HTA 257

MOVe-OUT: A Trial of Two Halves

The Impact of Heterogeneity on Cost-Effectiveness Outcomes for COVID-19

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BACKGROUND

In the phase 3 MOVe-OUT trial, non-hospitalised, unvaccinated adults with COVID-19 (at risk for severe illness) were randomised to molnupiravir or placebo. Merck disseminated outputs from the interim analysis via press release on 1 October 2021, which demonstrated a reduction in hospitalisations with molnupiravir [1]. On this basis, molnupiravir was conditionally authorised and subsequently reimbursed in a number of jurisdictions. The peer-reviewed final analysis of MOVe-OUT, published on 16 December 2021, demonstrated a considerable reduction in efficacy relative to the interim analysis [2]. The aim of this work was to explore the implications of this between-analysis heterogeneity for decision making, via the use of an acute phase decision tree model to estimate the effect of molnupiravir treatment on healthcare outcomes.

METHODS

Objective:
Estimate the acute-phase costs and health care outcomes for high-risk patients treated with molnupiravir compared with current standard-of-care (SoC), and how these differ between MOVe-OUT analysis sets.

Population
- SARS-CoV-2 Infected (symptomatic or asymptomatic)
- High risk of progression to severe COVID-19

Intervention and Comparator
- Molnupiravir
- SoC: no active treatment (prior to hospitalisation)

Outcomes
- Total and incremental costs, hospitalisations, ICU admissions, and deaths.
- Ratios of cost per hospitalisation, ICU admission, and death avoided.

Time horizon
- Acute phase: 28 days from treatment initiation

Perspective
- Health Service Executive (HSE): Irish public healthcare system

Model Structure

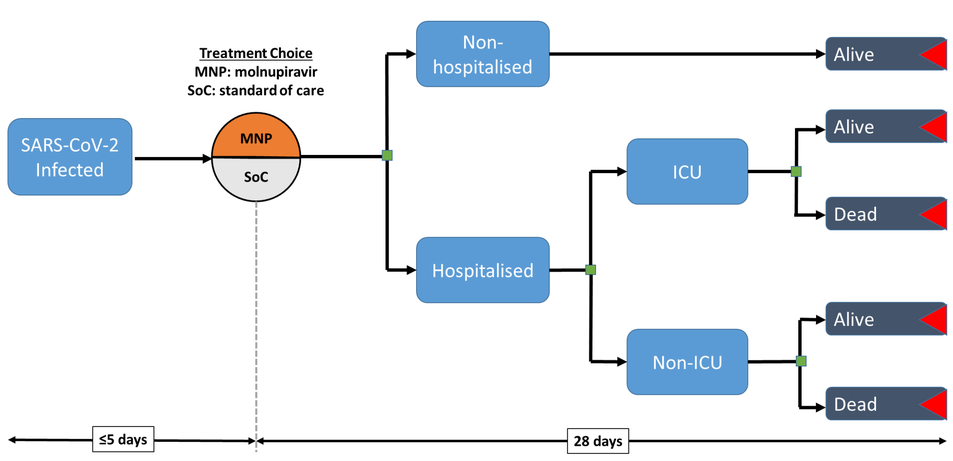

Figure 1: Decision tree model structure

Model Inputs

Clinical Effectiveness Inputs
Probabilities of hospitalisation and death derived from MOVe-OUT data [2]. Three separate analysis sets were considered:
- Final analysis: all randomised patients in MOVe-OUT
- Interim analysis: first ~50% of enrolled patients (informally, the 'first half' of MOVe-OUT)
- Post-interim analysis: remaining patients not included in the interim analysis ('second half')

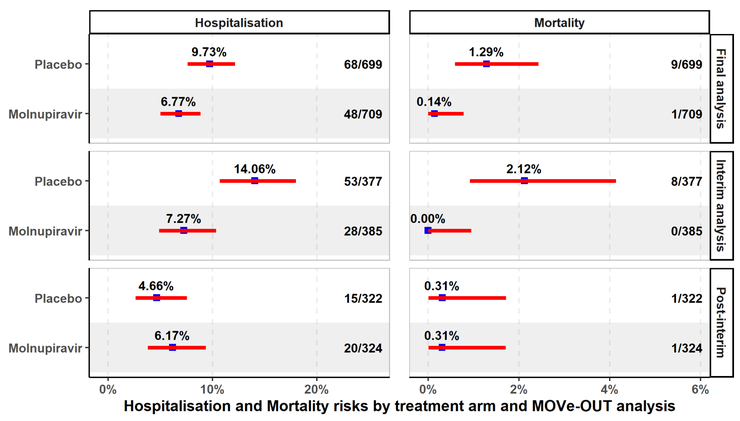

Figure 2: Rates of hospitalisations and death in MOVe-OUT by analysis set

ICU admission data not available from MOVe-OUT: Irish data and expert opinion utilised:
- Irish Central Statistics Office – proportion of hospitalisations leading to ICU admission under SoC [3]
- Assumptions elicited from clinical experts:
  - No mortality benefit of antiviral treatment following ICU admission
  - All deaths occur in hospital; 50% of these occur in ICU

Table 1: Summary of cost inputs for the decision tree

Cost	Value	Source/Calculation
Hospitalisation without ICU	€5,510	Healthcare Pricing Office [4]
Hospitalisation with ICU admission	€25,405	Healthcare Pricing Office [4]
GP Visit cost	€56.39	Connolly et al 2018 [5], adjusted for inflation
Molnupiravir AE cost	€10	Assumption
Molnupiravir, drug acquisition cost	€621.74	ICER report ($707) [6], converted to EUR @ rate $1=€0.8794 (1st January 2022)
Molnupiravir, additional costs	€118	Calculation: 2 GP visits @ €56.39 plus €10 AE costs
SoC, additional costs	€56.39	1 GP visit @ €56.39

RESULTS

Probabilistic and deterministic results are shown in Figure 3 for all MOVe-OUT cohorts. At first glance, the final analysis set appears to be the most appropriate source of efficacy data:
- Peer-reviewed
- Uses all available data

Using efficacy data from the MOVe-OUT final analysis, molnupiravir was estimated to be more costly and more effective than SoC.

