

Aligning Stakeholders from Regulatory, Clinical, Commercial and Health Outcomes to Develop a Impactful PRO Strategy

**Linda Deal, Senior Director
Patient-Reported Outcomes
Pfizer**

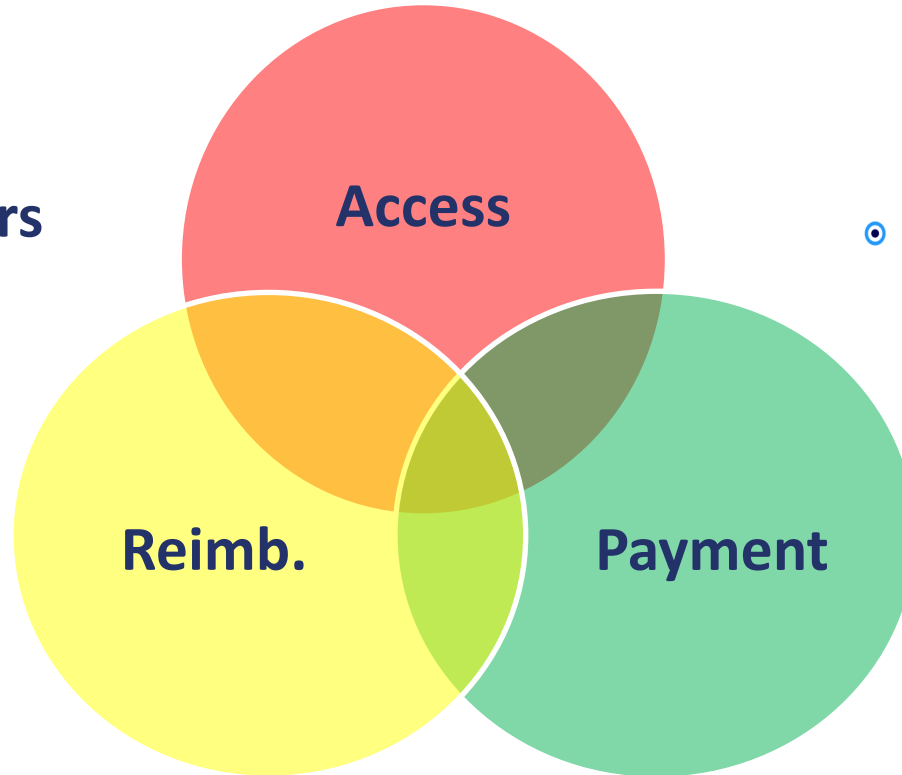
**Harris Kaplan, President and CEO
Healogix**

International Society for Quality of Life Research and
the
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The Future of Pharma Lies in the Ability to Develop Drugs that Create Value

PRO's are a Pivotal Part of Value Creation



- Patients and Payers are Increasingly Important in Assuring Access, Reimbursement and Payment

- Patients and Payers will only Pay for What They Value

The Steps for Creating Value in the New Rx World

- Identifying the right outcomes is critical as well as measuring the right outcomes “right”
- To have impact, you have to get engaged early
- You have to align customer outcomes with clinical and commercial interests



Agenda

- Case Study – Acute Ischemic Stroke
 - Background
 - Objective
 - Methods
 - Results
- Lessons to carry forward

***Background:* Acute Ischemic Stroke**

- **Second leading cause of mortality in the Western world**
- **The leading cause of disability with more than 4 million stroke survivors in the United States alone.**
- **Approximately 90% of stroke survivors are left with some residual deficit.**
- **There is a maximum of 6 hours time to salvage cells that haven't died.**
- **The goal in treating AIS is to preserve healthy brain tissue.**
- **The only drug currently approved to treat acute ischemic stroke is tPA**
- **tPA must be administered within three hours of the onset of stroke**

The Oppty: Large and Growing

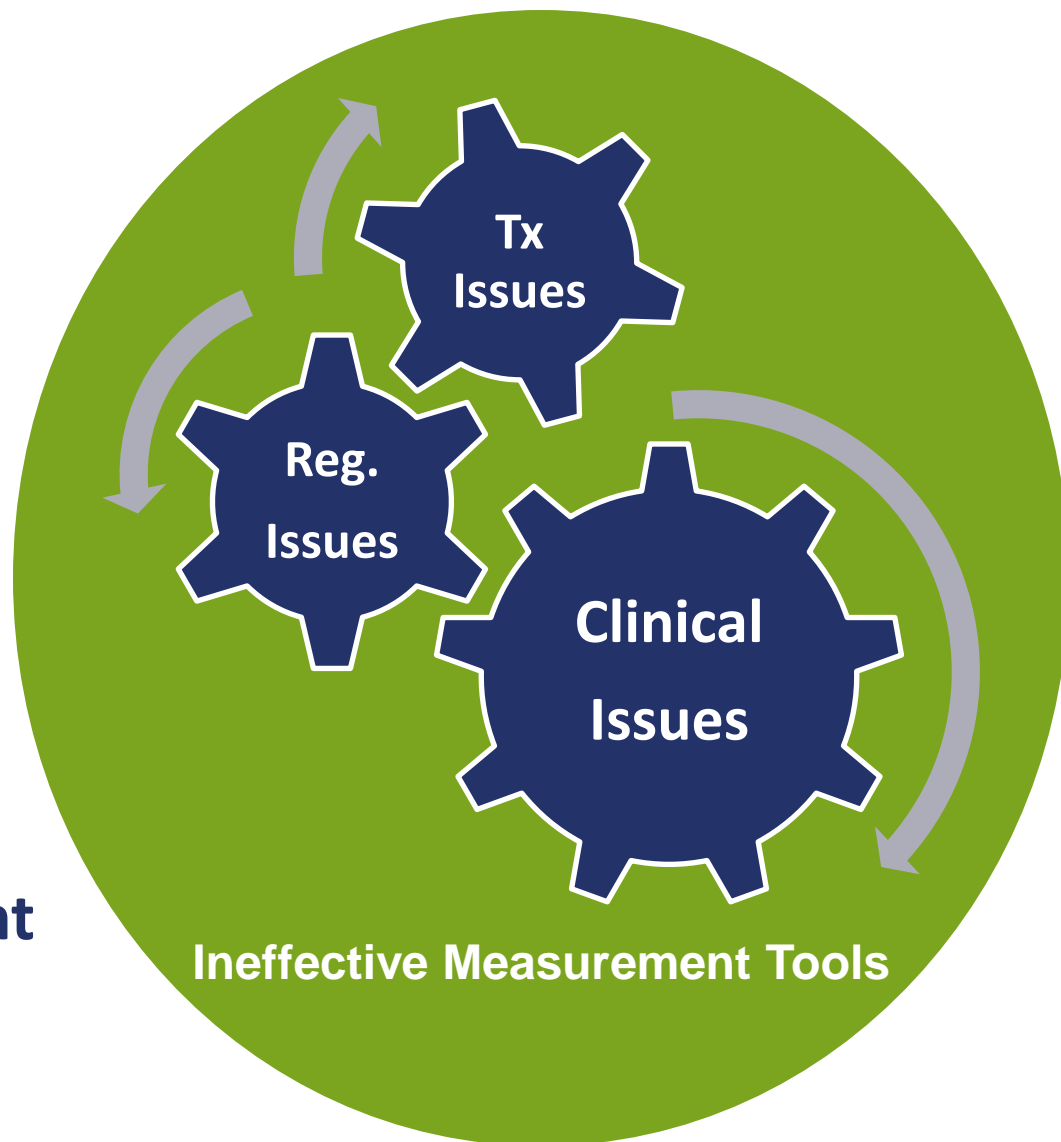
- **Large Market**
- **Growing Market – Aging Population**
- **High Unmet Need – Big Opportunity**
- **Little Competition**
- **High Cost of Care**

