Challenges in assessing the economic value of treatments for rare diseases: Hemophilia prophylaxis

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Effectiveness of therapies in improving outcomes

- **Types of outcomes**
  - Natural outcomes
    - Life-years saved
  - Preference-weighted outcomes
    - Quality-adjusted life-years or QALYs
    - Willingness to pay or WTP

- **Evidence based for effectiveness**
  - Limited RCT data
    - Limits to generalizability
  - Use of observational data
    - Spectrum of disease
    - Controlling for comorbidities
    - Representativeness of clinical case series or registries
Economic value of outcomes

- How much is it worth to save/extend a life?
- How much is it worth to improve quality of life?
- Does the economic value of life or quality of life depend on context?
  - Is it higher for someone with a serious, life-threatening disorder?
  - Does it depend on the type of disorder?
  - Does it vary with prevalence of the disorder? Are we willing to spend more per person for conditions that affect fewer people?
Congenital hemophilia – overview

- **Two types**
  - Hemophilia A caused by factor VIII deficiency
  - Hemophilia B caused by factor IX deficiency
  - Total incidence 1 in 5000 males, all races and ethnicities
    - 85% hemophilia A, 15% hemophilia B
  - X-linked inheritance
    - Predominantly affects males

- **Classification by level of clotting factor in blood**
  - Severe – <1% of normal
  - Moderate – 1-5% of normal
  - Mild – 6-49% of normal
Complications of hemophilia

- **Bleeding**
  - Intracranial
  - Joint bleeds
    - Joint damage
    - Pain

- **Treatment complications**
  - Inhibitors
  - Bloodborne infections
  - Port for infusion
    - Infections
    - Thrombosis
Treatment options

- Episodic or on-demand treatment for bleeds
- Ad hoc prophylaxis to prevent bleeds, e.g., surgeries
- Intermittent prophylaxis
- Routine prophylaxis
  - Timing of initiation
    - After joint bleeds
    - Before first joint bleed – primary prophylaxis
  - Intensity of use
Economic value of prophylaxis

- Clinically recommended but costly
- Varying estimates of incremental cost-effectiveness (ICER)
  - Miners et al. (2002) – UK: £46,500 per QALY
  - Lippert et al. (2005) – Europe: >€1 million per QALY
  - Risebrough et al. (2008) – Canada: >CA$1 million per QALY
  - Miners et al. (2009) – UK: £38,500 per QALY
  - Colombo et al. (2011) – Italy, €40,000 per QALY
  - Farrugia et al. (2013) – USA, US$68,000 per QALY

- What drives the differences in ICERs?
Studies of preferences on prophylaxis and health states in hemophilia: hypothetical scenarios

- Canadian standard gamble study (Naraine et al. 2002)
- 30 members of the public, 30 parents of children with hemophilia, and 28 adults with hemophilia
- 7 hypothetical scenarios
  - Least-preferred: episodic treatment with frequent bleeds (1 per month)
    - 0.825 (public), 0.895 (patients), 0.915 (parents)
    - Averaged across scenarios, on-demand treatment had SG weights lower by 8% relative to prophylaxis
  - Low-dose prophylaxis without port preferred to standard high-dose prophylaxis
US standard gamble study (Wasserman et al. 2005)

- 64 adult patients, 64 pediatric patients (parent proxies)
- 9 health states
  - 2 states for severe hemophilia A without severe joint disease with episodic vs. prophylactic treatment
    - Adult patients: 0.799 for episodic, 0.811 for prophylaxis (difference of 1.5%)
    - Pediatric patients no difference in SG weights by treatment type: 0.868 and 0.872
- Hypothetical comparisons
European survey using SF-36 and SF-6D (Lippert et al. 2005)

- 500 males ages 14-83 in 4 European countries
- Mean SF-6D utility scores by age and treatment type
  - Age 30 or under
    - 0.76 prophylaxis
    - 0.73 episodic
  - Over age 30
    - 0.68 prophylaxis
    - 0.66 episodic
European survey using EQ-5D (Noone et al. 2011)

- 58 respondents from France, Ireland, Sweden, UK ages 20-35 with severe hemophilia

- Mean weight by country
  - Sweden 0.93 – universal prophylaxis
  - France, Ireland, UK 0.73 – 0.76

- Individual lifetime experience with prophylaxis
  - Lifetime (primary) – 0.88 (mostly Swedish patients)
  - >50% of lifetime – 0.77
  - <50% of lifetime – 0.79
  - Never on prophylaxis – 0.72
European and Canadian patient survey using EQ-5D (Noone et al. 2013)

- 116 respondents from Canada, France, Ireland, Netherlands, Poland, UK ages 18-35 with severe disease

- **Mean weight by country and % with on-demand**
  - Netherlands: 0.915 and 8%
  - Canada: 0.791 and 13%
  - Ireland: 0.786 and 20%
  - UK: 0.768 and 8%
  - France: 0.687 and 62%
  - Poland: 0.629 and 79%
Noone et al. (2013)

