord Clin Pract*. 2020;7(3):343-345.
Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders*. 2010;25(15):2649-2653.
Verber D, Novak D, Borovič M, Dugonik J, Flisar D. EQUIDopa: A responsive web application for the levodopa equivalent dose calculator. *Computer Methods and Programs in Biomedicine*. 2020;196:105633.

LEDD Frequency Distribution



Calculation of LEDD (Levodopa Equivalent Daily Doses) as Disease Severity Proxy

*Drug**	*Daily dose*		*Factor*	*Levodopa equivalent dose*
Immediate-release levodopa[1]	800	mg	*1*	800 mg
Controlled-release levodopa[1]	0	mg	*0,75*	0 mg
Extended-release levodopa[2]	0	mg	*0,5*	0 mg
Levodopa+entacapone[1]	0	mg	*1,33*	0 mg
Levodopa+opicapone[2]	0	mg	*1,5*	0 mg
Levodopa+tolcapone[1]	0	mg	*1,5*	0 mg
Rotigotine[1]	0	mg	*30*	0 mg
Ropinirole[1]	0	mg	*20*	0 mg
Pramipexole[1]	0	mg	*100*	0 mg
Rasagiline[1]	0	mg	*100*	0 mg
Selegiline (oral)[1]	0	mg	*10*	0 mg
Selegiline (sublingual)[1]	0	mg	*80*	0 mg
Apomorphine[1]	0	mg	*10*	0 mg
Amantadine[1]	0	mg	*1*	0 mg
Piribedil[1]	0	mg	*1*	0 mg
Safinamide[2]	☐ yes		*LED=100mg*	0 mg
			Levodopa equivalent dose (LED):	**800 mg**

Nyholm D & Jost WH, 2021; https://neurolrespract.biomedcentral.com/articles/10.1186/s42466-021-00157-6

Summary Value Proposition for New Brand Name Agent vs CR+IR						
Benefit		**LEDD Overall**	**150-350**	**351-600**	**601-900**	**901-10,000**
Less Resource Use	Hospital LOS	✓	✓	✓	✓	✓
	Hospital Admission Probability	✓	✓	✓	✓	=
	Number of Hospital Admissions	✓	✓	✓	✓	=
	SNF/LTC	✓	✓	✓	✓	✓
Equivalent or Reduced Overall Costs	Hospital Costs	=	×	✓	=	=
	SNF Costs	=	×	✓	=	=
	DME Costs	✓	✓	×	✓	✓
Greater Mobility	↑ Exercise		×	✓	✓	✓
	↑ Use of Walking Aids		✓	✓	×	=
	↓ Use of Wheelchairs		=	✓	✓	✓

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Total Product Life Cycle (TPLC) Advisory Program (TAP) Overview

Douglas Kelly, MD
Deputy Center Director for Science, Chief Scientist, Center for Devices & Radiological Health (CDRH), FDA, Bethesda, MD

Total Product Life Cycle (TPLC) Advisory Program (TAP) Program Overview

Doug Kelly, MD
Deputy Center Director for Science

douglas.kellymd@fda.hhs.gov

Difference between Biopharma & Medtech

Biopharma

- **FDA study is the major risk inflection point**
- **Post-FDA pathway transparent & predictable**
- **Risk capacity can be devoted to product**
- **Radical new txs- CRISPR, CART-T, Gene Tx**
- Public market able to assess trial risk
- Drug candidates can go public w/ initial data
- Upside not constrained by pricing
- "Why do I need to own this now?"
  - Because a positive study means 10X+
- Venture liquidity <10 years
- $B acquisitions, new incumbents all the time
- Robust start-up investment ecosystem

MedTech

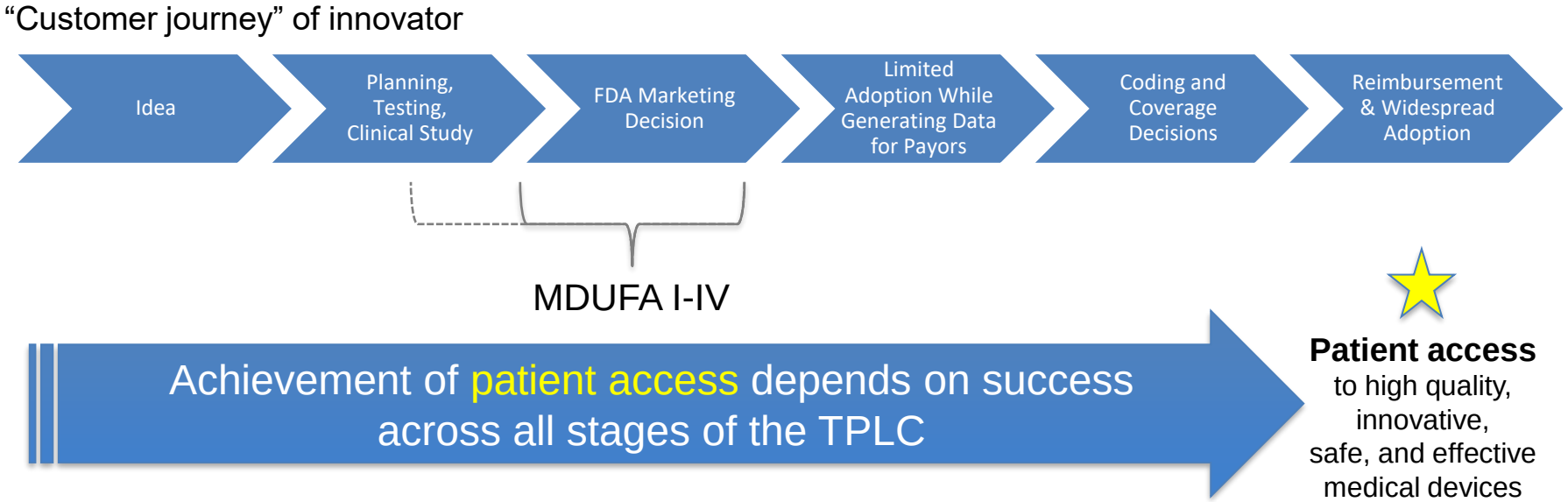
- **Coding, coverage, payment major risk inflection point**
- **Post-FDA pathway opaque, long & unpredictable**
- Risk capacity to CPT/RUC, payers, not product
- New tech is **incremental- little true innovation**
- Public market can't assess post-FDA risk
- Device candidates **cannot** go public w/ initial data
- Upside constrained by pricing, procedure, CMS, CPT
- "Why do I need to own this now?"
  - You don't
- Venture liquidity >20 years if no M&A for PMA
- $X00M acquisitions, **few new incumbents**
- **Almost non-existent start-up ecosystem**