Sad Reality:

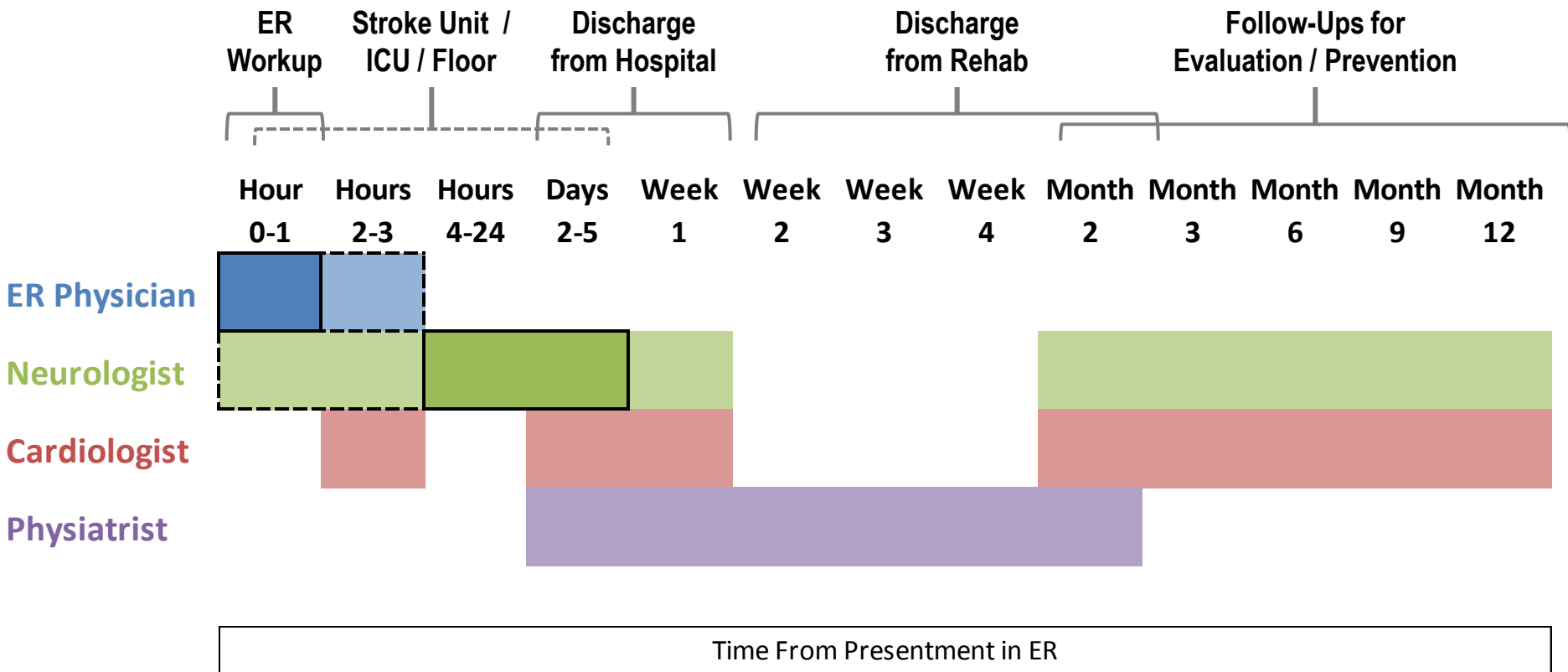
Stroke Has Been a Graveyard for New Drugs

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- Multiple stakeholders
- Challenging therapeutic issues
- Difficult clinical development
- Poorly addressed regulatory issues
- Ineffectual Measurement Tools



The Challenge: Current Treatment of AIS Involves Multiple Stakeholders



***Bold outline and darker shading indicates certain involvement with patient;
Lighter color shading indicates potential involvement with patient***

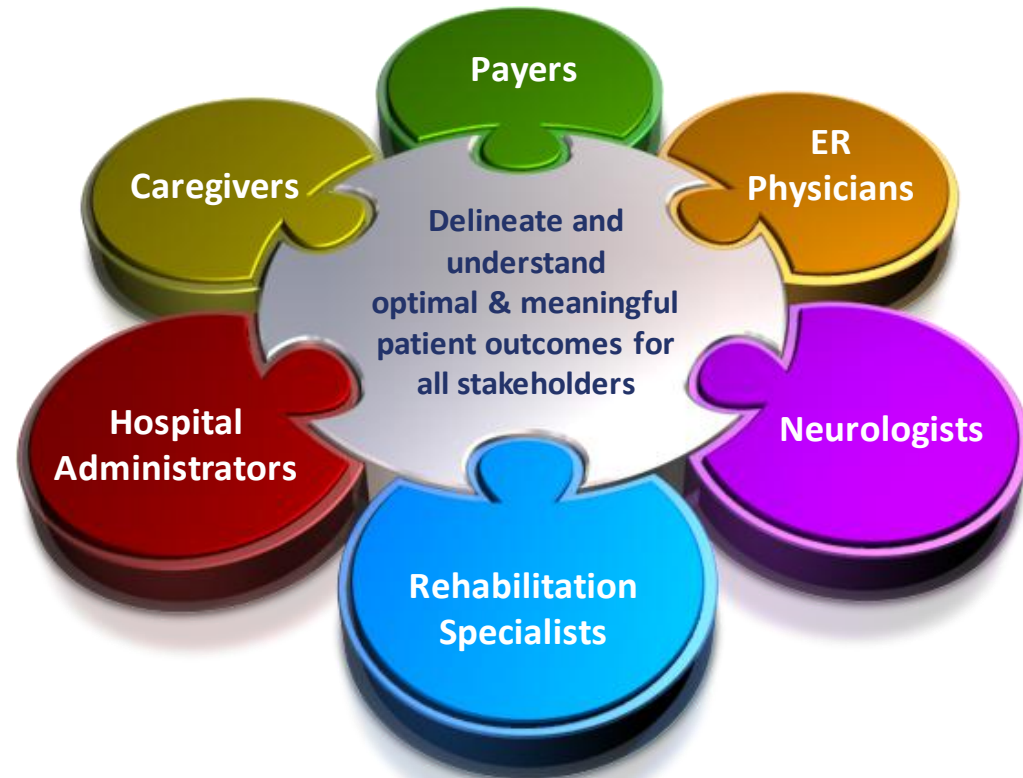
Engagement Goal:

Identify a Framework for Moving Forward....