However, the **final analysis set masks considerable differences between the two 'halves' of MOVe-OUT.**

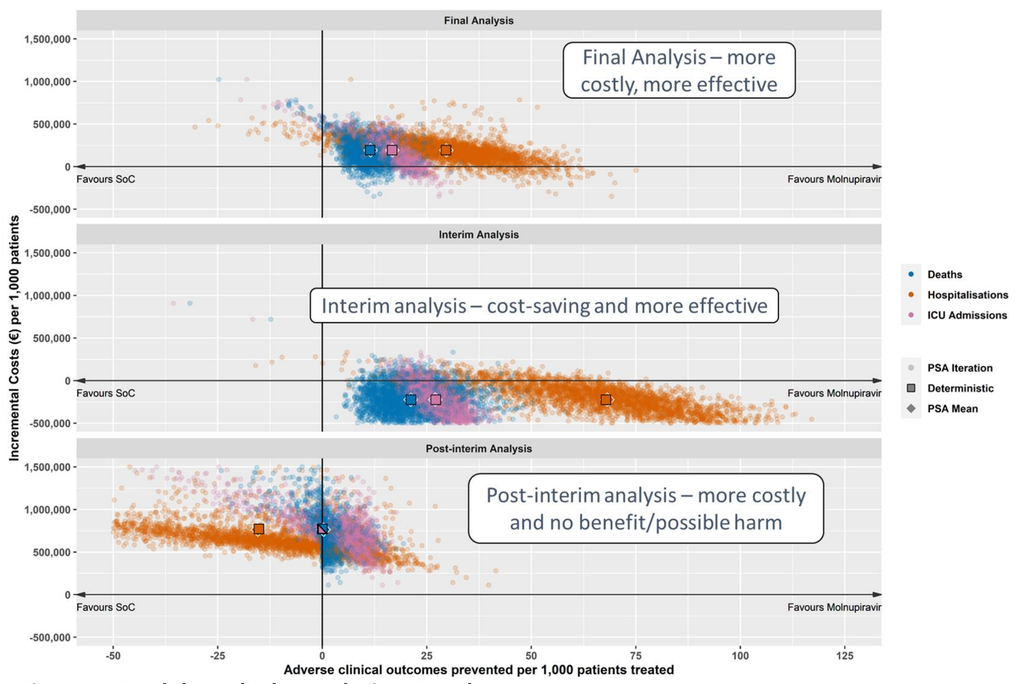

Figure 3: Model results by analysis set and outcome

Model results differed dramatically between the two underlying cohorts included in the final analysis (Figure 3):
- Using the interim analysis, the clinical benefits of molnupiravir were greater and healthcare costs were reduced compared with SoC. In fact, molnupiravir appeared to be cost-saving in this scenario.
- Using the 'post-interim' analysis, there was no benefit associated with molnupiravir, and a possible increase in hospitalisations. Incremental costs were also higher.

Key learning: Conclusions on the clinical and economic value of MOVe-OUT differ considerably between analyses of MOVe-OUT. Clinical benefit observed in the final analysis is derived entirely from the interim analysis cohort.

Discussion

Heterogeneity within the MOVe-OUT study

Difference in outcomes between the two 'halves' of MOVe-OUT is a major source of uncertainty.
- Considerably lower baseline risk in the post-interim analysis cohort
- No observed reduction in risk with molnupiravir in this analysis

Why? Some differences in risk factors for severe COVID-19 between cohorts (Table 3), but no clear pattern.

Risk Factor	Interim Analysis	Post-interim analysis	Difference	
Male sex	52%	45%	+7%	Some COVID-19 risk factors more prevalent among interim analysis cohort
Obesity	77%	70%	+7%	
Seronegative	76%	72%	+4%	
Age > 60	14%	21%	-7%	Others more prevalent among post-interim analysis cohort
Diabetes	14%	19%	-5%	
Serious CVD	10%	14%	-4%	

Table 3: Differences in distributions of some known risk factors between MOVe-OUT analysis cohorts

- Differences in the geographic distribution of trial sites - healthcare systems, criteria for hospitalisation, hospital capacity
- Change in circulating variants between analysis periods and trial sites
- Unobserved prognostic and/or treatment effect-modifying factors

Unclear which analysis is more suitable to inform decision making – in light of mass vaccination and newer variants, possibly neither.

Of note, preliminary results from the PANORAMIC study [7] (not yet peer-reviewed) showed no reduction in hospitalisations or deaths with molnupiravir compared to SoC. By contrast to MOVe-OUT, the PANORAMIC study was conducted in a highly-vaccinated population.

Early clinical data

This work also highlights the challenges of the use of early clinical data for decision making:
- Decision based upon interim analysis would almost certainly overestimate the benefit and underestimate cost of molnupiravir
- Other examples in COVID-19: antivirals, neutralising monoclonal antibody therapies, vaccines
- Also problematic in other disease areas – for example, the use of immature survival data in oncology and rare disease.

References

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