Value Over Volume:

The Future of Pay for Performance in Irish Health

Lesley Tilson BSc (Pharm), Dip Stat, PhD

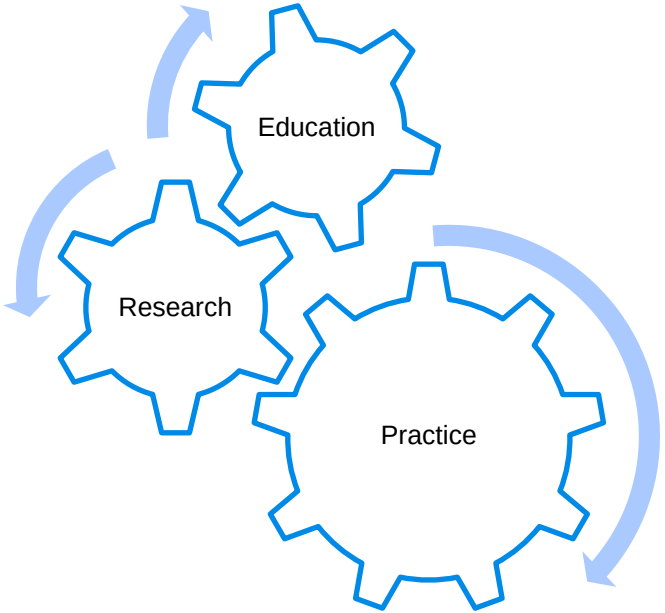
National Centre for Pharmacoeconomics
NCPE Ireland

Outline

- Background:
  - Description of NCPE HTA Process
  - Performance Based Agreements
- Case Studies of Once-Off Cell and Gene Therapies
- Future Challenges

The National Centre for Pharmacoeconomics in Ireland

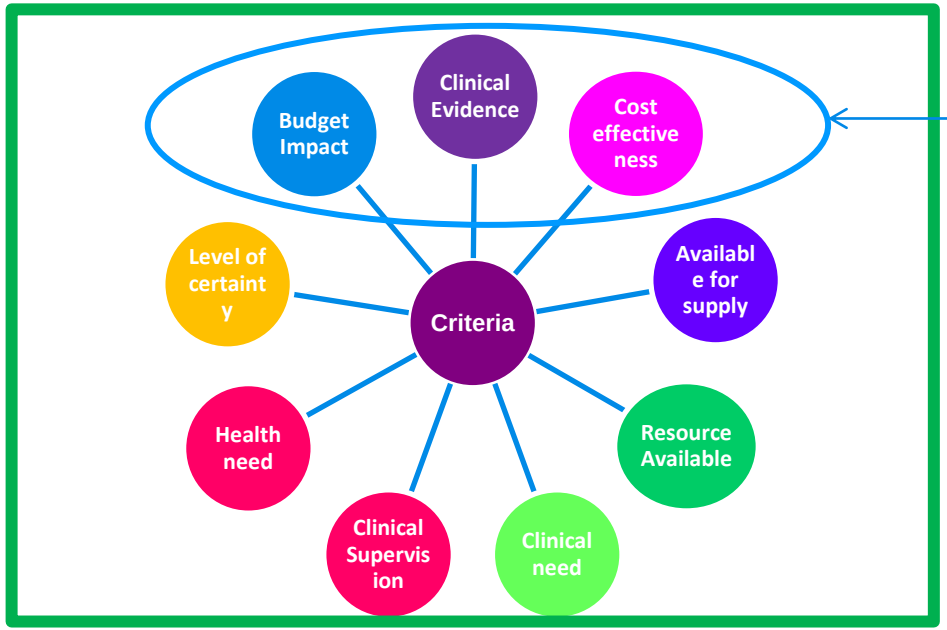
The NCPE is an autonomous, independent body whose primary activity is to conduct Health Technology Assessment of all new drugs and also existing drugs for the Irish Health Service within the national Framework Agreement on the Supply and Pricing of Medicines 2021.