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- Identify Relevant Value Measures / Outcomes for each stakeholder
- Determine if common ground exists
- Help understand current measures
 - Stroke Impact
 - Post Stroke Progress & Rehabilitation

Identifying & Understanding Patient Outcomes for Stroke



...That Overcomes Multiple Obstacles and Gets Internal Stakeholders Excited and Aligned

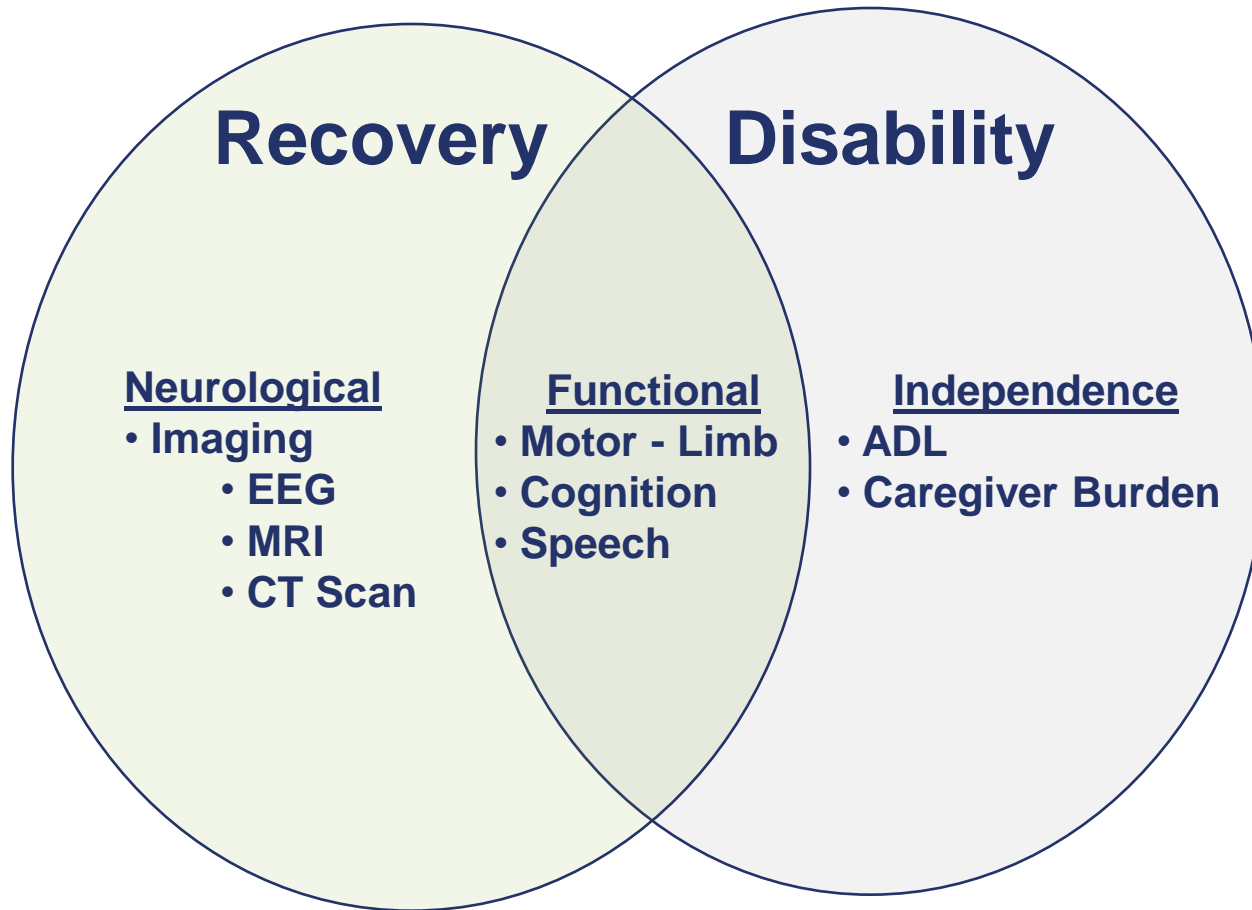
- **The current endpoints are not “good endpoints”.**
 - Not fit for purpose
 - Modified Ranking not sensitive, poor resolution (only measures mobility, observer variability)
 - Don't reflect the true patient experience
- **Deficits vary from patient to patient**
- **Getting regulatory agencies to accept a new endpoint is difficult, at best.**
- **Proving that new endpoint is superior to an existing one is a major challenge**



Engagement Objective

- Identify relevant stroke measure(s)
 - Suitable for evaluating a novel treatment efficacy
 - ◆ Go/No go decisions
 - Acceptable for use as a registration endpoint
 - Practical for use in a clinical trial setting
 - Easily understood and completed by clinicians, patients or caregivers
 - Commercially relevant – able to support market access, pricing and reimbursement

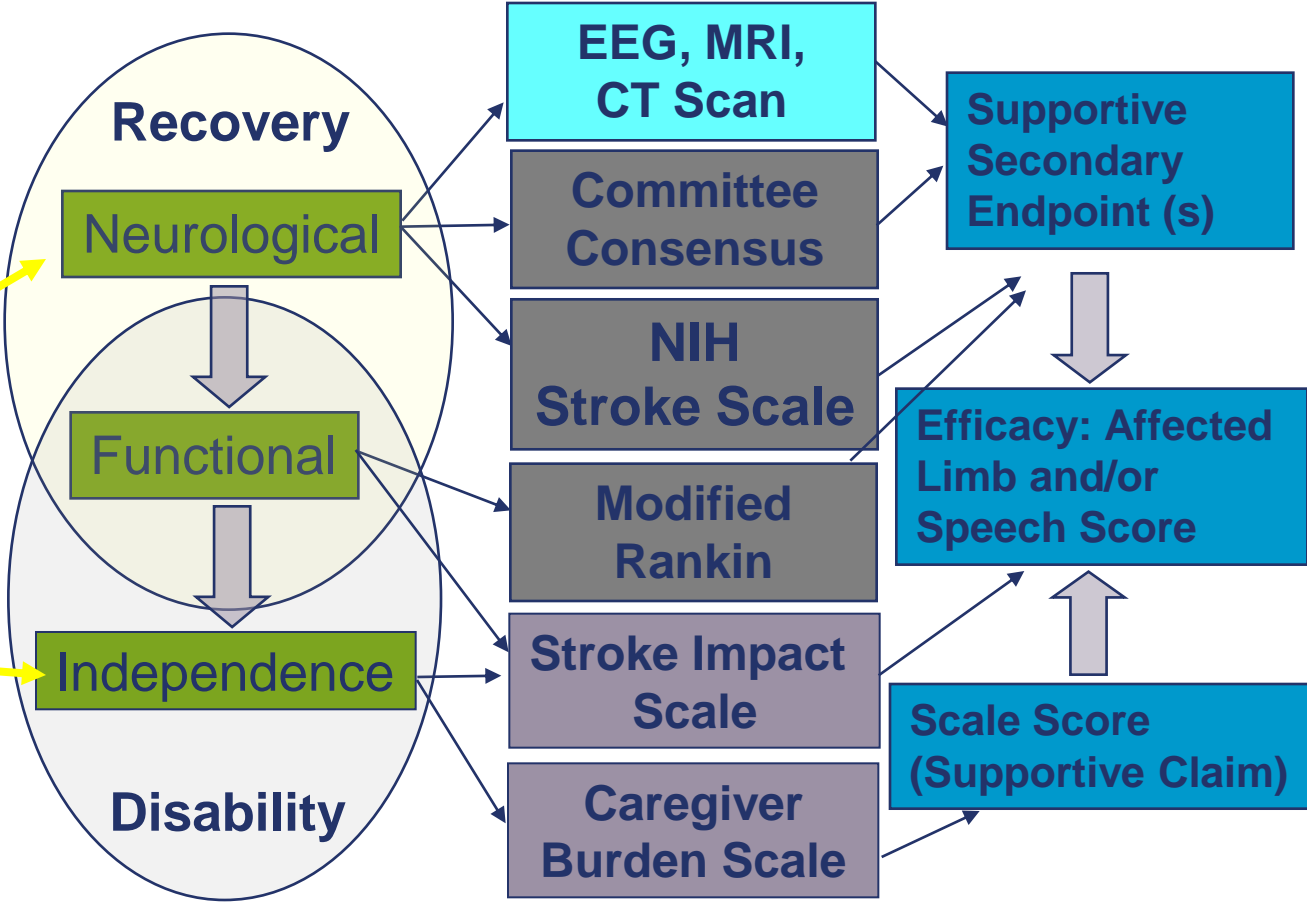
What Do We Measure?



