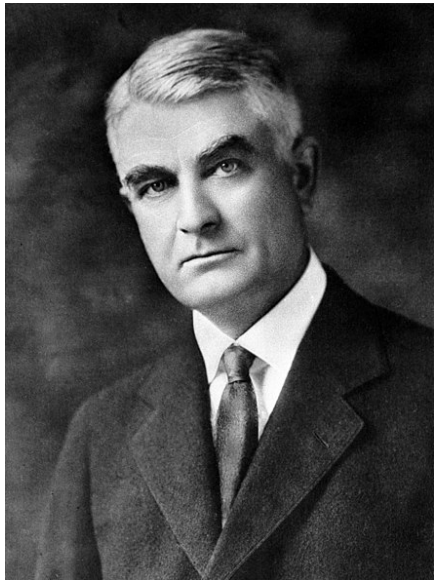
Importance of Early Active Engagement of Patients Throughout the Life Cycle of Drug Development

Mark W Skinner, JD
ASGCT 22nd Annual Meeting
28 April 2019
Washington, DC

Conflict Disclosures

Research Support	PROBE study principal investigator, an independent investigator initiated research study, supported by Shire part of Takeda, Bayer, Bioverativ a Sanofi company, CSL Behring, Novo Nordisk, Roche, Sobi, National Hemophilia Foundation and McMaster University
Director, Officer, Employee	WFH USA, ICER
Shareholder	None
Honoraria	Institution received fees / honoraria for attending advisory boards or educational presentations: Bayer, Biomarin, Novo Nordisk, Pfizer, Roche/Genentech
Advisory Committee	US HHS ACBTSA, Bayer, Blue Cross Blue Shield MAP, NHF MASAC, Roche/Genentech, Pfizer (DMC), Spark (DSMB)
Consultant	NHF



"The aim of medicine is to prevent disease and prolong life, the ideal of medicine is to eliminate the need of a physician."