Reference: Framework Agreement on the Supply and Pricing of Medicines 2021.
Available at: FRAMEWORK AGREEMENT ON THE SUPPLY AND PRICING OF MEDICINES (netdna-ssl.com)

Reimbursement Process in Ireland

Marketing Authorisation → Reimbursement application by company to HSE → HSE commission NCPE to conduct HTA → CPU/ HSE Drugs Group / HSE Leadership → Reimbursement Decision by HSE



Reference: Health (Pricing and Supply of Medical Goods) Act 2013. Available at: http://www.irishstatutebook.ie/eli/2013/act/14/enacted/en/html.

The Challenge of Once-off Cell and Gene Therapies

Once-off treatments	Repeat dose treatments
Discontinuing treatment (and payment) due to non-response or disease progression is not possible	Continue until patient no longer benefits or experiences toxicities or completes course of treatment. Payment also ceases.

- Upfront payment
- Irrecoverable costs if treatment not effective
- Greater financial risk with once-off therapies vs repeat dose therapies

Performance Based Agreements are a Type of Risk Sharing Agreement (RSA)

Types of RSAs	Examples	Description
Financial	Simple price discounts, budget caps, dosage caps, utilisation caps, free initiation, price match with comparator	Simple to administer Reduce budget uncertainty Widely used in Irish reimbursement system Do not address the challenge of once-off treatments
Population level performance based	Coverage with Evidence Development	Usually implemented at population level e.g. UK Cancer Drugs Fund Require collection of additional clinical evidence Address clinical and value uncertainty
Patient level performance based	Performance linked reimbursement Managed Access Protocols	Implemented at individual level May require collection of outcome data Address clinical and value uncertainty More pertinent to the Irish reimbursement setting

CASE STUDIES OF ONCE-OFF CELL AND GENE THERAPIES

NCPE Assessments of:

1. Gene Therapy for Spinal Muscular Atrophy
2. Chimeric Antigen Receptor (CAR) Therapy

Once off Gene Therapy for Spinal Muscular Atrophy

Onasemnogene abeparvovec (Zolgensma®)
€2,000,000 per patient

New gene therapy to treat children with Spinal Muscular Atrophy approved in Ireland

8th October 2021

Development welcomed by Trinity College, St James's Hospital and Children's Health Ireland following first successful clinical trials on four Irish babies and children.

Trinity College Dublin, St. James's Hospital and Children's Health Ireland have welcomed the news that the HSE has agreed a reimbursement price on Zolgensma gene replacement therapy for the treatment of Spinal Muscular Atrophy (SMA) in children.

NCPE HTA of Onasemnogene abeparvovec (Zolgensma®)

Onasemnogene abeparvovec is indicated for the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene*.

*A joint HTA undertaken as part of the Beneluxa process.

HTA completed	April 2021
ICER vs current standard of care (nusinersen)	€298,469 per QALY
Cost per patient in subgroup of licensed population^	€2,285,375
5 year net drug budget impact in subgroup of licensed population^	€26.2 million

^ The Applicant requested reimbursement in a subgroup of the licensed population: all symptomatic SMA type 1 patients and pre-symptomatic SMA patients with up to three copies of the SMN2 gene.

Clinical Evidence for Onasemnogene abeparvovec

- Four single arm studies and two long term follow-up studies
- Comparative effectiveness vs standard of care (nusinersen) is unknown
- Quality of evidence is low:
  - single arm, uncontrolled studies
  - small patient numbers
  - limited follow up

"The clinical evidence suggests benefit in some patients, however, the design and follow-up of the clinical trials are such that there remains significant uncertainty as to medium to long term outcomes in terms of both safety and efficacy"

NCPE HTA of OA:https://www.ncpe.ie/wp-content/uploads/2020/05/Executive-summary-Zolgensma-Beneluxa-IrelandFinal-Version.pdf

Post HTA Negotiations / Reimbursement

- April 2021: NCPE recommended that onasemnogene abeparvovec not be considered for reimbursement unless cost-effectiveness be improved relative to existing treatments.
- NCPE evaluated impact of confidential commercial proposals on cost-effectiveness and budget impact.
- June 2021: HSE Drugs Group recommended reimbursement following commercial negotiations.
- October 2021: Pricing approval granted, following joint negotiations under the Beneluxa initiative.
- November 2021: HSE Medicines Management Programme **Managed Access Protocol.**