Naïve Medtech Innovator's Customer Journey

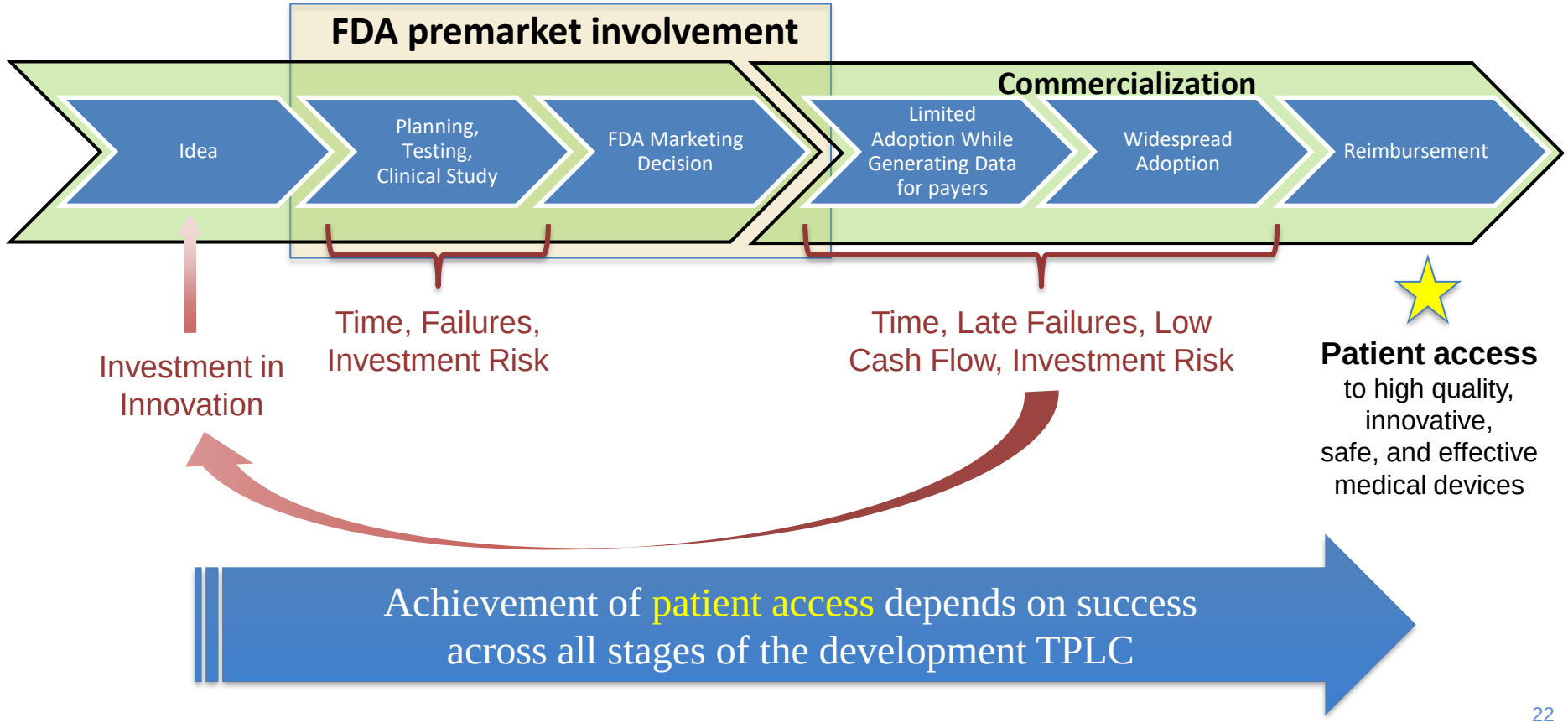
Patient access
to high quality, innovative, safe, and effective medical devices

FDA Marketing Authorization Is The Goal Of Financing And Will Lead To Financially Rewarding Exit

In Reality the Total Product Life Cycle (TPLC) From Idea to Adoption Is Much Longer