William J. Mayo, MD
Co-Founder Mayo Clinic
1861-1939

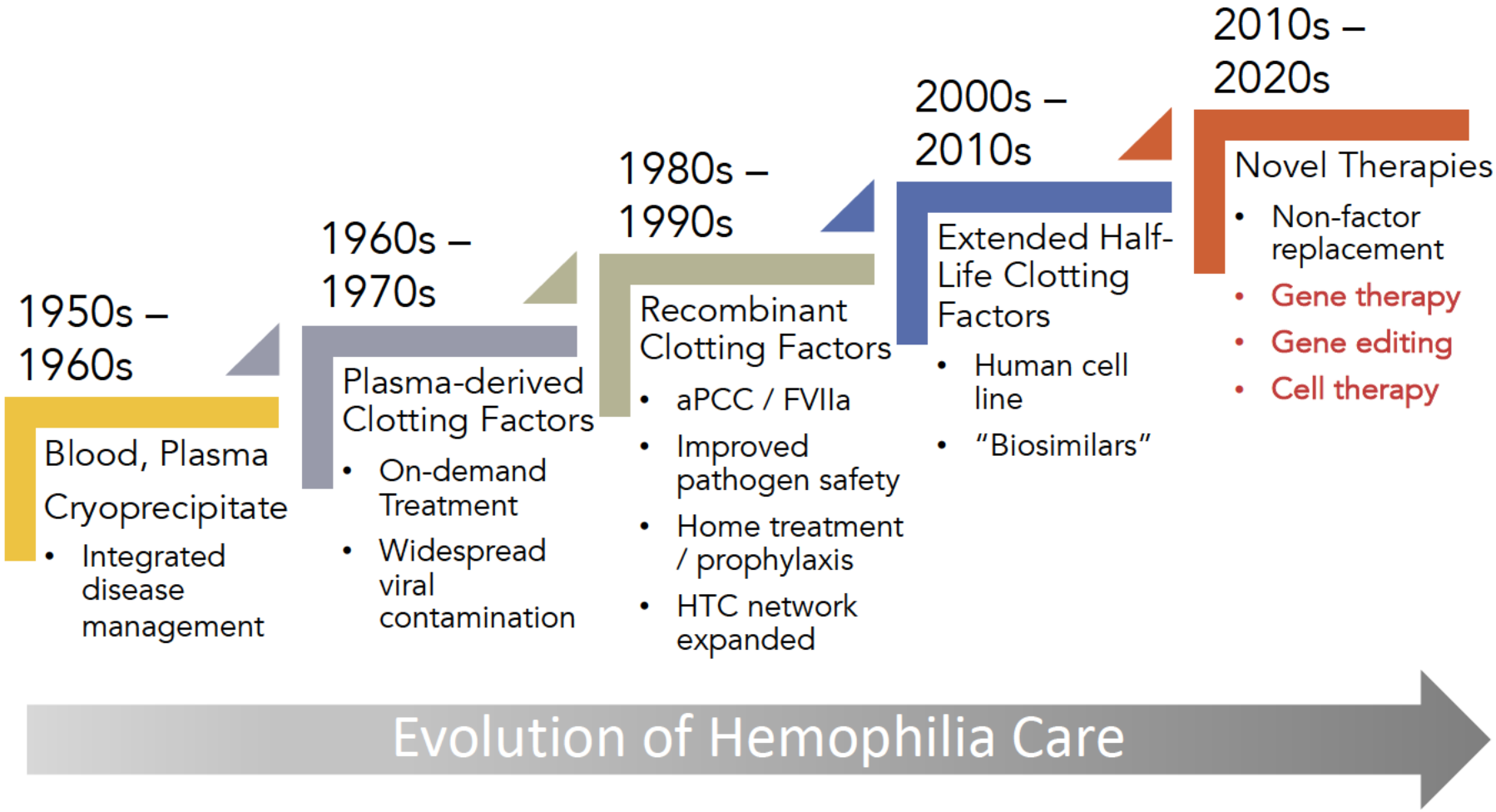


Table 1 | **Selected agents in clinical development for haemophilia**

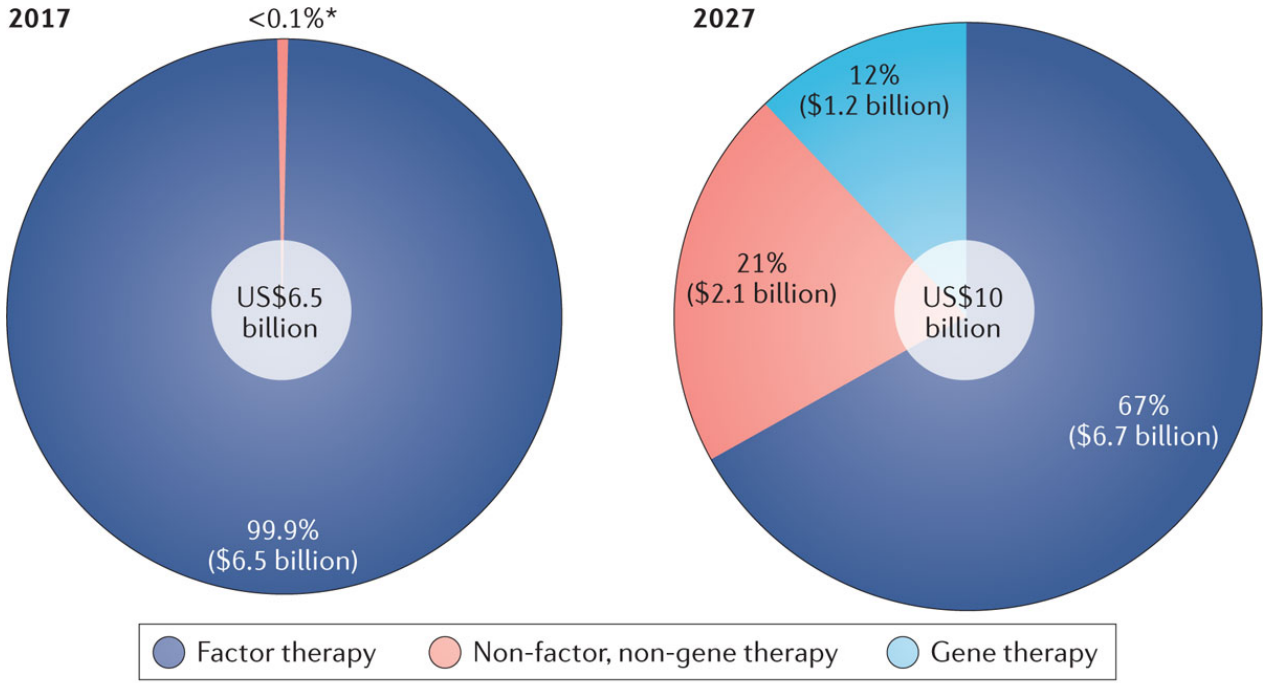
Drug	Company	Therapy type	Patient population	Trial phase
Emicizumab (Hemlibra)	Roche/Chugai	Bispecific antibody	Haemophilia A	III
BAY-94-9027	Bayer	PEGylated FVIII	Haemophilia A	III
BMN 270	Biomarin	Gene therapy ★	Haemophilia A	III
N8 GP	Novo Nordisk	PEGylated FVIII	Haemophilia A	III
Concizumab	Novo Nordisk	Anti-TFPI antibody	Haemophilia A or B	II
Fitusiran	Alnylam/Sanofi	ATIII RNAi	Haemophilia A or B, +/− inhibitors	II
OPK88005	OPKO Biologics	FVIIa–CTP	Haemophilia A or B with inhibitors	II
AMT-061	uniQure	Gene therapy ★	Haemophilia B	I/II
SB-525	Sangamo/Pfizer	Gene therapy ★	Haemophilia A	I/II
SB-FIX	Sangamo	Gene therapy (gene editing) ★	Haemophilia B	I/II
SPK-8011	Spark	Gene therapy ★	Haemophilia A	I/II
SPK-9001	Spark/Pfizer	Gene therapy ★	Haemophilia B	I/II
NN7170	Novo Nordisk	Subcutaneous N8-GP	Haemophilia A	I
PF-06741086	Pfizer	Anti-TFPI antibody	Haemophilia A or B	I
SHP654	Shire	Gene therapy ★	Haemophilia A	I
BAY 1093884	Bayer	Anti-TPFI antibody	Haemophilia A or B	I

