

A Patient-Centered Approach to Understanding the Burden of Inhibitors

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FDA-CERSI Collaborative Workshop on Predictive Immunogenicity for Better Clinical Outcomes

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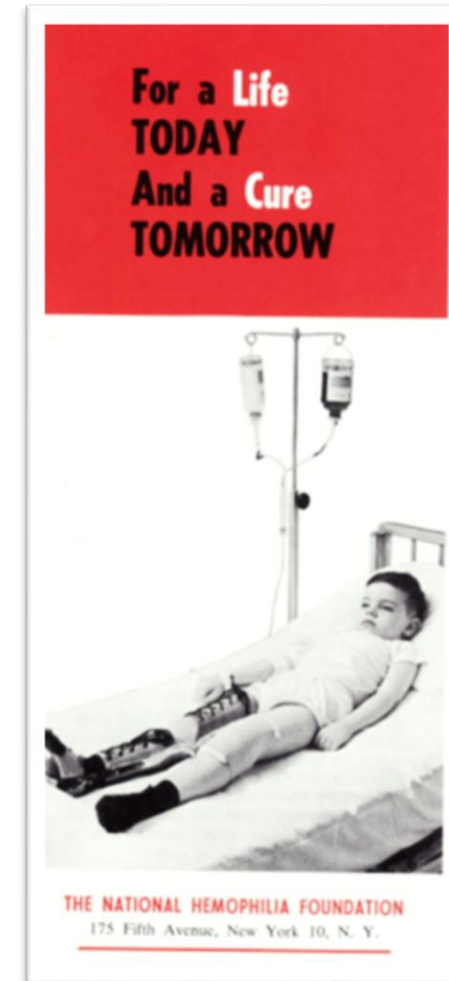
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Disclosures for: Mark Skinner

CONFLICT	DISCLOSURES (If potential for conflict of interest exists)
RESEARCH SUPPORT:	Principal investigator for the PROBE study an independent investigator initiated research study supported by Baxalta (part of Shire), Bayer, Bioverativ a Sanofi company, CSL Behring, Novo Nordisk, Roche, and Sobi
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CONSULTANT	NHF

What is Hemophilia?