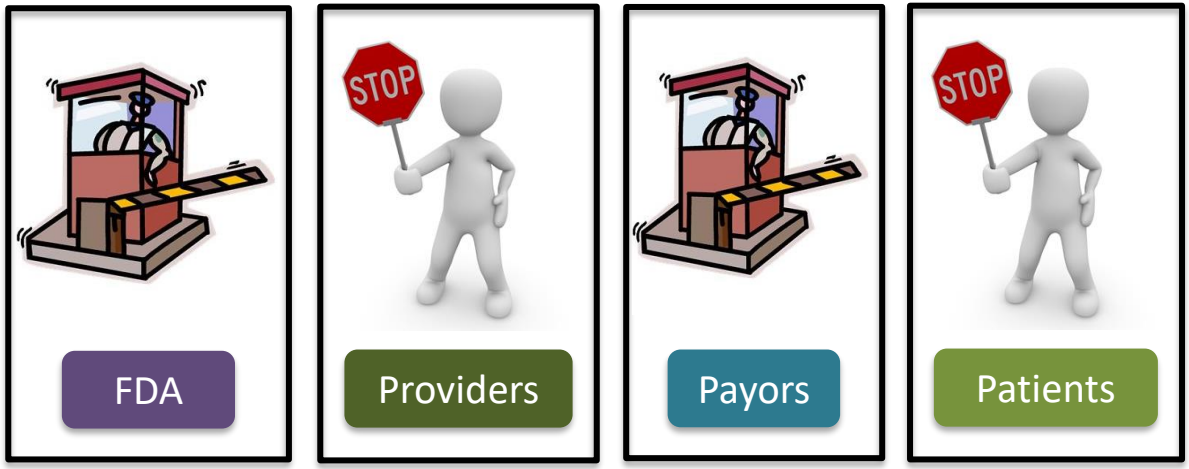
Medical Device Total Product Lifecycle (TPLC)



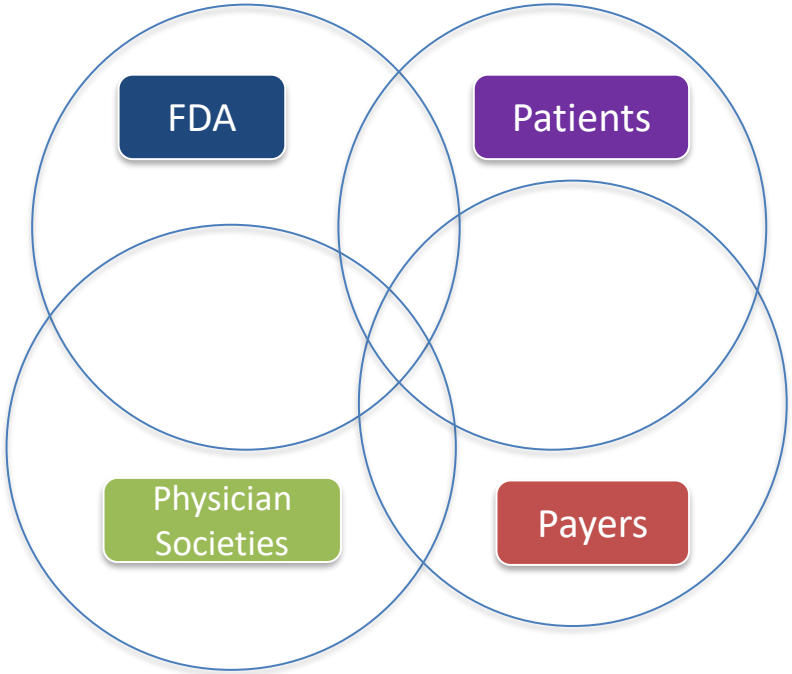
Lack of transparency makes the process of innovation too risky, costly & time consuming.

No single stakeholder has ownership of the total process.

It's not laying blame; it's just the way the system evolved.

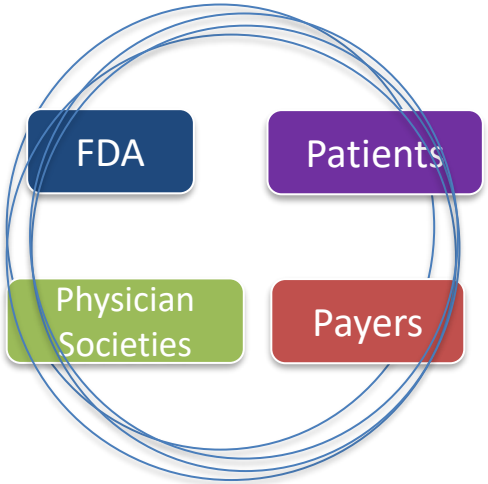


Every Stakeholder Has A Different Evidence Requirement For Advocacy



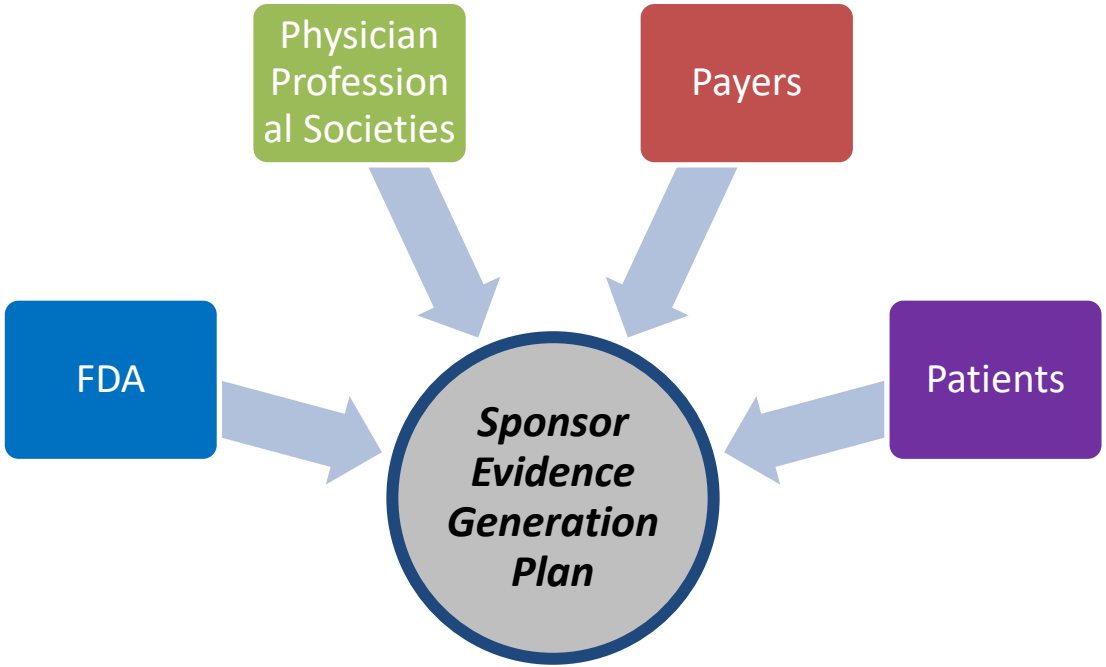
Lack of early coordination of stakeholder evidence requirements is a formula for failure