ATIII, antithrombin III; CTP, C-terminal peptide; FVIII, factor VIII; TPFI, tissue factor pathway inhibitor.

Brown & Green. Nature Reviews Drug Discovery volume17, pages541–542 (2018)

In 2017, EU5 and United States hemophilia drug sales exceeded US$6 billion.

The market value is forecast to reach $10 billion by 2027.



Nature Reviews | Drug Discovery

Brown & Green. Nature Reviews Drug Discovery volume17, pages541–542 (2018)

Availability, Affordability and Access

- In the past, choice of drugs in developed countries was driven by the views of patients and clinicians on the relative value of the available drugs
  - Cost, "value for money" and affordability were not often considered, and the "health system" paid for what was used
- Today, health care systems, insurers and governments increasingly consider "value for money" and affordability.
  - Driven by concerns that health care opportunities, demands and costs are increasing faster than the funds available

Annual cost per patient with severe hemophilia

- USA € 400,000
- Germany € 319,024[1]
- Italy € 220,344[1]
- France € 196,117[1]
- Spain € 173,771[1]
- UK € 129,365[1]
- Ireland € 100,000[2]
- Australia € 57,000[2]
- Canada € 54,000[2]

"Payers, manufacturers, and policy makers need to recognize the seriousness of financial toxicity in the hemophilia treatment landscape and seek new approaches to address it."

ICER report reviewing clinical effectiveness and value of emicizumab for patients with hemophilia A and inhibitors to factor VIII – April 2018

O'Mahony WFH Gene Therapy Roundtable 2019; [1]O'Hara et al. Orphanet Journal of Rare Diseases (2017) 12:106; [2]Current Data

Defining Value – Relevant Outcomes

- Achieving access to high-value (*and potentially high-cost*) care requires we improve our capacity to collect and interpret patient relevant outcomes.
- In assessing the value of treatments for hemophilia, payers should be aware of important benefits and contextual considerations that are not typically captured in cost-effectiveness analyses.
- There is an urgent need to supplement traditional economic and clinical information decision-makers currently use.