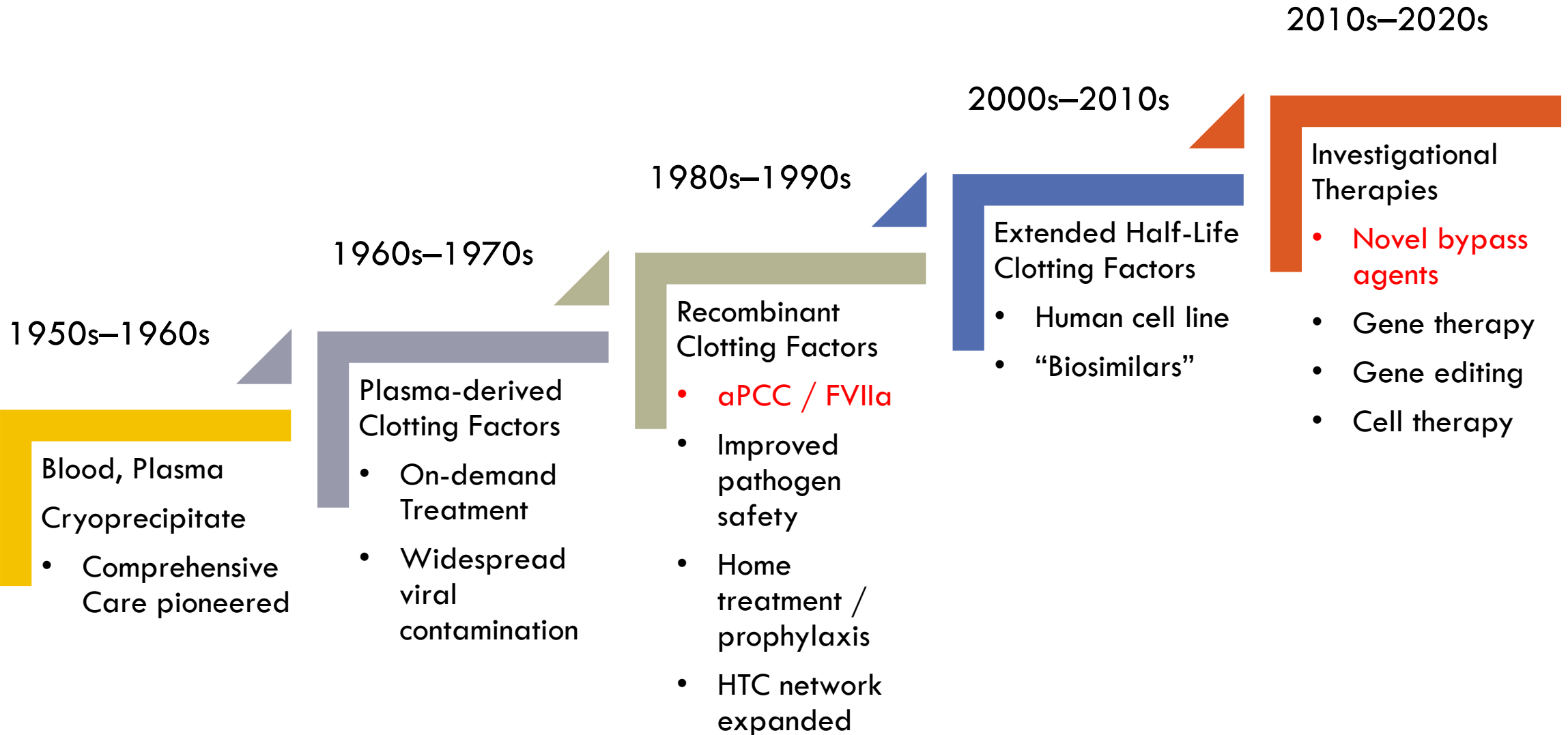
- Deficiency of clotting factor protein in blood
 - Blood does not clot properly
 - Severe patients (<1% clotting factor) at most risk
- Clinical manifestations
 - Internal bleeding into joints, soft tissues
 - Significant morbidity and mortality
- Well characterized genetically and clinically
 - Type: FVIII (Hemophilia A) 80-85%
 - Type: FIX (Hemophilia B) 15-20%
 - Severity: Severe 60%, Moderate 15%, Mild 25%
- Incidence 1 in 10,000 (X-linked recessive)
 - ~50,000 PWH in Europe and North America
 - Does not discriminate by race or region of the world
 - Predominantly male
 - One-third no known family history of the disease