TAP Is Trying To Increase The Overlap Early With Information



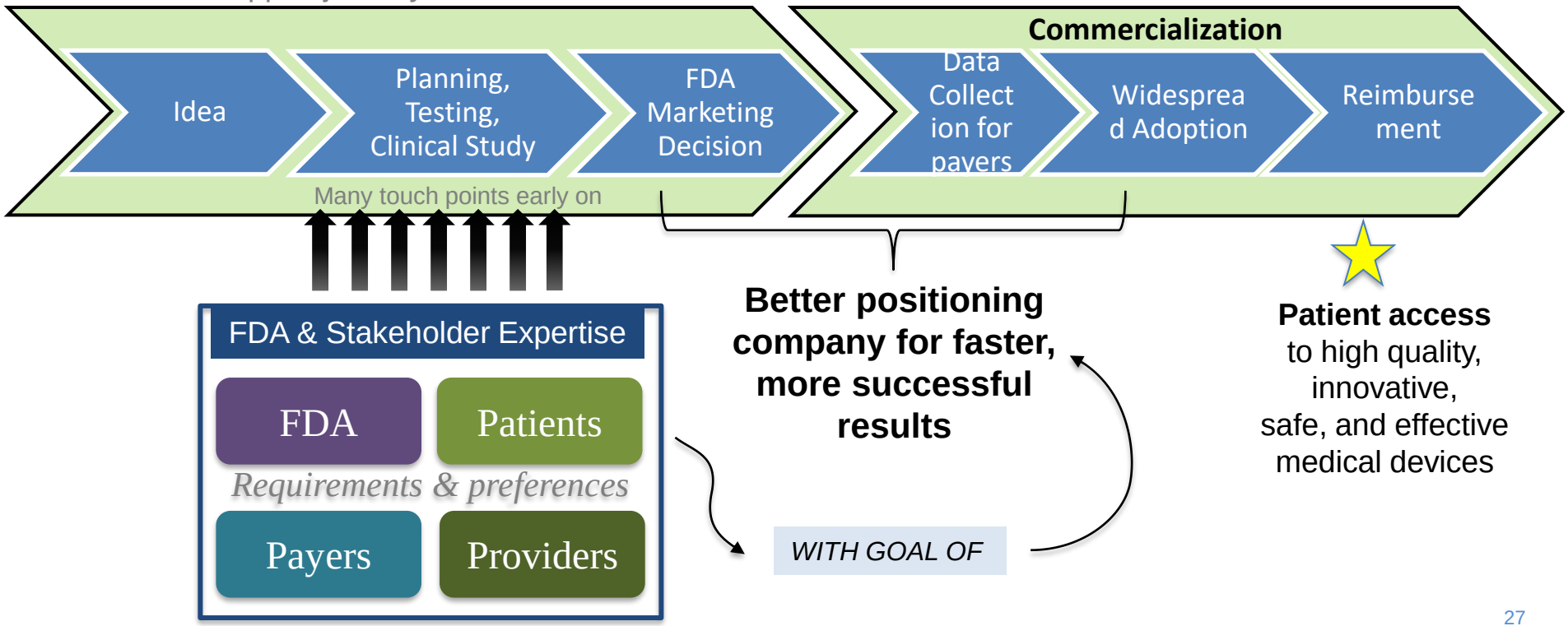
Early coordination of stakeholder evidence requirements should greatly decrease late-stage failure