Starting Point: Linking Indication to Concepts, Measures and Endpoints

tPA Indication Language

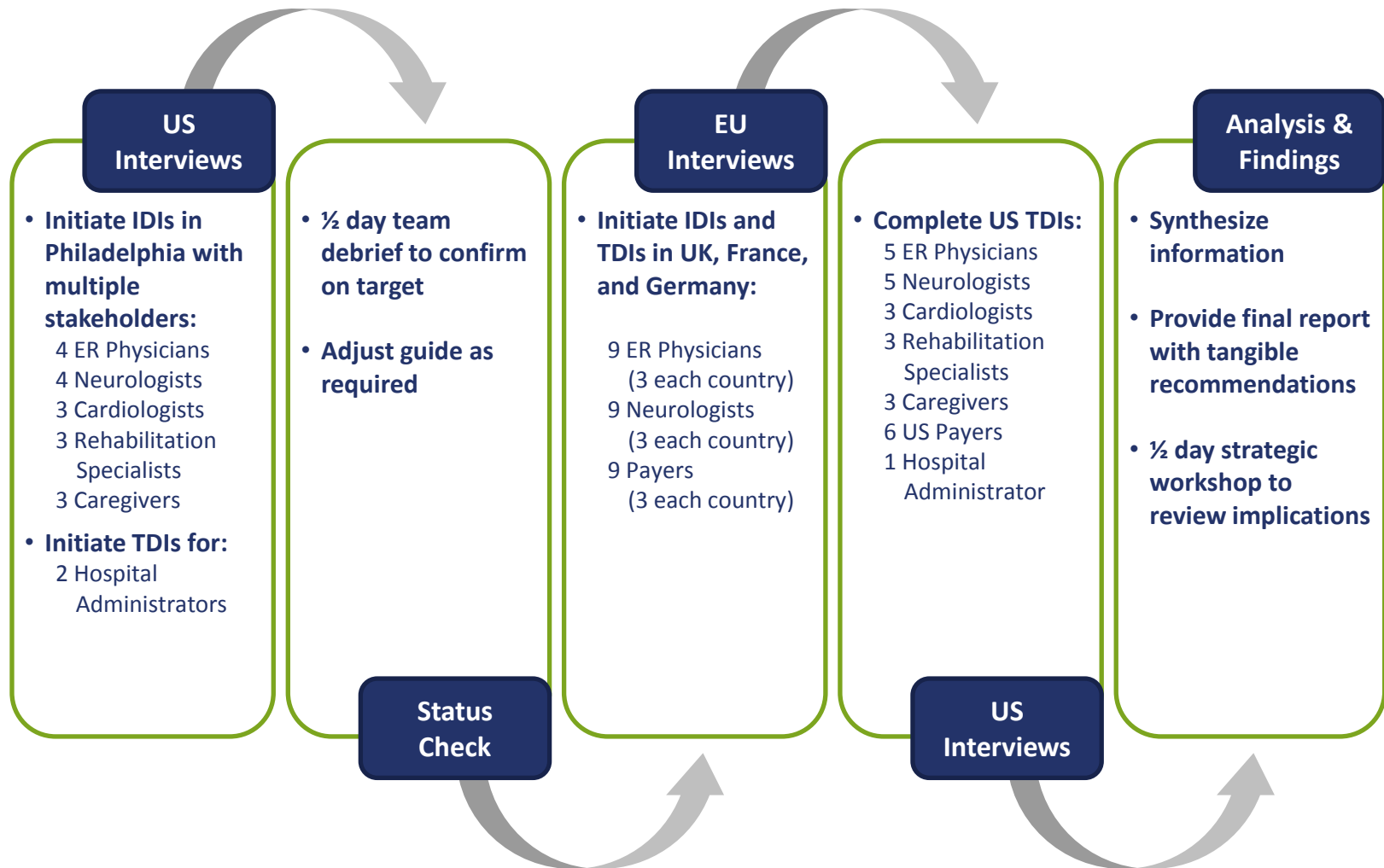
Drug X is indicated for the management of acute ischemic stroke in adults for improving **neurological recovery** and reducing the **incidence of disability**.



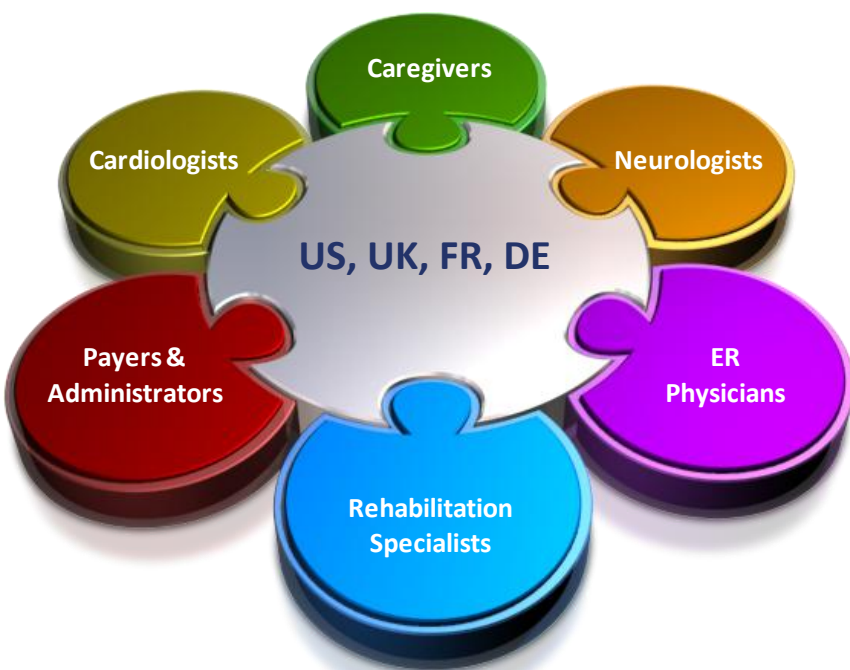
Concepts	Objective Measure	Clinical Measure	PRO	Endpoint
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Methodologies Employed

