Clinical Trial Learning Curves May Impact Both Clinical and Economic Outcomes and Influence Health Technology Assessment and Reimbursement Decision Making

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BACKGROUND

- The presence of learning curves (LCs) in the performance of clinical procedures has been firmly established, and their implications on clinical and economic outcomes have been suggested in the literature.[1-7]
- There is also evidence suggesting the presence of LCs in the context of clinical trials.[1]
- Although the presence of LCs has long been accepted as a fact of medical device trials,[8-11] recent studies suggest that clinical trial LCs can be present also in drug trials and may have a significant impact on clinical outcomes, especially when the success of outcomes depends on provider skill and experience.[12-16]
- The PROWESS trial for drotrecogin alpha activated (DrotAA) in severe sepsis was identified in a previous study[15] as a trial whose primary clinical outcome (28-day mortality) potentially was influenced by LC effects, especially in the patient subgroup with lower risk of death (i.e., patients with APACHE II score < 25)[14] (Table 1).

Table 1. LC Effect Observed in the PROWESS Trial for DrotAA for Patients With Severe Sepsis With APACHE II Score < 25 Only

	28-Day Mortality With Corresponding Treatment, % (n)	
	DrotAA	Placebo
Including LC patients in calculation	18.8 (436)	19.0 (437)
Excluding LC patients from calculation	16.6 (282)	18.9 (291)

Data are with (including) and without (excluding) the first 4 patients enrolled per clinical site (i.e., LC/training patients).

Source: Derived from data on first and second APACHE II quartile patients in Macias et al., 2004.[14]

- The cost-effectiveness analyses and health technology assessments (HTAs) for DrotAA were based on PROWESS trial data[17] published before the identification of potential LC effects inherent to the trial. Table 2 shows the incremental costs per life-year gained (LYG) for DrotAA use in patients with severe sepsis calculated by Manns et al., 2002[18] before identification of the LC effect by Macias et al., 2004.[14]

Table 2. Cost-effectiveness of DrotAA in Subpopulations With Severe Sepsis

Group of Patients	Incremental Cost per LYG
All patients	$27,936
APACHE II score	
< 25	$575,054
≥ 25	$19,723

Source: Manns et al., 2002.[18]

OBJECTIVE

- The current analysis explores the potential impact of clinical trial LCs on cost-effectiveness analysis, coverage decisions, and market access for drugs, using DrotAA for patients with severe sepsis as a case study.

METHODS AND FINDINGS

- To understand whether the LC effect present in the PROWESS trial influenced the estimated cost-effectiveness of DrotAA in patients with severe sepsis with an APACHE II score < 25, we replicated the simple cost-effectiveness model published by Manns and colleagues[18] and reanalyzed the incremental cost-effectiveness ratio (ICER) for DrotAA using data that excluded LC patients.
- To determine whether the LC effect influenced coverage recommendations for DrotAA in patients with severe sepsis with an APACHE II score < 25, we reviewed DrotAA labels, HTAs, and coverage recommendations/decisions from multiple countries.
- To determine the extent to which the lack of coverage of DrotAA in Australia and Scotland potentially influenced market access, we estimated the total number of patients in Australia and Scotland who experienced severe sepsis with an APACHE II score < 25 in the first 8 years after product approval in these countries.

Methods: Replication of Cost-effectiveness Analysis of DrotAA Using PROWESS Trial Data

- Manns and colleagues[18] present a simplified version of the calculation of the ICER for DrotAA when used in all patients (i.e., not differentiated by APACHE II score) as a means of validating the more sophisticated model on which their analyses are based. Table 3 presents the simplified ICER calculation.
- Because of the authors' clear description of the simple model (which produced results [$23,839/LYG] similar to the results produced by the more sophisticated model), we were able to replicate the simple model and use it to conduct a cost-effectiveness analysis of patients with APACHE II score < 25, including and excluding patients subject to the clinical trial LC.

Table 3. Simple Cost-Effectiveness Calculation That Approximates the Results of the More Sophisticated Markov Analysis

Parameter	Derived Value
Incremental survivors per treatment with DrotAA of 100 unselected patients	6
Life expectancy after sepsis survival (years)	8.1
Total LYG by treatment of 100 patients with DrotAA	48.6
Cost of DrotAA for 100 patients	$680,000
Cost of caring for 6 incremental survivors for 8.1 years	$478,565
Total cost to treat 100 patients	$1,158,565
Simplified ICER ($/LYG)	$23,839

Source: Manns et al., 2002.[18]

Findings: Cost-effectiveness Analysis of DrotAA Adjusting for LC Effects

- After replicating the simple version of the cost-effectiveness model published by Manns et al.,[18] we populated the model with incremental survivorship data published by Macias et al.[14] for patients with severe sepsis with APACHE II scores < 25 from the PROWESS trial, both with LC patients included and with LC patients excluded.
- The cost-effectiveness of DrotAA in patients with severe sepsis with APACHE II score < 25 with LC patients included was of similar magnitude to the estimates used as the basis for HTA recommendations (see below). The cost-effectiveness of DrotAA in patients with severe sepsis with APACHE II score < 25 with LC patients excluded was substantially better ($46,395/LYG), with the ICER dropping to a value nearly 1/10 of the ICER that included LC patients ($411,333/LYG).