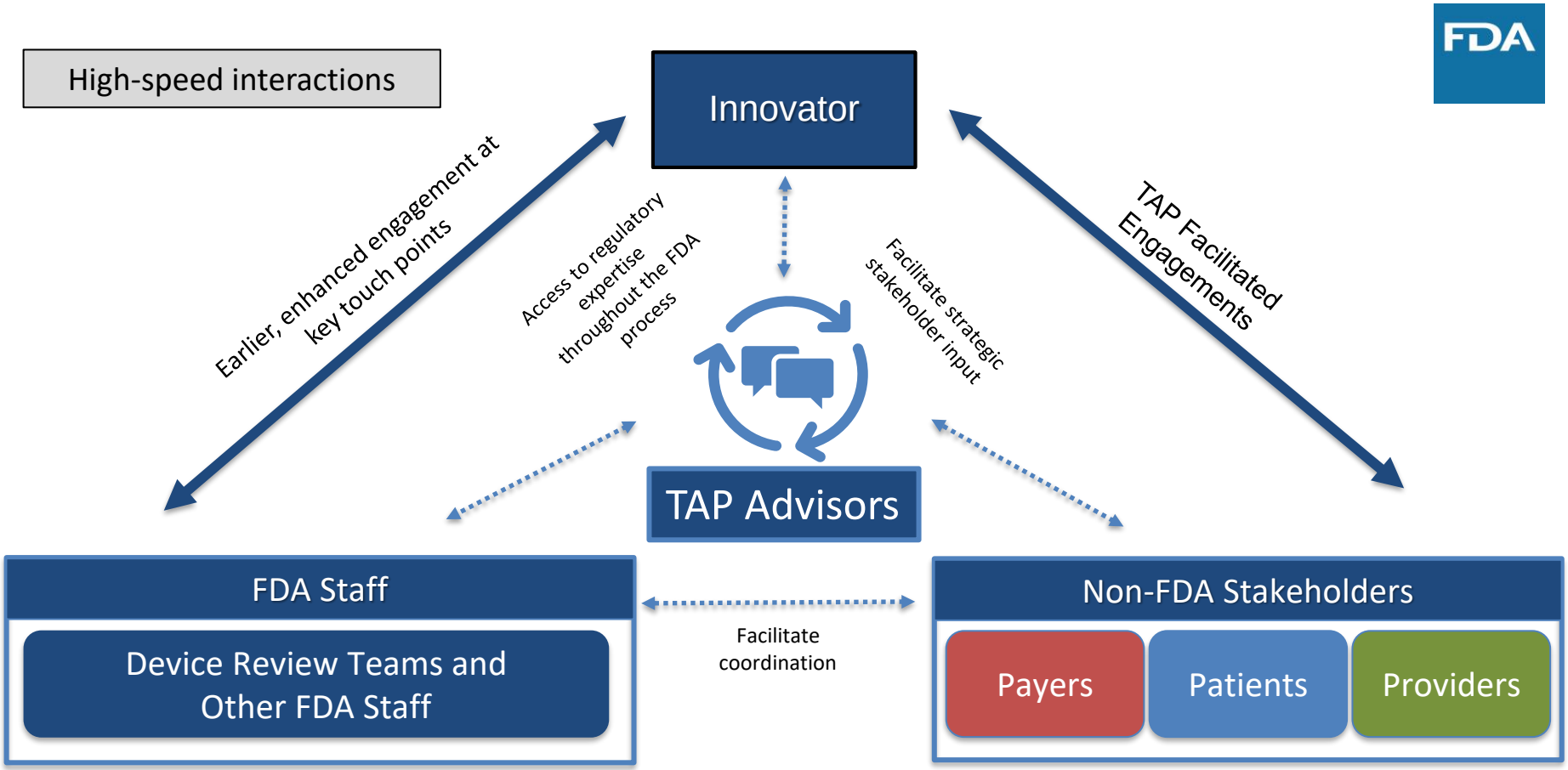
Communication, Trust Relationships and Coordination/Parallelization Are The Keys To Success



Early, frequent, coordinated stakeholder interaction increases transparency, predictability; lowers failure, risk, time, cost & speeds patient access

A shorter, happier journey



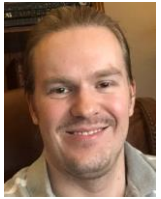

High-speed interactions
Innovator
Earlier, enhanced engagement at key touch points
Access to regulatory expertise throughout the FDA process
Facilitate strategic stakeholder input
TAP Facilitated Engagements
TAP Advisors
FDA Staff
Device Review Teams and Other FDA Staff
Facilitate coordination
Non-FDA Stakeholders
Payers
Patients
Providers

Our team of TAP Advisors have deep regulatory, clinical, operational, consulting and commercial payer experience

AJ Baumel
- 20+ yrs MedTech industry experience
- MDIC Case for Quality Program Director
- 10 yrs DoD R&D

April Marrone, PhD, MBA
- 10 yrs FDA CDRH
- Device Regulatory Expertise

Kim Ferlin, PhD
- 8 yrs FDA CDRH
- Device Regulatory Expertise



John Kosowicz, PhD
- 5 yrs FDA CDRH
- FDA Internal Consultant and Auditor

Mark Hayes, MD
- 20 yrs practicing Cardiologist
- Chief of Cardiovascular Services, eviCore
- Medical Director, Ascension Healthcare

Julius Torelli, MD
- 24 yrs practicing Cardiologist
- CMO Novocardia
- Chief of Cardiovascular Services, eviCore

Kai Kadoich, MBA
- 14 yrs MedTech industry experience
- Strategy, Business Development, and Marketing at Medtronic
- L.E.K. Consulting

Laura Gottschalk, PhD
- 5 yrs FDA
- Device and Biologics Lead
- BARDA

Conclusions

CDRH Vision

Timelier patient access to **better characterized**, safer and **more** effective medical devices

- **Earlier continuous interactive** FDA/Innovator/Stakeholder **communication**
- More risk capacity dedicated to **real clinically relevant product innovation**
- Help Innovators understand and **plan early for stakeholder risk**
- Help Innovative devices achieve **rapid & broad commercialization**
- **Further CDRH's public health mission**