Methods



Sample Details by Stakeholder and Country

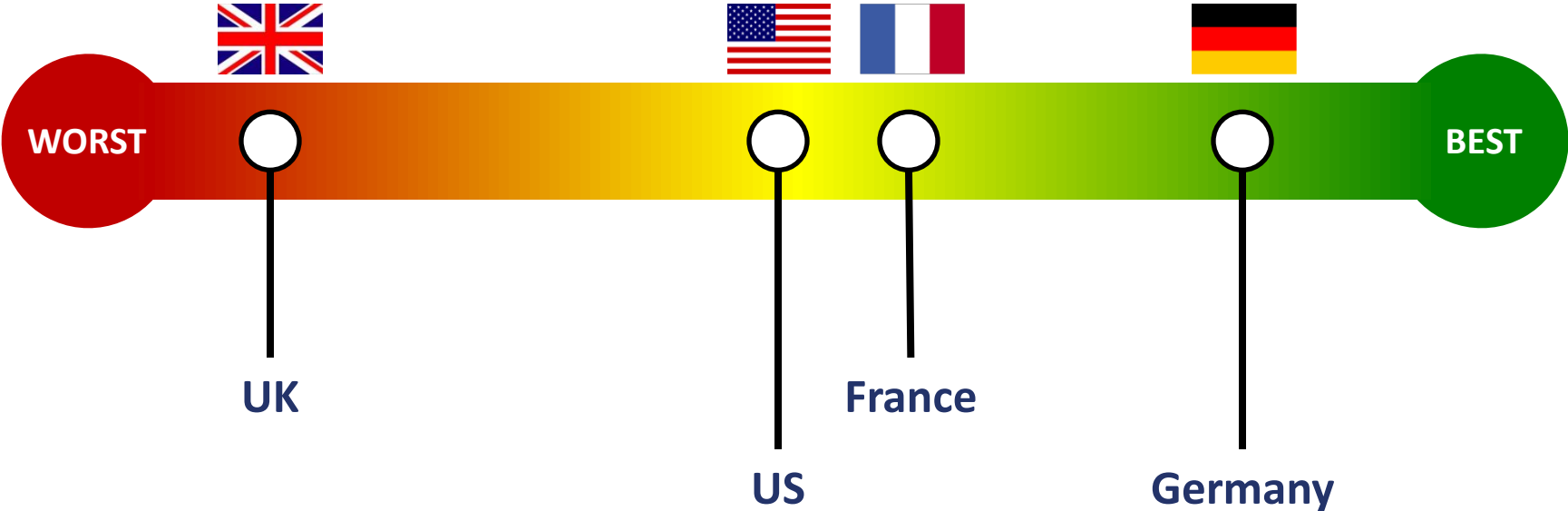


Respondent Type	US	UK	FR	DE	Total
Neurologist	9	2	3	3	17
ER Physician	9	3	3	2	17
Rehabilitation Specialist	6	1	-	2	9
Payer	3	3	3	3	12
Administrator	6	-	-	-	6
Cardiologist	6				6
Caregiver	6	-	-	-	6
Total	45	9	9	10	73

Stroke Treatment: All Countries Recognize the Importance of Speedy Treatment

- How they've organized to support that and the ability of patients to get speedy treatment varies considerably.

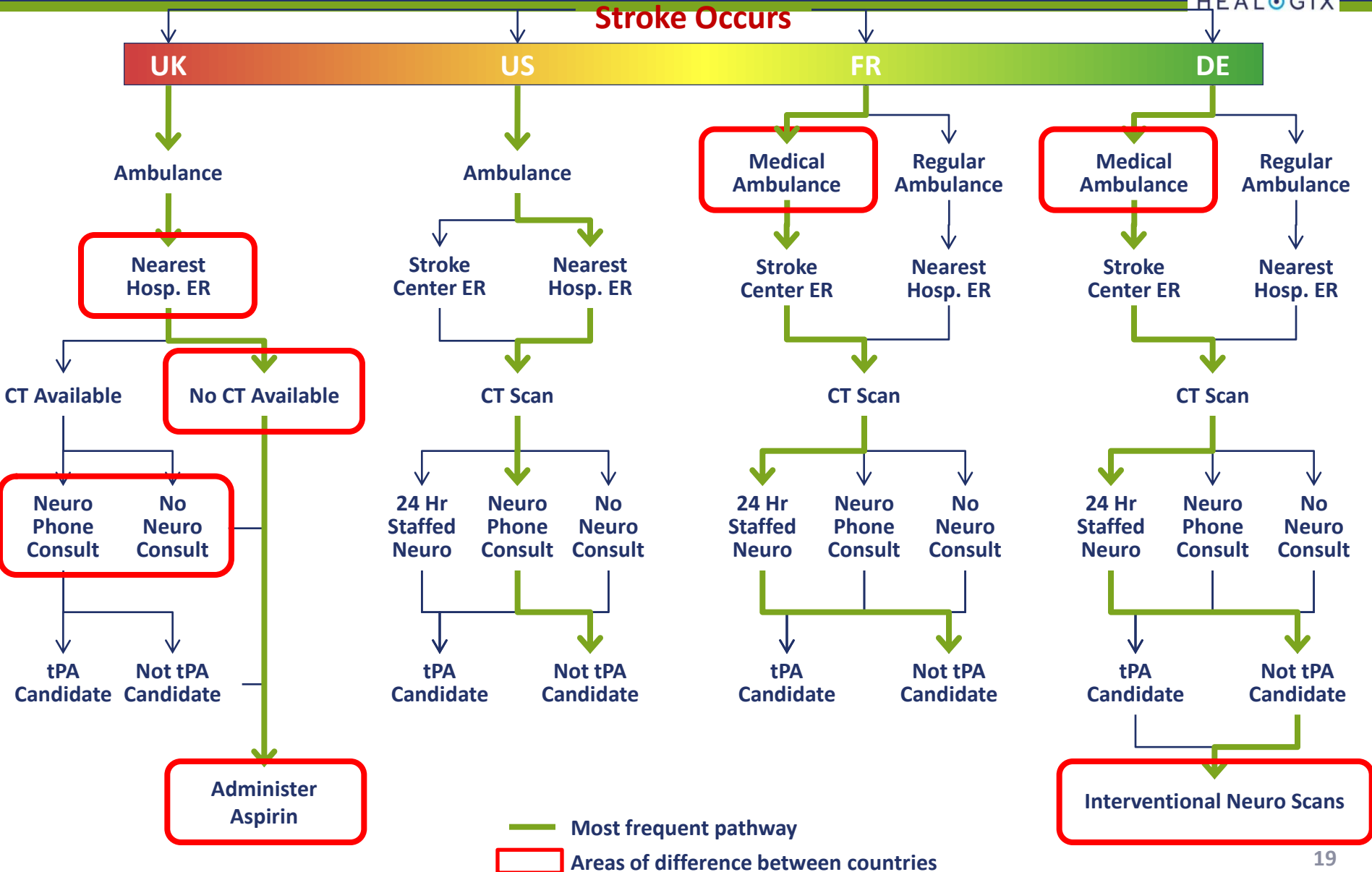
Continuum of Stroke Treatment



The biggest challenge in treating stroke today is getting patients to the hospital in time to use tPA

- The traditional 3-hour window for tPA is expanding to 4.5 or 6 hours, depending on facility and country
- Despite the wider window and efforts of individual countries, the percent of patients receiving tPA has not changed significantly
- 10% or less of stroke patients receive tPA, due to:
 - Length of time between when stroke occurred and when first recognized by patient/caregiver
 - Length of time between when recognized and when admitted to ER (due to distance to hospital or timing of ambulance)
 - Availability of diagnostic equipment and/or Neurologist consult
 - Risk of hemorrhage as side effect of tPA (7% bleed out rate)
 - Exclusion based on severity of stroke as determined by the NIH Stroke Scale (NIH SS)

The treatment of stroke challenges the capacity and physical boundaries of hospitals