Porter ME, et al. N Engl J Med 2016; ICER report reviewing clinical effectiveness and value of emicizumab for patients with hemophilia A and inhibitors to factor VIII – April 2018

Value – A Matter of Perspective

Patients have a unique perspective and will consider issues differently than regulators, manufacturers, scientists, clinicians and payers.

[1]FDA Patient Focused Drug Development Initiative

Different Perspectives – Different Value Determinations

- Regulatory
  - Efficacy & Safety
    - Risk / Benefit
- Health Technology Assessment
  - Comparative Effectiveness
    - Cost / Benefit
- Clinician
  - Effectiveness & Utility
    - Clinically appropriate / Benefit
- Patient
  - Education, work, family, activity
    - Burden / Benefit

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, rem... many condit... outcome who... to different... merely comp...

viders 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

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

Perspective

DECEMBER 23, 2010

What Is Value in Health Care?

Michael E. Porter, Ph.D.

In any field, improving performance and accountability depends on having a shared goal that unites the interests and activities of all stakeholders. In health care, however, stakeholders have myriad, often conflicting goals, including access to services, perf... ideal, not a code word for cost...

Value — neither an abstract

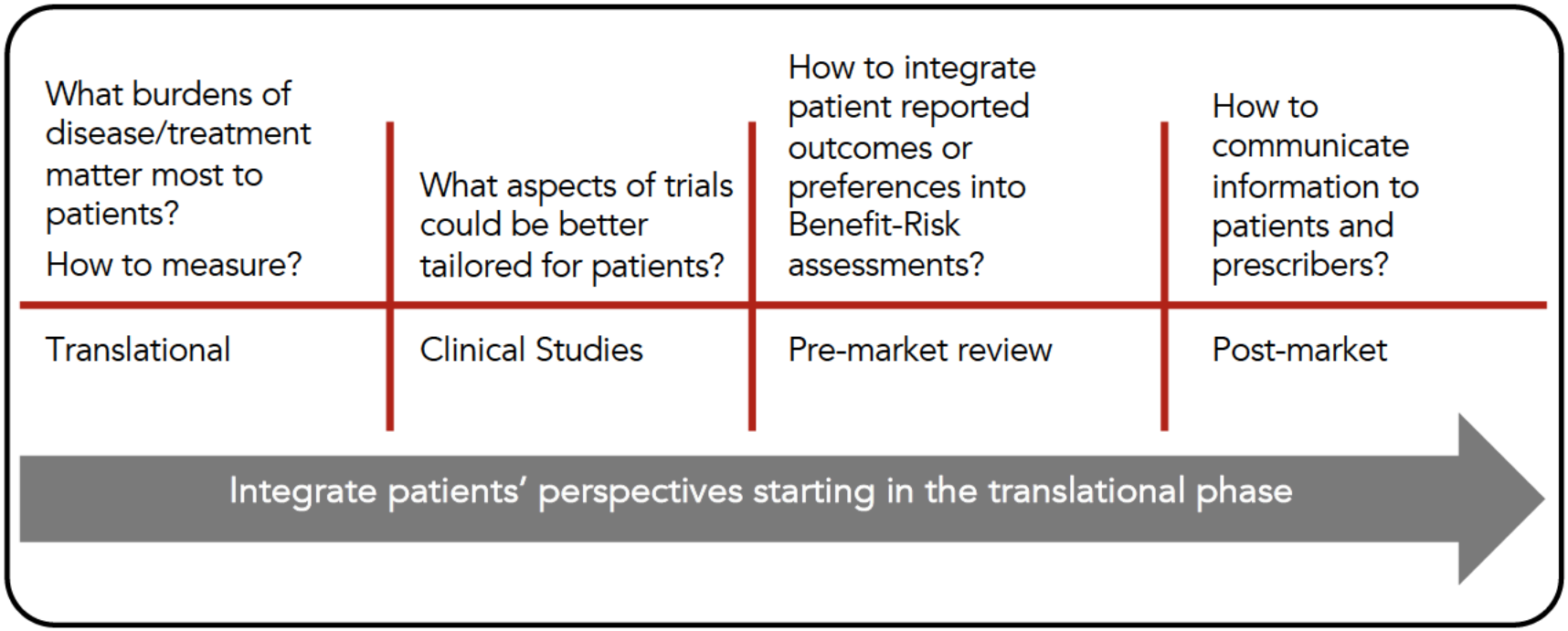
value is a central challenge. Nor is value measured by the process of care used; process measurement and improvement are important tactics but are no substitutes for measuring outcomes and costs.