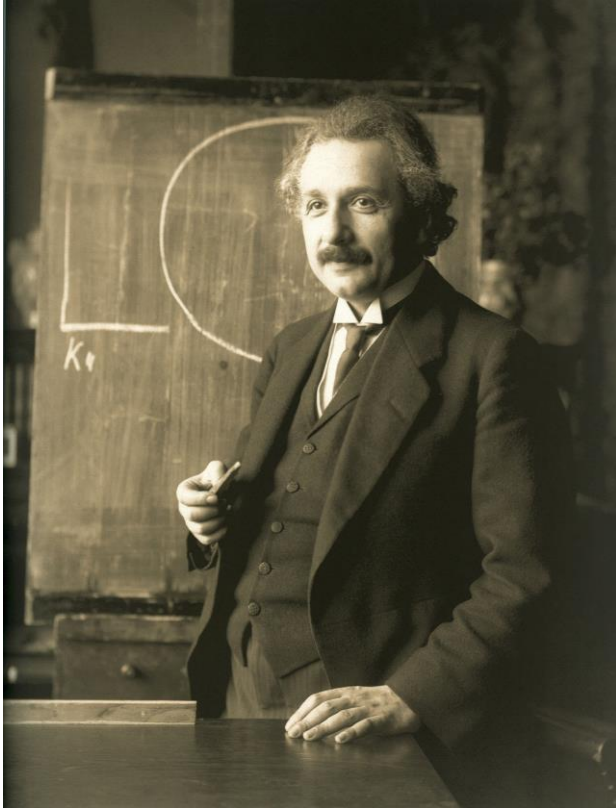
Hemophilia Treatment

- State of the Art treatment
 - Prophylaxis (factor concentrate replacement)
 - Wide range of plasma-derived and recombinant products available
 - Integrated disease management
- Inhibitors
 - ~20-30% PWH with severe hemophilia A develop neutralizing antibodies (inhibitors)
 - Genetic risk factors: Severity of hemophilia, Large mutations of factor VIII gene, Family history, Ethnicity
 - Environmental risk factors: Intensive factor VIII treatment, Early intensive exposure to factor VIII treatment, Factor VIII product, Immunologic/inflammatory/infectious events
 - Morbidity, Mortality, Cost of Treatment all dramatically increased
- There is no cure, at least yet

Evolution of Hemophilia Care



Are We Collecting the Right Data?



“Not everything that can be counted counts.
Not everything that counts can be counted.”

Attributed to Albert Einstein
German-born theoretical physicist
1879-1955

Value in Healthcare = Value Created for Patients



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Standardizing Patient Outcomes Measurement

Michael E. Porter, Ph.D., M.B.A., Stefan Larsson, M.D., Ph.D., and Thomas H. Lee, M.D.

The arc of history is increasingly clear: health care is shifting focus from the volume of services delivered to the value created for patients, with “value” defined as the outcomes achieved relative to the costs.¹ But progress has been slow and halting, partly because measurement of outcomes that matter to patients, aside from survival, remains limited. And for many conditions, death is a rare outcome whose measurement fails to differentiate excellent from merely competent providers

to embrace accountability for results.

If we’re to unlock the potential of value-based health care for driving improvement, outcomes measurement must accelerate. That means committing to measuring a minimum sufficient set of outcomes for every major medical condition — with well-defined methods for their collection and risk adjustment — and then standardizing those sets nationally and globally.

Why has arriving at the essen-

example, only 139 (7%) are actual outcomes and only 32 (<2%) are patient-reported outcomes (see bar graph).² Defaulting to measurement of discrete processes is understandable, given the historical organization of health care delivery around specialty services and fee-for-service payments.

Yet process measurement has had limited effect on value. Such measures receive little attention from patients, who are interested in results. Process measures don’t truly differentiate among provid-

- What matters to patients are outcomes that encompass the whole cycle of care
 - Survival, functional status, quality of life
- Historically, outcomes measurement has focused on clinical status and left out functional status
 - Survival and “objective” outcomes that are readily captured by laboratory tests

Focus on Outcomes Important to Patients

- Traditional clinical dimensions
 - Lifespan (survival)
 - Factor levels (peaks & troughs)
 - Bleeding frequency (ABR, target joints)
 - Joint outcomes (structure, ROM)
 - Function and mobility
- Patient-centric dimensions¹
 - Educational pursuit
 - Work / Career opportunities
 - Family / Social life engagement
 - Activity / Sports goals
 - Decreased burden of illness