- Among 103 with no history of inhibitor
  - Lifetime (primary) – 0.866
  - >50% of lifetime – 0.812
  - <50% of lifetime – 0.755
  - Never on prophylaxis – 0.619

- Among 13 with inhibitor, 0.798
Comparison of Noone et al. surveys

- **Contrasts for France and Ireland**
  - **France**
    - 2011 article (n=10) mean EQ-5D weight 0.74
    - 2013 article (n=14) mean EQ-5D weight 0.687
  - **Ireland**
    - 2011 article (n=19) mean EQ-5D weight 0.68
    - 2013 article (n=17) mean EQ-5D weight 0.786

- **High weight for Dutch sample not confirmed by Den Uijl et al. (2012)**
  - Mean EQ-5D weight for 60 young adults with severe hemophilia 0.80 despite lifetime prophylaxis
Conclusions

- No clear evidence of magnitude of difference in QALY weights in severe hemophilia by duration of use of prophylaxis
  - Contradictory findings for Dutch samples from Noone and Den Uijl
  - Inconsistent rankings of countries between surveys by Noone et al.
  - No information on differences by prophylaxis use within populations
Cost-utility analyses: mean utilities for patients on prophylaxis vs. on-demand treatment

- **Systematic review (Miners 2013):**
  - Miners et al. (2002) – UK: 0.86 vs. 0.67 (28% higher for Prophy)
  - Lippert et al. (2005) – Europe: 0.77 vs. 0.73 (8% higher for Prophy)
  - Risebrough et al. (2008) – Canada: 0.950 vs. 0.905 (5% higher for Prophy)
  - Miners et al. (2009) – UK: 0.71 vs. 0.50 (42% higher for Prophy)
  - Colombo et al. (2011) – Italy, copied Miners et al. (2002)

- **Farrugia et al. (2013) – Sweden, 1.00 vs. 0.67 (50% higher for Prophy)**
Explanation of QALY estimates in Miners analyses

- Prophylaxis assumed to improve HRQL for severe hemophilia to that of mild/moderate disease

- Miners et al. (1999) reported EQ-5D weights for 166 UK patients not on prophylaxis
  - Mean of 0.67 for severe hemophilia (n=66)
  - Mean of 0.85 for mild/moderate hemophilia (n=100) (27% higher)
Issues with assumptions

- No control for comorbidity with HIV infection
- Prophylaxis does not make severe hemophilia equivalent to mild/moderate hemophilia
  - Den Uijl et al. (2012) report mean weight of 0.80 for severe hemophilia with lifetime prophylaxis vs. 0.92 for moderate hemophilia (15% higher)
Canadian study of HUI weights stratified by HIV seropositivity (Barr et al. 2002)

- Not controlling for HIV, mean HUI2 and HUI3 weights
  - 0.75 and 0.66 for severe hemophilia
  - 0.85 and 0.77 for mild/moderate hemophilia (12-14% higher)

- Among those without HIV infection
  - 0.80 and 0.71 for severe hemophilia
  - 0.85 and 0.77 for mild/moderate hemophilia (6-8% higher)

- Implications
  - Not controlling for HIV status can bias differences
  - Important differences between studies
Conclusions about QALY estimates

- Not clear how much prophylaxis improves HRQL in severe disease, may not be equivalent to mild/moderate hemophilia not supportive
  - Farrugia et al. also assume age-specific mortality much lower with prophylaxis, equivalent to mild-moderate hemophilia

- Published estimates of utility for adults with severe hemophilia confounded by HIV

- Direct estimates of utilities for prophylaxis confounded by differences between populations
  - No data on differences by treatment status within national populations
Framing New Studies

- Need to ask specific questions, such as
  - What is the incremental cost of introducing primary prophylaxis in a population where prophylaxis is usually started after 2 years of age?
  - How long should prophylaxis continue in adults?
- Are less resource intensive forms of prophylaxis cost-effective?
- Can discrete choice experiments provide additional information about perceived value of prophylaxis?
Economic costs of hemophilia treatment in US

- Analysis of private and public health insurance claims data for years 2004-2008 (Guh et al. Haemophilia 2012)
- Mean and median annual per person treatment costs of approximately US$150,000 and US$50,000 for both insurance types
  - Unable to classify patients by level of severity
  - Pharmacy data on factor use could not be used to identify who was on prophylaxis
- Mean costs for those using bypassing agents for an inhibitor about $500,000 per year
  - 3% of hemophilia A patients with employer-sponsored insurance
  - 8% of hemophilia A patients with public insurance
Financial Implications of Prophylaxis

- Estimates of the impact of routine prophylaxis on health care payers are not well documented
  - Cost varies by body weight, dose, and frequency
  - Lack of data on actual amount of factor concentrate used in prophylaxis

- Farrugia et al. (2013) propose that primary prophylaxis can reduce inhibitor development
  - Assumed 90% reduction
  - Inhibitor treatment is costly