Since value is defined as out...

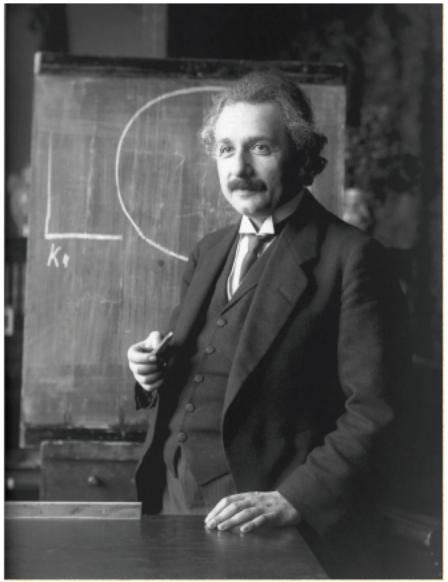
- Historically, outcomes measurement has focused on clinical status and left out functional status
  - Survival and "objective" outcomes that are readily captured by laboratory tests
- What matters to patients are outcomes that encompass the whole cycle of care
  - Survival, functional status, quality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

Porter ME, et al. N Engl J Med 2010, 2016

FDA Patient-Focused Drug Development



Are We Collecting the Right Data?



"Not everything that can be counted counts.
Not everything that counts can be counted."

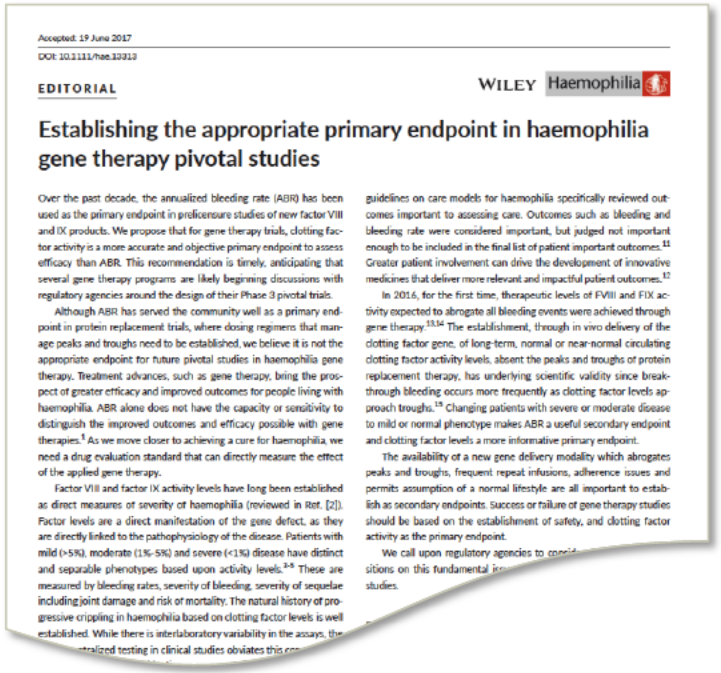
Attributed to Albert Einstein
German-born theoretical physicist
1879-1955

Historical Hemophilia Clinical Outcomes
Lifespan (survival)
Clotting Factor activity levels (peaks & troughs)
Bleeding frequency – annualized bleed rate (ABR), target joints

What is the right endpoint for gene therapy trials?

"Clotting factor activity is a more accurate and objective primary endpoint to assess efficacy than ABR."

"ABR alone does not have the capacity or sensitivity to distinguish the improved outcomes and efficacy possible with gene therapies."