Patient Reported Relevant Outcomes

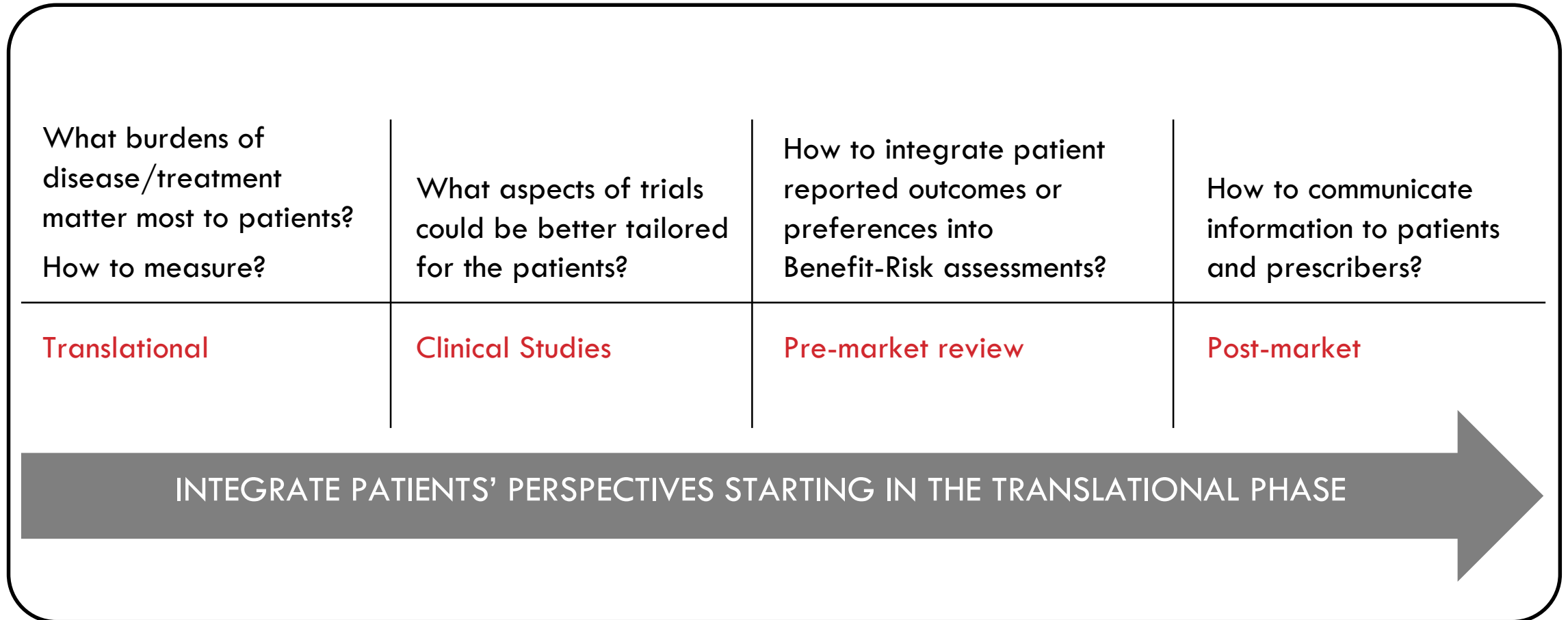
Patient Reported Outcome Data Vital

- Patient Reported Outcome (PRO) data are not only useful, but are in fact vital if we desire to have a complete and real-world understanding of the true burden and impact of living with a disease or the associated benefits from an intervention¹
- Improved patient involvement can drive the development of innovative medicines that deliver more relevant and impactful patient outcomes and make medicine development faster, more efficient, and more productive²

¹O'Mahony, B. et al. Assessments of outcome in haemophilia - a patient perspective. Haemophilia, v. 22, n. 3, p. e208-9 (2016)

²Hoos, A et al. Partnering with patients in the development and lifecycle of medicines: a call for action. Ther Innov Regul Sci. 49:929-39.(2015)

FDA Patient-Focused Drug Development – Increased Focus on Patient Engagement



Symptoms / Impacts that Matter Most to Patients

- Joint damage and/or Pain
 - 2/3 rated as the most significant
- Anxiety/Depression/Stress
 - 2nd most important impact
- Disease symptoms exacerbated by aging
- Other impacts on daily life
 - Career choices
 - Residence
 - Sports
 - School
 - Family Life
 - Social Life

“It is clear that although there have been great advances ..., more needs to be done not only to develop new therapies ..., but to address broader economic, social, and educational barriers that still remain.”