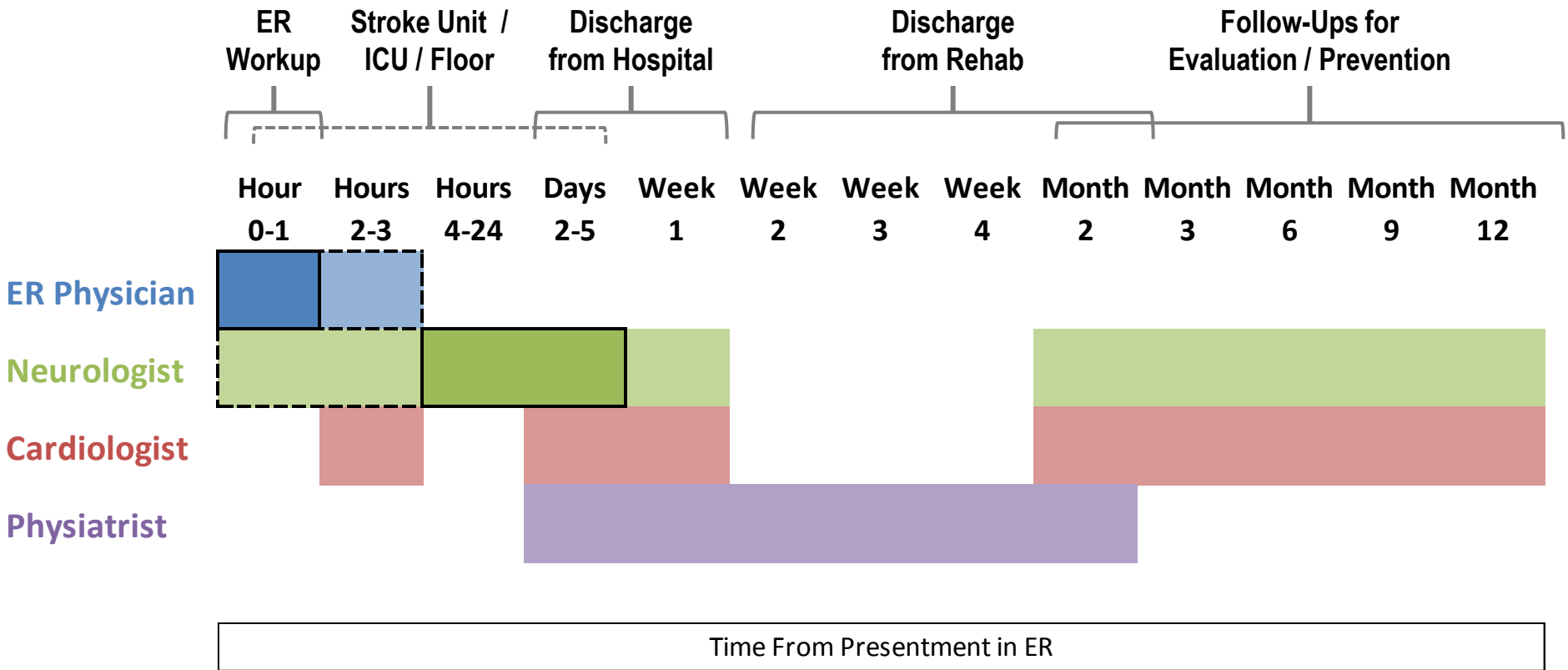
Summary of Key Findings: All stakeholders recognize “time is brain” and the more brain, in theory, the better the patient outcomes

- **Each stakeholder plays a critical role in stroke treatment and management**
 - **ER** determines if event was a stroke and tPA candidacy
 - **Neurologists** decide whether to use tPA, determine cause of the stroke, and proposes rehabilitation strategy
 - **Physiatrist** finalizes rehabilitation strategy and documents functional progress
 - **Payers and administrators** ensure total cost is minimized, but recognize there is little room for improvement while patient is hospitalized
 - **Caregivers** carry financial, physical, and emotional burdens as a result
- **Relevant scales used vary by time since stroke**; NIH Stroke Scale most frequently used in the hospital while the FIM* most frequently used in rehabilitation
- **Stakeholders are in alignment around maximizing patient functional status and preventing subsequent events**

Acute Ischemic Stroke

STAKEHOLDER ROLES IN STROKE TREATMENT / MANAGEMENT

Physician Roles in Acute Ischemic Stroke



Time From Presentment in ER

*Bold outline and darker shading indicates certain involvement with patient;
Lighter color shading indicates potential involvement with patient*

ER Physician Role:

Identify, workup, and move on

Primary Questions

- Is it a stroke?
- Are they a candidate for tPA?

Key Responsibilities

- Triage
- Have NIH Stroke Scale performed
- Order CT Scan and other tests according to hospital protocol
- Call for Neurologist consult, especially if patient is a tPA candidate
- GOMER
(Get Out of My ER)

Neurologist Role:

Figure out what happened and how to treat

Primary Questions

- What caused the stroke? Where is the damage and how severe is it?
- Should we treat with tPA or other neurologic intervention?

Key Responsibilities

- Primary decision maker for using tPA, considering time since event, type of stroke, and NIH SS score
- Potentially order neurologic interventional scans or other tests
- Usually follow patient daily through discharge
- Follow up with patient after discharge from rehab to manage medications to help prevent a secondary event
 - Diabetes
 - Dyslipidemia
 - Hypertension

Hospitalist Role:

Get them stable and get them out

Primary Questions

- What can we do to stabilize and prepare the patient?

Key Responsibilities

- Stabilize patient while on floor
 - Diabetes
 - Dyslipidemia
 - Hypertension
- Set up next layer of care or other services needed
 - Rehabilitation
 - Nursing care
 - Social services

Cardiologist Role: Stop it from happening again

Primary Questions

- Is there an underlying cardiac condition that may impact the decision to use tPA?
- How can we prevent a secondary event?

Key Responsibilities

- Involved while patient is in ER or on floor only if has a pre-existing cardiac condition
- Follow up with patient after discharge from rehab to manage medications to help prevent a secondary event
 - Diabetes
 - Dyslipidemia
 - Hypertension

Physiatrist Role:

Get the patient back as “normal” of a life as possible

Primary Questions

- Is the patient a candidate for rehab?
- Can we get them close to pre-stroke baseline?

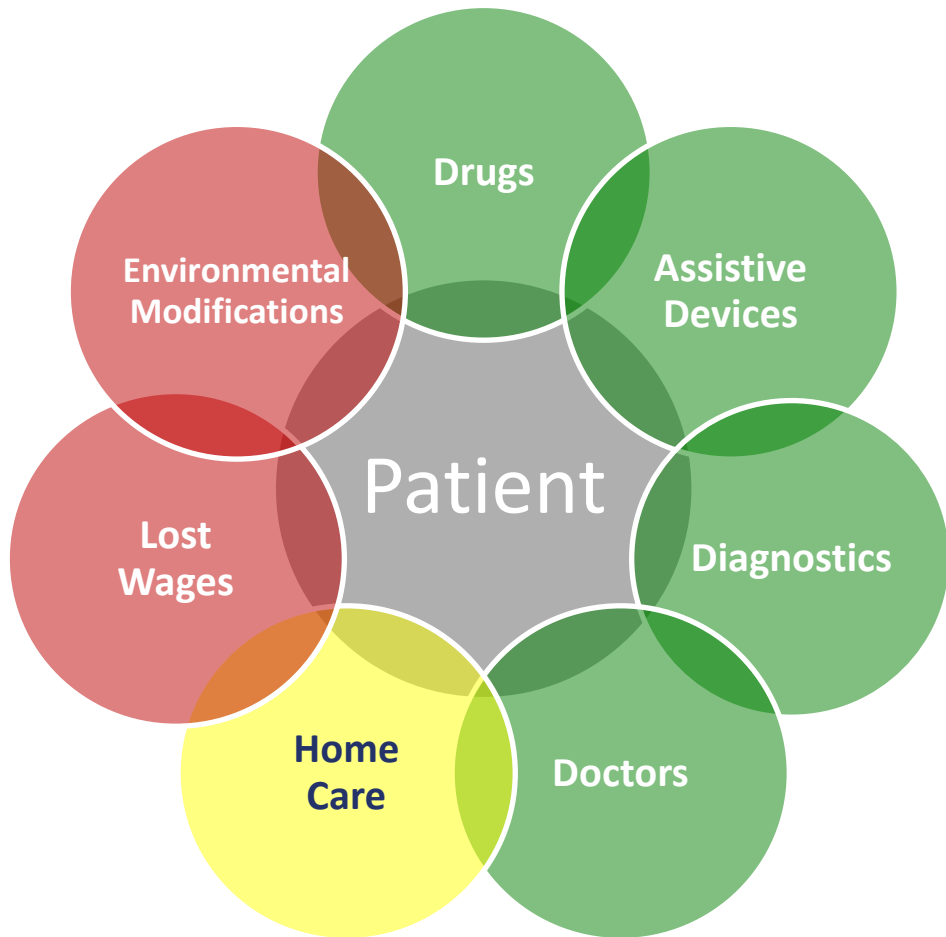
Key Responsibilities

- Assess candidacy and potential for rehabilitation while in hospital
- Assess goals and progress during rehabilitation
- Determines what functional tasks or home modifications patient will need
- May or may not complete FIM* (or similar) to track and justify progress