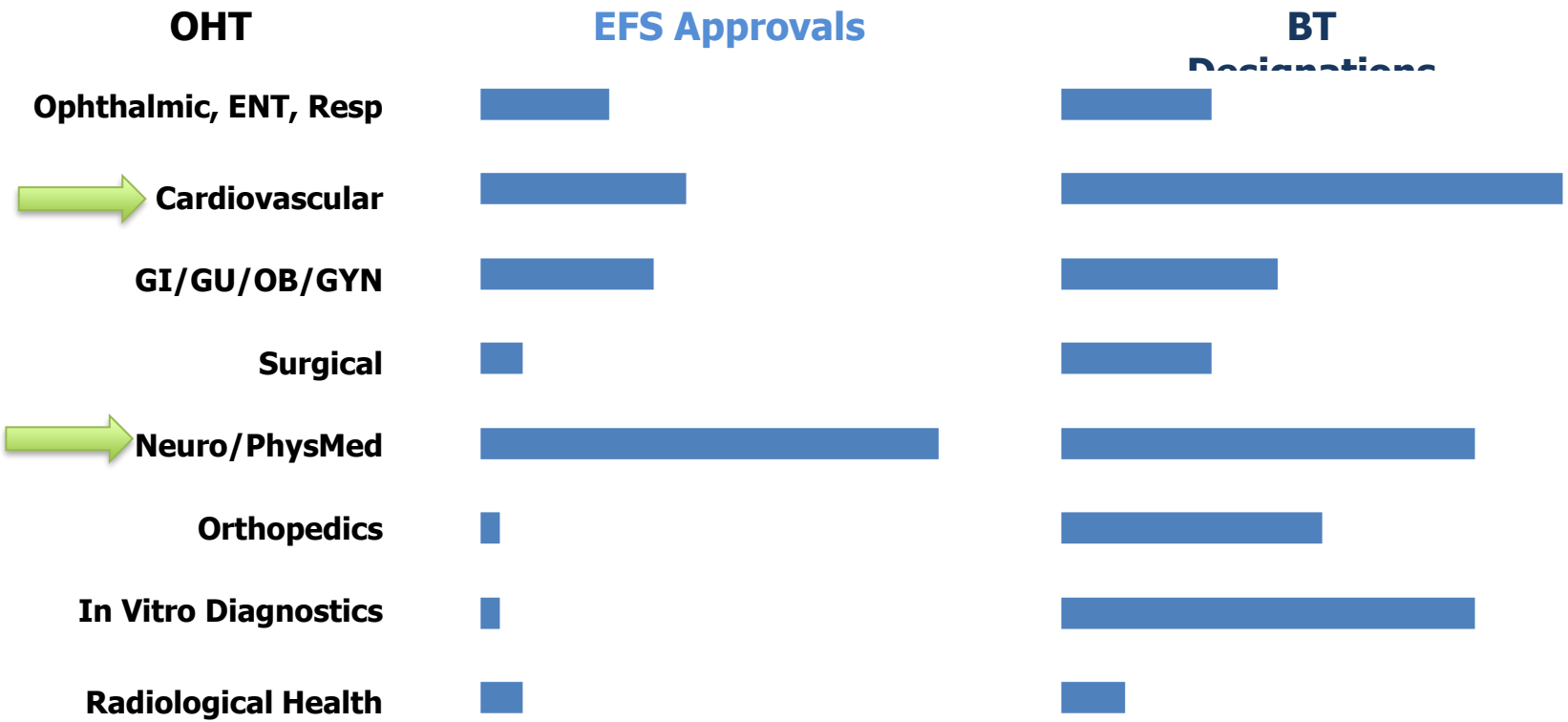
TAP Pilot - established by MDUFA V

- The TAP Pilot is a new component of the Medical Device User Fee Amendment (MDUFA) V Agreement (https://www.fda.gov/media/158308/download). FDA has committed to establish the TAP pilot during MDUFA V.

- TAP Pilot Objective: The TAP Pilot is intended to demonstrate the feasibility and benefits of process improvements to FDA's early interactions with participants and FDA's facilitation of interactions between participants and stakeholders that support the vision for TAP.

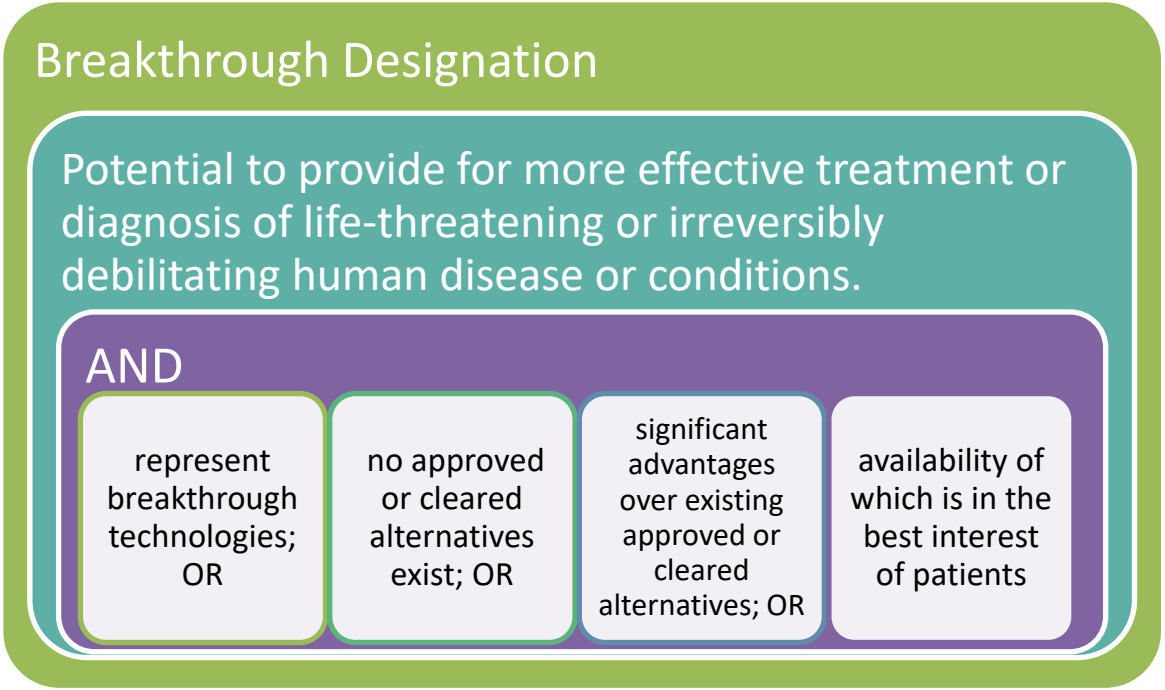
- Vision: The long-term vision for a successful TAP is to help spur more rapid development as well as more rapid and widespread patient access to safe, effective, high-quality medical devices of public health importance. A mature TAP will also help ensure the sustained success of the Breakthrough devices program.