Table 4. Assumptions for Modeling and Computation of Cost-effectiveness of DrotAA in Patients With Severe Sepsis With APACHE II Score < 25 Only

Parameter	LC Patients Included	LC Patients Excluded
Incremental survivors per treatment of 100 unselected patients	0.2	2.3
Life expectancy after sepsis survival (years)[a]	8.1	
Total LYG by treatment of 100 patients	1.7	18.4
Cost of DrotAA for 100 patients[a]	$680,000	
Cost of caring for 1 incremental survivor[a]	$77,036	
Cost of caring for incremental survivors for 8.1 years	$16,094.66	$175,338.82
Total cost to treat 100 patients	$696,094.66	$855,338.82
Simplified ICER ($/LYG)	$411,333.37	$46,394.63

[a] Data from Manns et al., 2002.[18]

Methods: Review of Product Labels and HTAs

- Regulatory approvals (i.e., product labels) and HTA documents for DrotAA (Xigris; Eli Lilly) were reviewed to evaluate the approved indication restrictions and reimbursement coverage restrictions specifically with regard to patient APACHE II score.
  - DrotAA regulatory approvals were reviewed from the following countries and agencies:
    - Australia: Therapeutic Goods Administration (TGA)
    - Canada: Health Canada
    - Europe: European Medicines Agency (EMA)
    - United States: Food and Drug Administration (FDA)
  - DrotAA HTAs were reviewed from the following countries and agencies:
    - Australia: Pharmaceutical Benefits Advisory Committee (PBAC)
    - Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)/ Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
    - England and Wales: National Institute for Health and Clinical Excellence (NICE)
    - France: Haute Autorité de Santé (the French National Authority for Health) (HAS)
    - Scotland: Scottish Medicines Consortium (SMC)

Findings: Product Labels

- DrotAA gained regulatory approval for severe sepsis in all markets examined. Explicit indication restrictions to subpopulations with APACHE II score ≥ 25 were not present in any of the market-specific product labels. Product label indications from Health Canada and the FDA specifically mentioned the use of APACHE II score as an indicator of risk of death, but no specific APACHE II score was mentioned. The product label indication from TGA mentioned only patients with a high risk of death. The product label indication from EMA mentioned only severe sepsis with multiple organ failure.

Findings: HTAs

- Coverage of DrotAA for severe sepsis was not restricted based on APACHE II score by CADTH (CCOHTA), NICE, or HAS, although an HTA from the United Kingdom (for England and Wales; NICE) reviewed the cost-effectiveness of DrotAA versus placebo for severe sepsis in patients with APACHE II score < 25 and found the ICER to be unacceptably high, citing published papers from Canada and the US.[19]
- Health technology assessments from Australia[20] and Scotland[21] recommend coverage of DrotAA only for patients with severe sepsis with APACHE II score ≥ 25, citing cost-effectiveness considerations. PBAC and SMC specifically limited coverage of DrotAA to patients with severe sepsis with APACHE II score ≥ 25.
- Therefore, although regulatory approvals did not place explicit restrictions on eligible patients based on APACHE II score, the HTA recommendations for coverage did. Table 5 summarizes HTA recommendations for reimbursement of DrotAA.

Table 5. Severe Sepsis Indication Restriction Based on APACHE II Score in Country-Specific HTAs

HTA Agency	Recommended Coverage Limited to Patients With APACHE II Score ≥ 25
PBAC	**Yes**
CADTH/CCOHTA	No
NICE	No
HAS	No
SMC	**Yes**

Methods: Derivation of Incidence of Patients With Severe Sepsis With APACHE II Score < 25 in Australia and Scotland

Estimation of Patients Presenting to Emergency Departments With Severe Sepsis

- A targeted literature review was conducted to identify peer-reviewed articles relevant to the incidence of severe sepsis in Australia and Scotland to estimate the total number of patients in these countries who would have presented to emergency departments for the period from 2003 (the year in which DrotAA [Xigris] was first available in these countries) to 2010.
- Our targeted search identified three articles from which incidence data were used.[22-24] The incidence of severe sepsis for Australia and Scotland was as follows:
  - 0.77 per 1,000 population in Australia[22,23]
  - 0.51 per 1,000 population in the United Kingdom (including Scotland)[23,24]
- To estimate the annual incidence of severe sepsis in these countries from 2003-2010, population data from reputable sources were accessed. Population data were identified for Australia and Scotland from the Australian Bureau of Statistics and UK National Statistics, respectively. Population data from 2003 and 2010 for each country were averaged to arrive at an estimated average population for each country from 2003-2010 inclusive. This average then was used with the severe sepsis incidence data to derive an estimate for the total number of severe sepsis cases during the 8-year period.
- Table 6 summarizes the data used to estimate the total incidence of severe sepsis for Australia and Scotland (i.e., 130,000 and 20,900, respectively).