Accepted: 19 June 2017
DOI: 10.1111/hae.13313

EDITORIAL

WILEY Haemophilia

Establishing the appropriate primary endpoint in haemophilia gene therapy pivotal studies

Over the past decade, the annualized bleeding rate (ABR) has been used as the primary endpoint in prelicensure studies of new factor VIII and IX products. We propose that for gene therapy trials, clotting factor activity is a more accurate and objective primary endpoint to assess efficacy than ABR. This recommendation is timely, anticipating that several gene therapy programs are likely beginning discussions with regulatory agencies around the design of their Phase 3 pivotal trials.

Although ABR has served the community well as a primary endpoint in protein replacement trials, where dosing regimens that manage peaks and troughs need to be established, we believe it is not the appropriate endpoint for future pivotal studies in haemophilia gene therapy. Treatment advances, such as gene therapy, bring the prospect of greater efficacy and improved outcomes for people living with haemophilia. ABR alone does not have the capacity or sensitivity to distinguish the improved outcomes and efficacy possible with gene therapies.[1] As we move closer to achieving a cure for haemophilia, we need a drug evaluation standard that can directly measure the effect of the applied gene therapy.

Factor VIII and factor IX activity levels have long been established as direct measures of severity of haemophilia (reviewed in Ref. [2]). Factor levels are a direct manifestation of the gene defect, as they are directly linked to the pathophysiology of the disease. Patients with mild (>5%), moderate (1%-5%) and severe (<1%) disease have distinct and separable phenotypes based upon activity levels.[3-5] These are measured by bleeding rates, severity of bleeding, severity of sequelae including joint damage and risk of mortality. The natural history of progressive crippling in haemophilia based on clotting factor levels is well established. While there is interlaboratory variability in the assays, the [illegible] tralized testing in clinical studies obviates this con[illegible]

guidelines on care models for haemophilia specifically reviewed outcomes important to assessing care. Outcomes such as bleeding and bleeding rate were considered important, but judged not important enough to be included in the final list of patient important outcomes.[11] Greater patient involvement can drive the development of innovative medicines that deliver more relevant and impactful patient outcomes.[12]

In 2016, for the first time, therapeutic levels of FVIII and FIX activity expected to abrogate all bleeding events were achieved through gene therapy.[13,14] The establishment, through in vivo delivery of the clotting factor gene, of long-term, normal or near-normal circulating clotting factor activity levels, absent the peaks and troughs of protein replacement therapy, has underlying scientific validity since breakthrough bleeding occurs more frequently as clotting factor levels approach troughs.[15] Changing patients with severe or moderate disease to mild or normal phenotype makes ABR a useful secondary endpoint and clotting factor levels a more informative primary endpoint.

The availability of a new gene delivery modality which abrogates peaks and troughs, frequent repeat infusions, adherence issues and permits assumption of a normal lifestyle are all important to establish as secondary endpoints. Success or failure of gene therapy studies should be based on the establishment of safety, and clotting factor activity as the primary endpoint.

We call upon regulatory agencies to consid[illegible] sitions on this fundamental is[illegible] studies.

ABR, Annual Bleed Rate; Pierce, et al. (2017), Establishing the appropriate primary endpoint in haemophilia gene therapy pivotal studies. Haemophilia. doi:10.1111/hae.13313

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

FDA Patient-Focused Drug Development Initiative Voice of the Patient Series Report on Hemophilia A/B, VWD, and Other Heritable Bleeding Disorders. May 2016

Every man dies,
not every man really lives.