Early Feasibility Study & Breakthrough Device Distribution Across CDRH



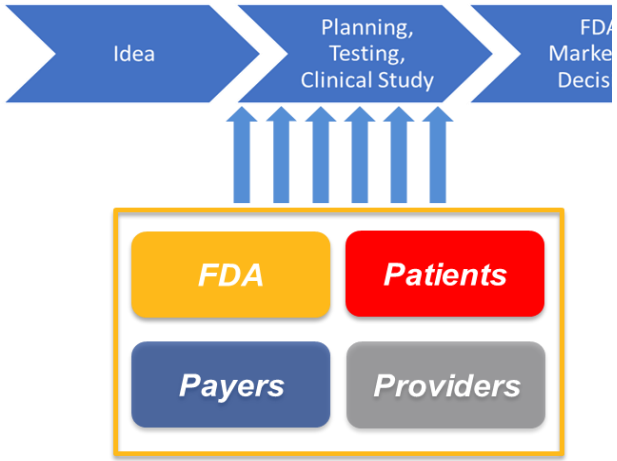
TAP Enrollment Criteria

✓ Devices with a granted Breakthrough designation**



TAP Enrollment Criteria

- ✓ No Pre-Submissions submitted after granted Breakthrough designation**
- ✓ Devices will be early in their device development process (e.g., have not yet initiated a pivotal study) at time of enrollment
- ✓ Each participant will have a maximum of one device enrolled in the pilot per fiscal year
- ✓ Devices regulated by CBER and combination products are outside the scope of the Pilot at this time



TAP Enrollment Process

Submit an amendment to the file under which Breakthrough designation was granted (Document Control Center/portal)

FDA has 30 days to assess if request meets enrollment criteria

Enrolled on a first-come, first-served basis, using the date of receipt until the maximum number of devices have been enrolled for a given FY

Enrollment numbers are updated on the TAP web page. Will only consider requests for a given FY at the start of the FY

TAP Program Resources

- MDUFA V Commitment Letter
  - https://www.fda.gov/media/158308/download
- TAP Pilot Federal Register Notice (87 FR 61605)
  - https://www.federalregister.gov/documents/2022/10/12/2022-21835/medical-devices-voluntary-total-product-life-cycle-advisory-program-pilot
- TAP Pilot Docket Number FDA-2022-N-2274
  - https://www.regulations.gov/docket/FDA-2022-N-2274/document
- TAP Pilot Web Page
  - https://www.fda.gov/medical-devices/how-study-and-market-your-device/total-product-life-cycle-advisory-program-tap
- TAP Pilot Program Email Address
  - TPLC-Advisory-Program@fda.hhs.gov

3

CMS TCET pathway to reimbursement

Steve Farmer, MD, PhD
Chief Strategy Officer for Coverage at Centers for Medicare & Medicaid Services, Baltimore, MD
Associate Professor of Medicine & Health Policy and Management, George Washington University, Washington, DC

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Transitional Coverage for Emerging Technologies (TCET)

Steve Farmer, MD PhD
Chief Strategy Officer
Coverage & Analysis Group
Center for Clinical Standards and Quality

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This presentation is a general summary that explains certain aspects of the Medicare Program but is not a legal document. The official Medicare Program provisions are contained in the relevant laws, regulations, and rulings. Medicare policy changes frequently, and links to the source documents have been provided within the document for your reference

The Centers for Medicare & Medicaid Services (CMS) employees, agents, and staff make no representation, warranty, or guarantee that this compilation of Medicare information is error-free and will bear no responsibility or liability for the results or consequences of the use of this guide.

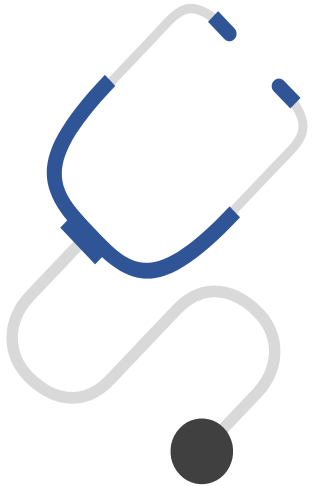
No financial conflicts to disclose

CMS Mission: Promoting Evidence-based Care

Evidence-based coverage underpins the HHS / CMS value mission

CMS is uniquely positioned to establish evidence-based care standards

CMS may extend coverage to an item or service that is considered "reasonable and necessary" as defined under the Social Security Act



Reasonable and Necessary is defined for Medicare contractors as[1]:

- **Safe and effective;**
- **Not experimental or investigational; and**
- **Appropriate for Medicare beneficiaries.**

[1]https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/pim83c13.pdf

Coverage Challenges for Emerging Technologies

Benefit Categories

- Medicare is a defined benefit program
- Emerging technologies may not neatly align with existing benefit categories

National Coverage Determinations

- Open and transparent public process
- Strength of Evidence in Medicare population (Benefits, Harms)
- Current standard of medical care
- Context of care (ordering, furnishing, site of care, related services)

Coding

- AMA, CDC, CMS
- Timings vary, not coordinated with FDA market authorization
- Use of claims for RWE data requires coding specificity, consistency