Table 6. Estimation of Total Numbers of Severe Sepsis Cases in Australia and Scotland

	Australia	Scotland
Population in 2003 (in '000s)	19,881	5,055
Population in 2010 (in '000s)	22,330	5,194[a]
Average population from 2003-2010 (in '000s)	21,106	5,125
Annual incidence of severe sepsis per 1,000	0.77	0.51
Annual incidence of severe sepsis (in '000s)	16.25	2.61
Total incidence of severe sepsis cases from 2003-2010 (in '000s)	130.0	20.9

[a] Population value is for 2009.

Estimation of Patients With Severe Sepsis With APACHE II Score < 25

- A targeted literature review was conducted to identify peer-reviewed articles describing the distribution of APACHE II scores among patients with severe sepsis presenting to emergency departments in Western countries and to estimate the total number of such cases with APACHE II score < 25.
- Two articles were identified from which APACHE II score distribution was used.[25,26] APACHE II score distributions for patients with severe sepsis were presented as mean ± standard deviation: 29.6 ± 10.6,[26] and 32.7 ± 16.5 (combined severe sepsis survivors and nonsurvivors[25]).
- With the assumption that APACHE II scores are normally distributed about the mean in patients with severe sepsis reported in the studies, the z-score was computed for an APACHE II score of 25 and then converted to a percentage of patients/cases with APACHE II score < 25, yielding 32.0% of patients/cases with APACHE II score < 25 in one study[25] and 33.3% of patients/cases in the other.[26] These percentages were then applied to the total incidence of severe sepsis in Australia and Scotland from 2003-2010 to arrive at an estimated incidence of severe sepsis cases with APACHE II score < 25 during this period.

Findings: Estimated Number of Patients With Severe Sepsis With APACHE II Score < 25 in Australia and Scotland During First 8 Years After DrotAA Approval

Table 7. Estimation of Total Numbers of Severe Sepsis Cases in Australia and Scotland From 2003-2010 With APACHE II Score < 25

Total incidence of severe sepsis cases from 2003-2010 in Australia and Scotland	150,900
Percentage of severe sepsis cases in Western countries with APACHE II score < 25	32.0%[a] / 33.3%[b]
Total incidence of severe sepsis cases from 2003-2010 in Australia and Scotland with APACHE II score < 25	48,300[a] / 50,300[b]

[a] 32.0% derived from data provided in Bilevicius et al., 2001[25] and yields 41,600 cases in Australia and 6,700 in Scotland.

[b] 33.3% derived from data provided in Nguyen et al., 2007[26] and yields 43,300 cases in Australia and 7,000 in Scotland.

SUMMARY OF FINDINGS

- Potential LC effects present in the PROWESS trial impacted observed DrotAA cost-effectiveness in the subpopulation with severe sepsis and APACHE II score < 25.
  - Cost-effectiveness estimates in the literature for this subpopulation ranged from $342,550 per LYG[27] to $575,054 per LYG.[18]
  - Using a simple model presented by Manns et al.,[18] we estimated that before potential LC effects were taken into account, the ICER was $411,333 per LYG.
  - After the first block of patients enrolled at each trial site (the first 4 patients) was removed from the analysis, the ICER dropped to $46,395 per LYG, an improvement in cost-effectiveness of nearly 10-fold.
- Although the relevant product labels did not exclude patients with severe sepsis with APACHE II scores < 25, based in part on cost-effectiveness considerations, DrotAA was not covered for these patients in Australia and Scotland.
- Lack of coverage in Australia and Scotland for patients with severe sepsis with APACHE II scores < 25 may have resulted in a lack of market access to DrotAA for more than 50,000 patients during the first 8 years after DrotAA approval.

CONCLUSIONS

- Learning curve effects potentially present in the PROWESS trial may have influenced DrotAA reimbursement decisions in Australia and Scotland, specifically in the severe sepsis population with APACHE II score < 25.
- Our analysis suggests that LCs in the PROWESS trial may have profoundly affected not only clinical outcomes associated with use of DrotAA but also its observed cost-effectiveness in the subset of enrolled patients with APACHE II score < 25, substantially reducing cost-effectiveness to the point of unacceptability by typically accepted thresholds.
- Although follow-up studies to the PROWESS trial indicated that DrotAA is likely to be effective in patients with APACHE II score < 25,[13,14] clinical trial LC effects may have ultimately influenced the explicit HTA and/or reimbursement recommendations for DrotAA in patients with APACHE II scores < 25 in Australia and Scotland, potentially impacting the market access of DrotAA for more than 50,000 patients in each of these countries from 2003-2010.
- Regulatory approval and HTA processes ensure access to drugs, medical devices, and procedures that are safe and effective both clinically and economically; in light of evidence of trial LCs gathered from the PROWESS trial on DrotAA,[13,14] the validity of regulatory approval, HTA processes, and reimbursement decision making may require consideration of potential LC effects present in drug and medical device trials submitted for review and extrapolation of trial outcomes to effectiveness in the real world (especially for technologies, such as DrotAA, for which the success of outcomes depends on the skill of the provider).

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