Payer Role:

Pay for critical care; then pay for progress

Scope of Stroke Costs Covered



- All payers reimburse (US, UK, FR, DE)
- Some payers reimburse (FR, DE)
- No payers reimburse

- Payers are concerned with the total cost of care
 - Time in rehabilitation and hospital admission are the most costly in US and UK
 - Rehabilitation costs less of a concern in France, Germany
- Outcomes centric
- Conscious of diminishing returns
- US, UK, France, and Germany all cover associated drugs, devices, diagnostics, and doctor visits
- France and Germany cover cost of home care
- Lost wages and cost of environmental modifications (e.g. fitting bathroom to be wheelchair accessible) are not covered in any country

Administrator Role:

Maximize care while minimizing costs

- Hospital Administrators recognize there is little they can do while patient is hospitalized to reduce costs without decreasing quality of care
 - Stroke treatment is a necessary cost of doing business
- Hospital Administrators are concerned about:
 - Liability with regard to use of tPA
 - Fixed-rate reimbursement and increased patient length of stay due to lack of rehab beds
- Rehab Administrators are concerned about:
 - Minimizing length of stay while maximizing patient function
 - Inadequate reimbursement – a “wallet biopsy” – particularly for Medicaid / Medicare patients
 - Increasing time spent dealing with insurers and justifying additional reimbursement for increased length of stay

Caregiver Role:

Pick up the pieces and continue care and support

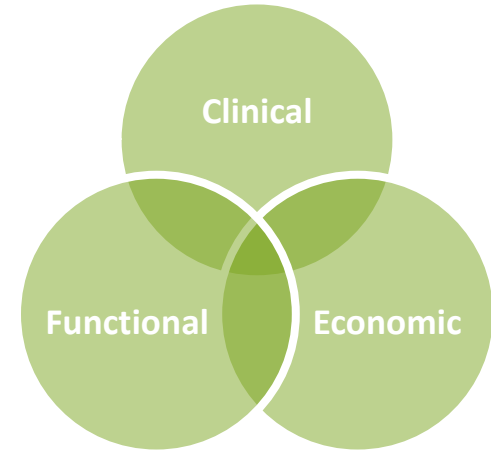
- Caregivers biggest frustration is not having a clear set of expectations
- Concerned about how well the stroke patient will be able to return to their previous life which includes:
 - ADLs – toilet, eat, drink, bathe, etc.
 - Communication (comprehension and ability to speak)
 - Memory
 - Mobility
 - Independence
 - Work (if relevant)
- Carry the emotional and financial burden of:
 - Home care (paying outside aide or loss of own wages)
 - Transportation to and from rehabilitation or physician visits
 - Home and/or environment modifications
 - Impact on own life and family's life

“After a loved one has had a stroke, life is never the same.”

All Stakeholders Indentify a Multi-Faceted Unmet Need

- **Clinical Unmet Need**

- Drug with broader window of use
- Drug with fewer serious side effects
- Drug that is easier to administer
- Drug that can be administered more broadly
- Drug that dissolves the clot and/or protects the penumbra
 - The concept of protecting the penumbra is fine in theory but is not perceived to necessarily translate to improved function or benefit



- **Functional Unmet Need**

- **Better outcomes:** Significant functional improvement as evidenced by a validated scale
 - FIM*, neurologic imaging, or other scales could be accepted but NIH SS is validated and currently linked to actionable guidelines
- **Equivalent outcomes more quickly:** Reduced time required in rehabilitation

- **Economic Unmet Need**

- Improve patient long-term functional status and productivity
- Reduce costly time required in rehabilitation

*FIM = Functional Independence Measurement

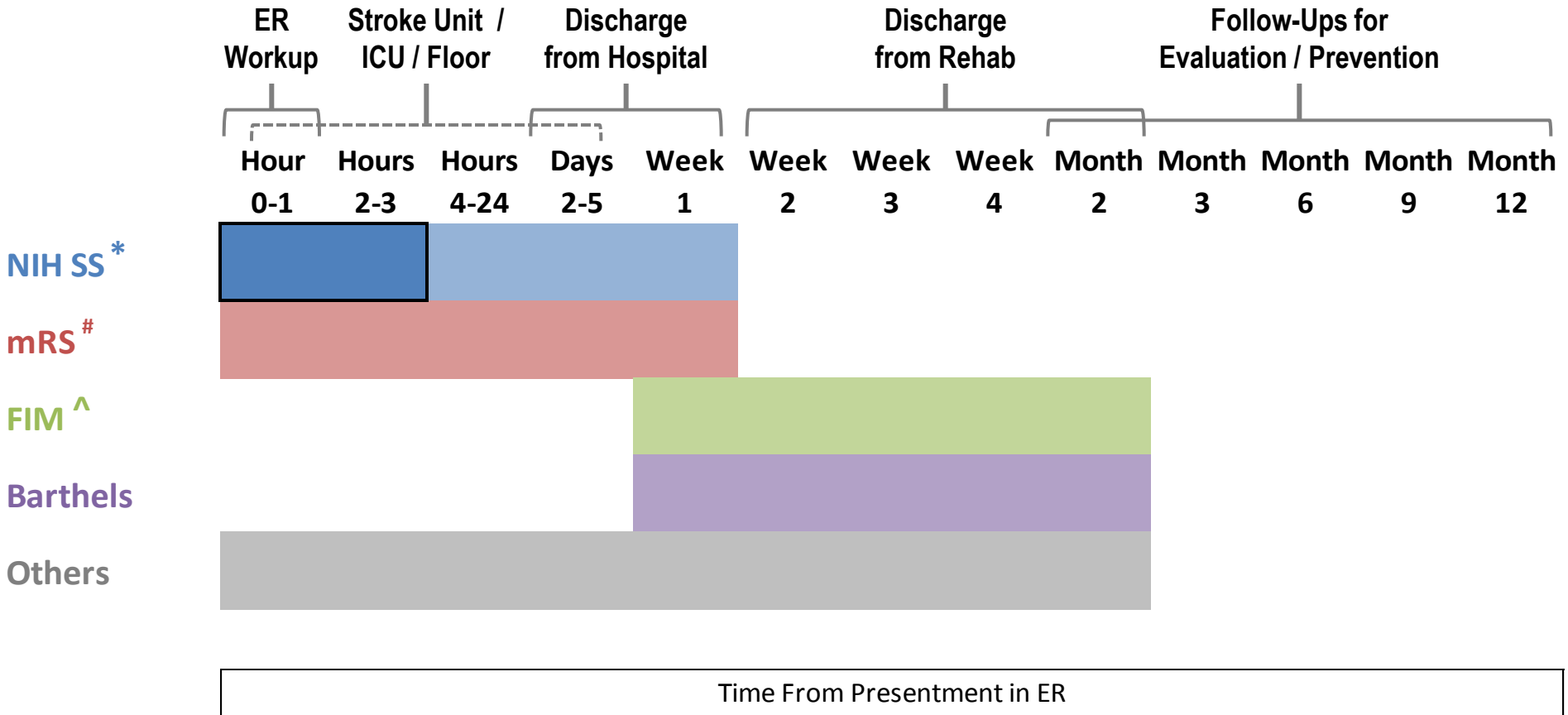
Acute Ischemic Stroke

**SO WHAT DID WE LEARN ABOUT
RELEVANT STROKE SCALES?**

Current scales offer standardized measurements but are only as good as the people who administer them