FDA Voice of the Patient
Report Conclusion
May 2016

Burden of Treatment – Quality of life, Chronic / Acute Pain

	No Bleeding Disorder (95% C.I.)	PWsHA (95% C.I.)	PWsHA with inhibitors (95% C.I.)	p
EQ-5D	0.937 (0.922-0.953)	0.726 (0.702-0.749)	0.556 (0.466-0.646)	<.001
Acute pain	34%	71%		<.001
		71%	93%	=.002
Chronic pain	29%	72%		<.001
		72%	90%	=.009

People with severe hemophilia A with a current inhibitor have lower quality of life and more chronic and acute pain than people with severe hemophilia A without inhibitors¹

Burden of Treatment – Caregiver



Impact of child's pain

Not always related to level of pain child experiences

Emotional Stress

~90% of caregivers were “sometimes” to “nearly always” worried about child’s future in their absence

Financial Burden

Burden assessment score increased if inhibitors developed

Average Hemophilia-related Costs Per Person Per Year

12-month costs ¹	Severe (n=137)	
	On-demand (n=51)	Prophylaxis (n=86)
Total Direct Costs ^{2,3}	184,518 [125,385] (160,758)	292,525 [272,892] (186,739)
Clotting Factor Costs ^{2,3}	170,037 [118,259] (151,846)	289,172 [272,236] (186,502)
Average percent attributable to Total Costs ^{2,3}	0.84	0.94
Other Medical Cost ³	14,481 [1,502] (41,881)	3,353 [500] (8,352)
Total Indirect Cost	16,952 [301] (26,068)	8,867 [376] (17,959)
Total Costs (Direct + Indirect) ^{2,3}	201,471 [143,431] (164,377)	301,392 [286,198] (188,977)

Direct Medical costs

- Cost of factor
- Hospitalizations and surgery
- Clinic visits – physician, nurse, physio, social work
- Emergency visits
- Rehabilitation