Attributed to William Wallace
Braveheart
Scottish revolutionary
1270-1305

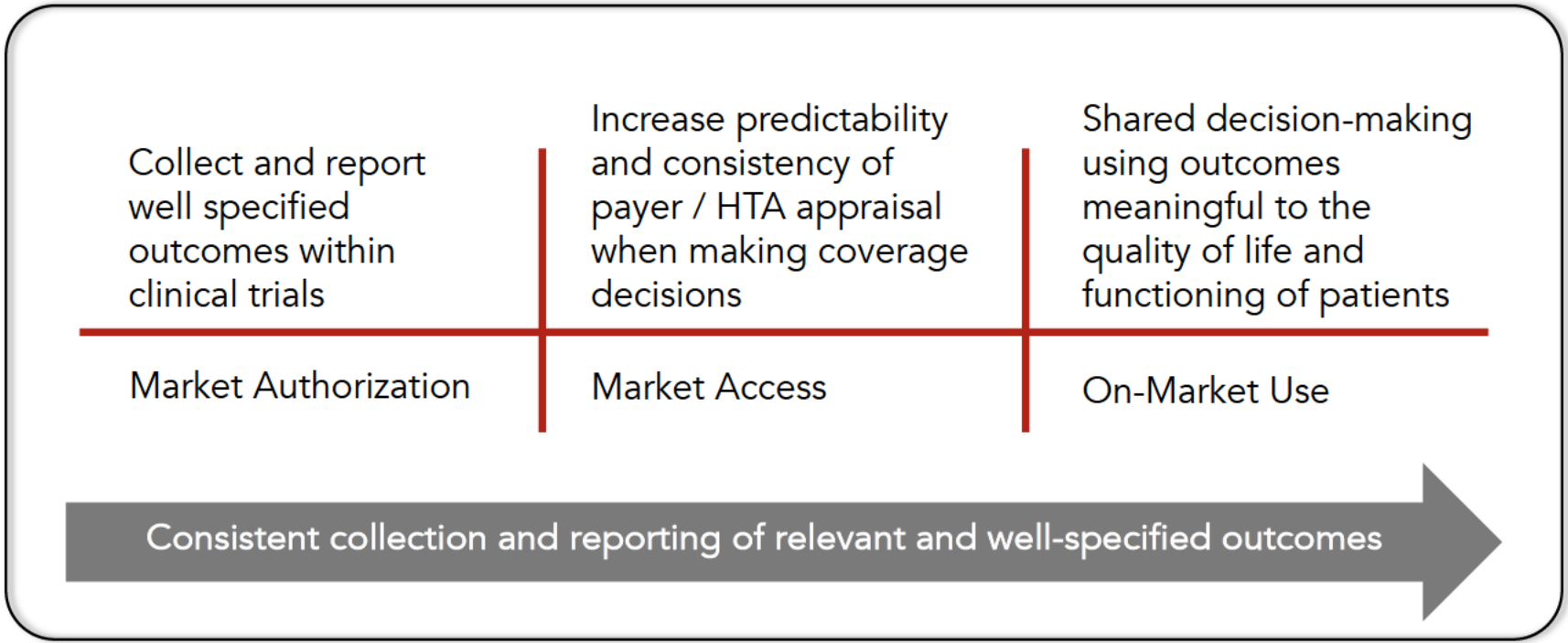
https://commons.wikimedia org/wiki/File:Wallace_Monument_20080505_Stained_glass_William_Wallace.jpg

Comparing Outcomes for Gene Therapy

- Important outcomes associated with novel or curative technologies will be different than those used to assess the value of current treatment.
- A "Core Outcome Set" to measure, demonstrate and differentiate the effectiveness and value of gene therapy relative to current standard of care is essential.
- Patient involvement ensures that the outcomes measured are meaningful and relevant to patients.

[1]Skinner et al. DIA Global Forum (2017) Vol. 9 Issue 5; [2]Iorio et al. Haemophilia. 2018;00:16.

Across the Life Cycle



Core Outcomes	• Frequency of bleeds • Factor activity level • Chronic pain • Mental health status (transformational impact) • Duration of expression • Utilization of healthcare system (direct costs)
Additional Outcomes	• Duration/frequency/type of physical activity/sport/play • Physical health/general health perception
Adverse Events	• Short-Term, Long-Term, Mortality

coreHEM

Green Park Collaborative
A partnership for innovation and effectiveness

National Hemophilia Foundation
for all bleeding disorders

McMaster University

Iorio et al. Haemophilia, 2018. DOI: 10.1111/hae.13504

Unifying Theme

"In God we trust; all others (must) bring data."

Attributed to W. Edwards Deming (1900 – 1993)

Conclusions – Early / Active Patient Engagement Vital

- Patients have a unique perspective and will consider issues differently than regulators, manufacturers, scientists, clinicians and payers
- Defining and measuring health outcomes with greater direct patient engagement will be vital for assessing value of novel technologies
  - to inform health care systems and supplement the economic and clinical data that decision-makers (regulators, payers, patients/clinicians) rely
- 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 productive[1]

[1]Hoos, 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)