- High inter-observer variability causes inconsistency
- Scales often take a long time to administer
- Certifications are required to administer certain scales such as the NIH Stroke Scale
- Focus is often high-level and not detailed enough to capture smaller, but meaningful, improvements

Use of Scales Varies by Time Since Stroke, Facility, and Country



Time From Presentment in ER

*NIH SS = NIH Stroke Scale

#mRS = Modified Rankin Scale

^FIM = Functional Independence Measurement

Bold outline and darker shading indicates certain utilization

Lighter color shading indicates potential utilization

Scales Used While Patient is Hospitalized

	NIH Stroke Scale	Modified Rankin Scale
Purpose	Evaluates level of impairment due to stroke	Evaluates degree of disability or dependence in ADLs
Prevalence	Utilized in almost 100% of stroke centers and some regular hospitals	Infrequently used, reserved for clinical trials
Frequency of Administration	Upon admission to ER, every 4-8 hours for the first 72 hours	Upon admission to ER, daily thereafter
Responsible	ER physician, ER nurses, or stroke coordinator	Neurologist, nursing staff
Positives	<ul style="list-style-type: none"> • Globally recognized and utilized • Good for acute measurement • Good “overall picture” • Plays role in determining tPA candidacy 	<ul style="list-style-type: none"> • Registry of MRS scores • “Validated” scale – not by guidance standards • Accepted by FDA
Negatives	<ul style="list-style-type: none"> • Variability between observers • Average 8 minutes to administer • Only measures broad level of function 	<ul style="list-style-type: none"> • High degree of variability between observers

Scales Used While Patient is in Rehabilitation

	Functional Independence Measurement (FIM)	Barthels
Purpose	Evaluates patient function and assess progress over time, focused on independence	Evaluates patient performance on ADLs and mobility; focused on dependence
Prevalence	Utilized in most US and UK rehab units	Infrequently used in rehab units in Germany
Frequency of Administration	At admission to rehab, weekly thereafter	At admission to rehab, weekly thereafter?
Responsible	Physiatrist or therapist	Physiatrist or therapist
Positives	<ul style="list-style-type: none"> • Accepted by insurers in the US • Demonstrates progression of function • Perceived less variability between observers 	
Negatives	<ul style="list-style-type: none"> • Not globally recognized or utilized • Still not specific enough to pick up on more subtle advancements (e.g. walker to four-prong cane, to single prong cane) 	

So, What Does This All Mean?

Acute Ischemic Stroke

**ENDPOINTS DRIVING
FUTURE ADOPTION
COMMERCIAL VALUE**

Stakeholders want larger impact for fewer patients vs less impact for more patients

Key Endpoints

Better Reduction or Elim. Of Clot vs tPA

Reduce amt. of Vessel Occlusion

Sign. Improve. In Pat. Funct. Status

Reduce # Days in Rehab

Increase amt. of Penumbra

Reduced incid. Of
Secondary Events

Reduced Days in
Hosp.

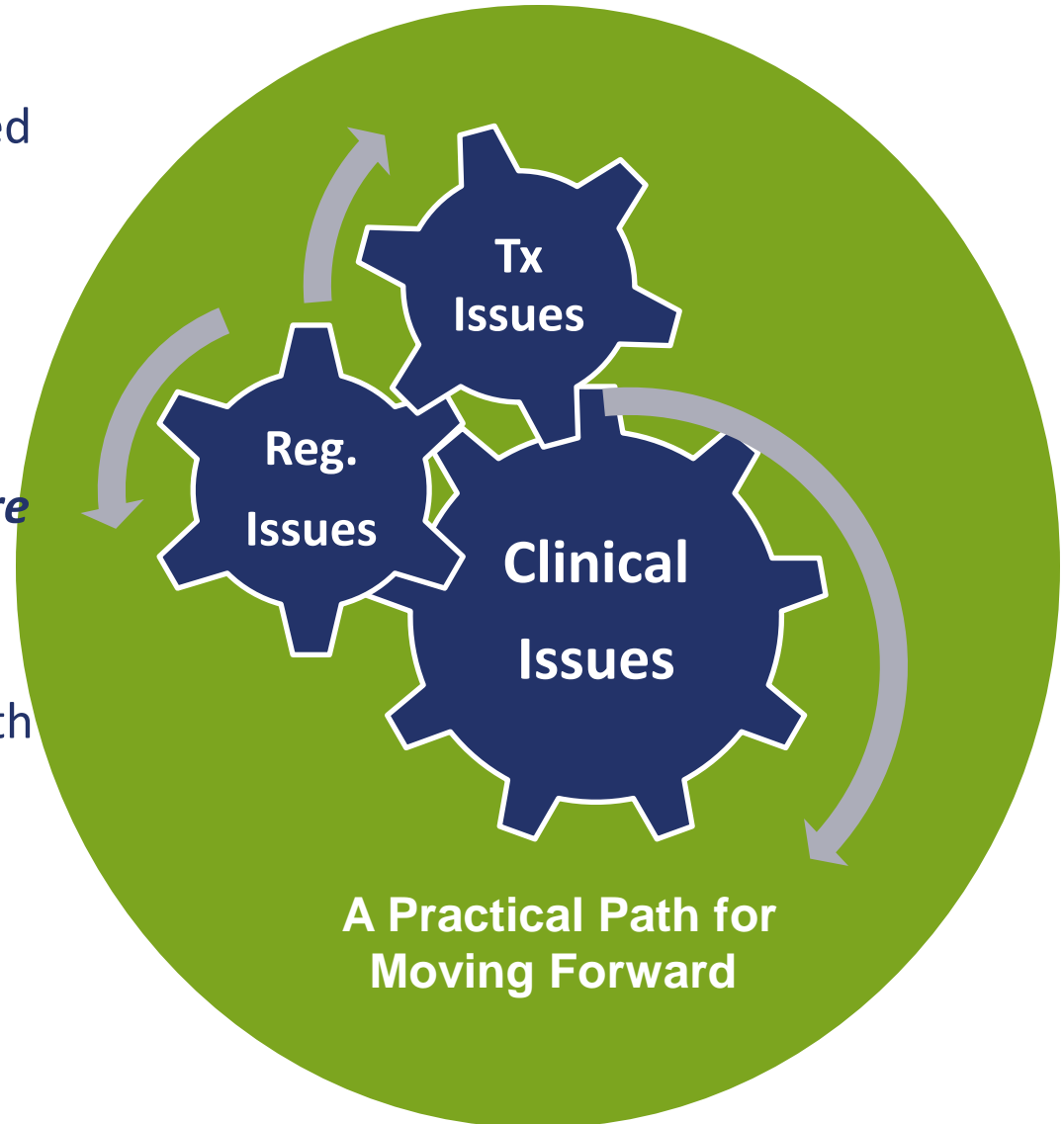
Rel.
Importance

- Key Improvements in Patient Functional Status
 - Breathing & swallowing
 - Ability to comprehend / retain memory
 - Ability to transfer from bed to sit/stand
 - Ability to toilet
 - Ability to bathe
 - Ability to speak
 - Ability to walk / mobilize / climb stairs
 - Ability to regain independent life – work, drive, use computer

Conclusions:

We Identified a Path For Creating Value

- Stakeholder Perspective Identified
 - *“What to Measure”*
 - *“When to Measure”*
 - *“Where to Measure”*
- Project Completed Early---” *Before Critical Decisions Made*”
- Aligned Stakeholder Interests with Commercial and Clinical



Best Practices to Carry Forward in Future Projects

- **PRO's have never been more important**
- **For drugs to create value they have to address what's valued by patients and payers**
- **Knowing what and whom to measure, how to measure, and when and where to measure is critical**
- **This type of analysis must be done early, before development decisions are made**

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