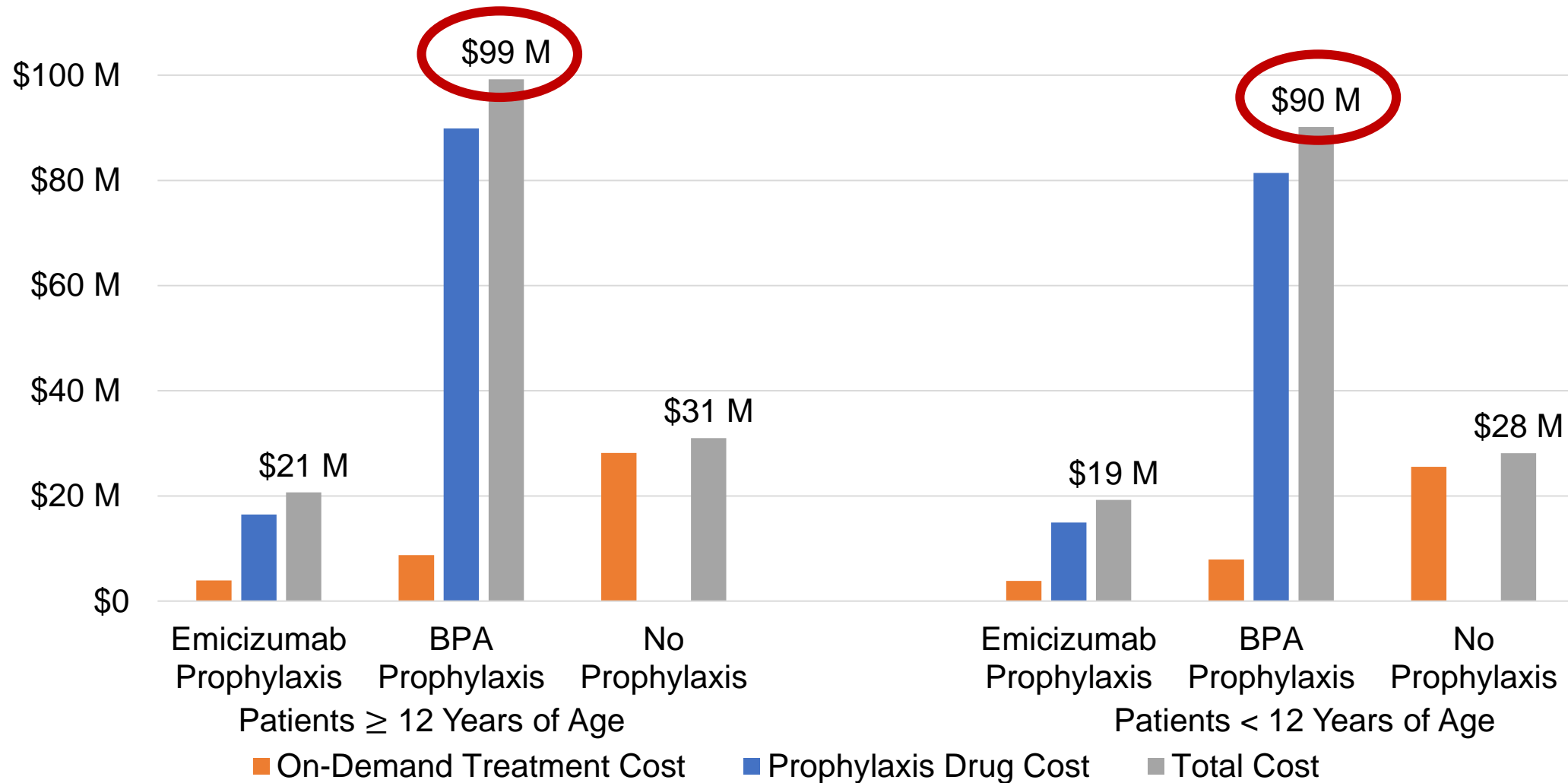
Indirect costs

- Time lost by PWH from work or school
- Time lost by caregivers from work
- Chronic pain and disability over time
- Reduced enjoyment of life

Costs were reported as mean [median] (standard deviation) during the 12-month period.

Zhou et al. (2015) Burden of illness: direct and indirect costs among persons with hemophilia A in the United States, Journal of Medical Economics, 18:6, 457-465

Lifetime costs of Hemophilia A with need for bypassing agent (BPA) prophylaxis



Goals for 21st Century Data Science & Bio-specimen Collection - Patient / participant-entered data collection

- Patient/participant perspective will be sought in all stages of research study development and performance, with feedback of study results to participants
- Maximize information gained from patient reported outcomes (PROs) while minimizing the burden of data collection
- Harmonize PRO data collection across research studies
- Use PRO data for well-defined purposes to positively impact the community.

coreHEM – Comparing outcomes for gene therapy

- A “core outcome set” to measure, demonstrate and differentiate the effectiveness and value of gene therapy in hemophilia relative to current standard of care is essential¹
- For the first time in hemophilia, a core outcome set has been developed, with the involvement of representatives of all relevant stakeholder groups
 - Includes outcomes supporting assessment of comparative effectiveness and value, with the goal of streamlining regulatory approval, health technology assessment and market access
- Patient involvement ensures that the outcomes are meaningful and relevant to those living with hemophilia