TCET Uses Existing CMS Authorities

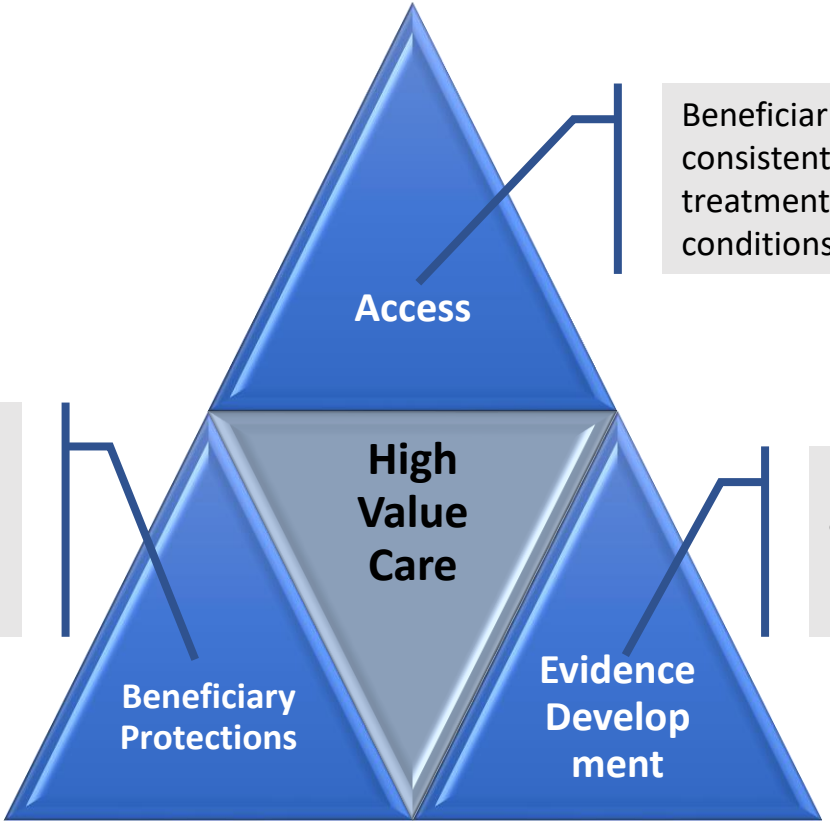
Open and transparent public process

- Once open, multiple opportunities for public comment

Most NCDs cover a class of items/services to the FDA labeling

- Agnostic to individual devices, covers to device – indication as a class
- Accommodates iterative refinements to devices
- Allows off-label coverage within approved study

CED Balances Access, Evidence Development, & Beneficiary Protections



Beneficiaries desire prompt and consistent access to new treatments, especially for conditions with limited options.

FDA approved indications may not address factors that CMS is required to consider when optimizing outcomes for Medicare Beneficiaries

Evidence at FDA market authorization may be limited, particularly for Medicare beneficiaries.

Pre-market stage

Objective: Set clear expectations for CMS coverage

CMS Actions:

- New: CMS National Coverage Analysis Evidence Review Guidance
- Updated: Coverage with Evidence Development Guidance
- New: Clinical Endpoints Guidance Series
- Forthcoming: Fit-for-purpose Study Guidance

Legend: CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; NCD = National Coverage Determination; CED-NCD = National Coverage Determination with Coverage with Evidence Development requirements.

Near-market stage

Objective: Engage manufacturers early to identify coverage options

CMS Actions:

- Enhanced: CMS-FDA coordination
- New: Initiate benefit category and coding reviews before FDA market-authorization
- New: Evidence Preview that summarizes the available evidence
- New: Stakeholder meeting(s) to review Evidence Preview, discuss options

Legend: CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; NCD = National Coverage Determination; CED-NCD = National Coverage Determination with Coverage with Evidence Development requirements.

Early post-market stage

Objective: Deliver consistent national coverage with safeguards

CMS Actions:

- New: With sufficient evidence, expedited NCD
- New: With material evidence gaps, time-limited CED-NCD that allows fit-for-purpose study designs
- New: Manufacturer-driven Evidence Development Plan
- Updated: Periodic study progress updates; safety surveillance

Legend: CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; NCD = National Coverage Determination; CED-NCD = National Coverage Determination with Coverage with Evidence Development requirements.

Post-market stage

Objective: Reduce burden through timely CED-NCD reconsiderations

CMS Actions:

- New: NCD reconsideration date specified in CED-NCD
- New: Streamlined reconsideration process against pre-specified objective success criteria

Legend: CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; NCD = National Coverage Determination; CED-NCD = National Coverage Determination with Coverage with Evidence Development requirements.

Fit-for-purpose studies

CMS is allowing greater use of fit-for-purpose studies for coverage

- Conventional studies often ideal conditions, smaller, shorter, narrow inclusion
- Fit-for-purpose often real-world conditions, larger, longer, more diverse inclusion

Fit-for-purpose studies include a study design, analysis plan, and study data that are appropriate for the research question

- Many make use of real-world data (Electronic Health Records, Administrative Claims, etc.)
- In some cases, registries may be necessary
- Rarely, the question may only be addressed through a conventional clinical study

Conclusions

CMS is committed to enhancing access to high-value emerging technologies

We are obligated to ensure that emerging technologies are appropriate for Medicare beneficiaries, who may have a different clinical profile than those studied in pivotal clinical studies

We published the proposed procedural notice and three guidance documents on June 22, 2023; we will propose fit-for-purpose guidance once those guidance documents are finalized

4

CMS as an HTA Agency

Peter Neumann, ScD
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Tufts Medical Center, Boston, MA
Professor, Tufts University School of Medicine, Boston, MA

TuftsMedicine

CMS as an HTA Organization

Presentation at ISPOR

Peter Neumann, ScD,
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PERSPECTIVE

CMS AND HEALTH TECHNOLOGY ASSESSMENT

Turning CMS into a Health Technology Assessment Organization

Peter J. Neumann, Sc.D., and Sean R. Tunis, M.D.

CMS evolution as an HTA organization

Going forward

- Address workforce and resource issues
- Improve FDA-CMS coordination
- Strengthen CED
- New legislative authority

Thank you!

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Discussion