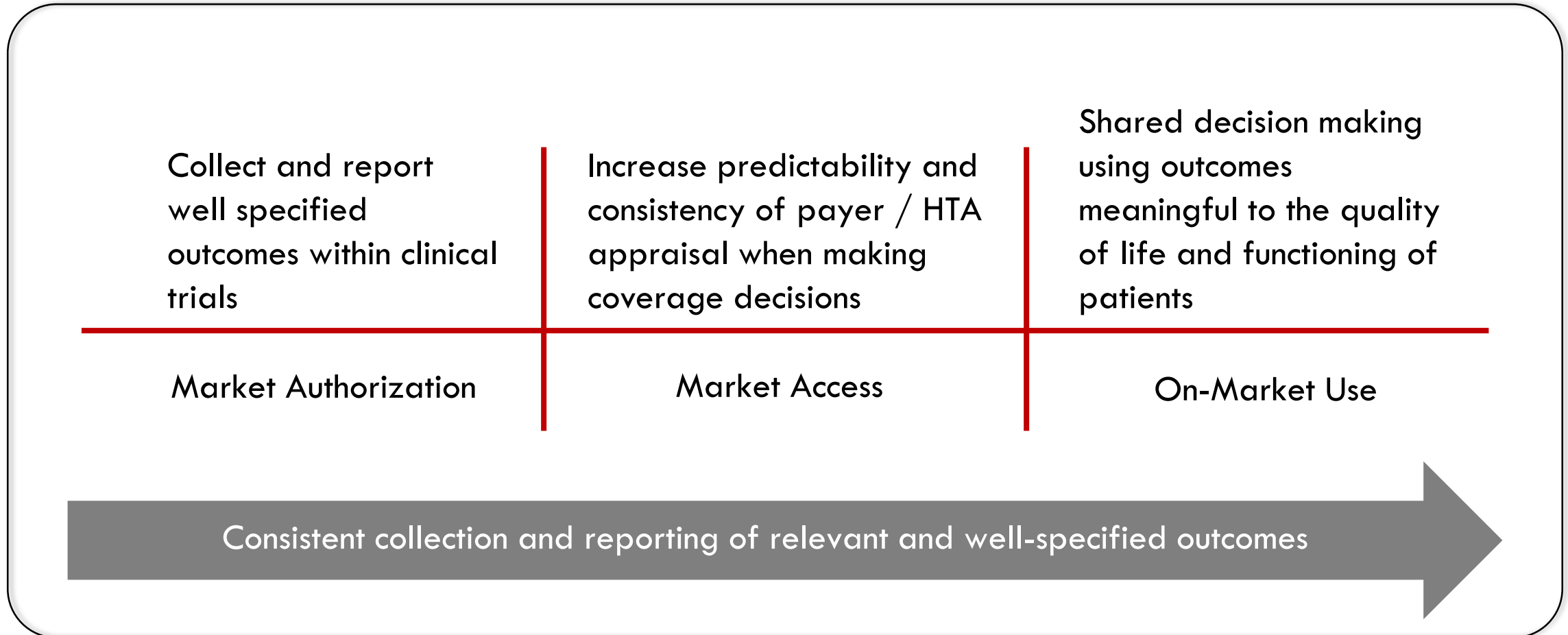
¹Skinner et al. Comparing Outcomes Across Clinical Trials: Core Outcome Set for Hemophilia Gene Therapy as a Model for Other Diseases (2017). DIA Global Forum Vol. 9 Issue 5;

²Iorio et al. ; for the coreHEM panel. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. Haemophilia. 2018;00:16.

Core outcome set for gene therapy in hemophilia: Results of the coreHEM multi-stakeholder project

Core Outcome Set		<ul style="list-style-type: none"> • Frequency of bleeds • Factor activity level • Duration of expression • Chronic pain • Mental health status • Utilization of healthcare system (direct costs)
Additional Outcomes		<ul style="list-style-type: none"> • Duration/frequency/type of physical activity/sport/play • Physical health/general health perception
Adverse Events	Short-Term	<ul style="list-style-type: none"> • Liver toxicity • Short-term immune response to FVIII/FIX • Immune response to gene therapy (cytotoxic) • Thrombosis
	Long-Term	<ul style="list-style-type: none"> • Development of other disorders • Vector integration into host genome • Duration of vector-neutralizing response • Cause of death
	Mortality	<ul style="list-style-type: none"> • Cause of death

Collect Core Outcomes Across the Life Cycle that Reflect the Priorities of the Hemophilia Community



Ultimately clinical research should improve patient care

- Trials must evaluate outcomes that genuinely reflect real-world settings and concerns
- However, many trials continue to measure and report outcomes that fall short of this clear requirement
- Complex issues include the use of surrogate, composite and subjective endpoints; a failure to take account of patients' perspectives when designing research outcomes
- The treatment choices of patients and clinicians should ideally be informed by evidence that interventions improve patient-relevant outcomes