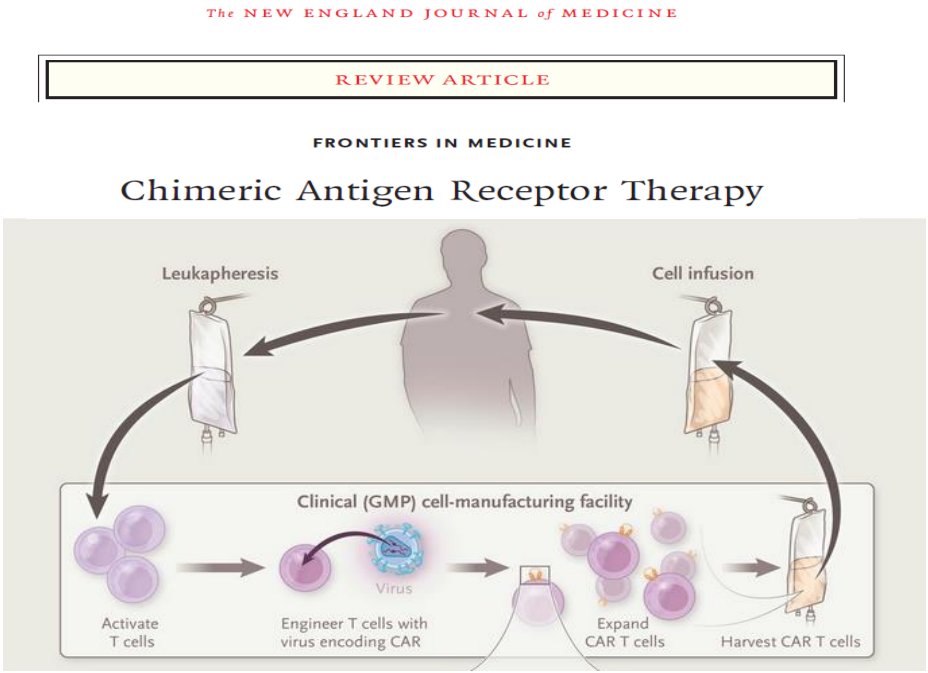
HSE Drugs Group Minutes: June 2021

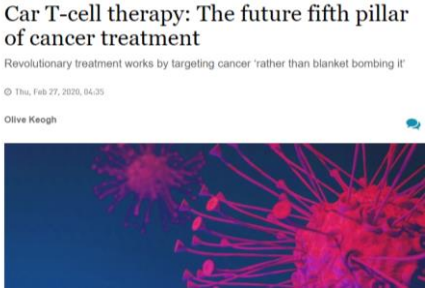
5. Medicines for Consideration assessed under the Beneluxa initiative

i. Onasemnogene abeparvovec for spinal muscular atrophy (SMA)

The Drugs Group considered the clinical and cost-effectiveness evidence available for Onasemnogene abeparvovec along with the patient group submission received during the HTA process. The Drugs Group, in the majority, were in favour of reimbursement, if the specific terms set out in a proposed joint mandate were to emerge. This positive recommendation is conditional on the applicant company (Novartis Gene Therapies) agreeing to these terms, which will be sought by the HSE in conjunction with the equivalent Dutch and Belgian health authorities via the Beneluxa initiative. The terms were based on the recommendations arising from the HTA report conducted on a collaborative basis by HTA bodies in Ireland, the Netherlands and Belgium.

Chimeric Antigen Receptor Therapy (CAR-T)





T cells are engineered to express a chimeric antigen receptor (CAR) targeting the CD19 antigen expressed on the surface of B cells

This personalised therapeutic approach involves (a) removal of peripheral blood T-cells followed by (b) in vitro activation, genetic modification and expansion of the T cells and (c) infusion of the cells back into the patient.

N Engl J Med 2017;377:2593-2596

NCPE HTA of Tisagenlecleucel (Kymriah®)

Tisa-cel is indicated for the treatment of:

- adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
- paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

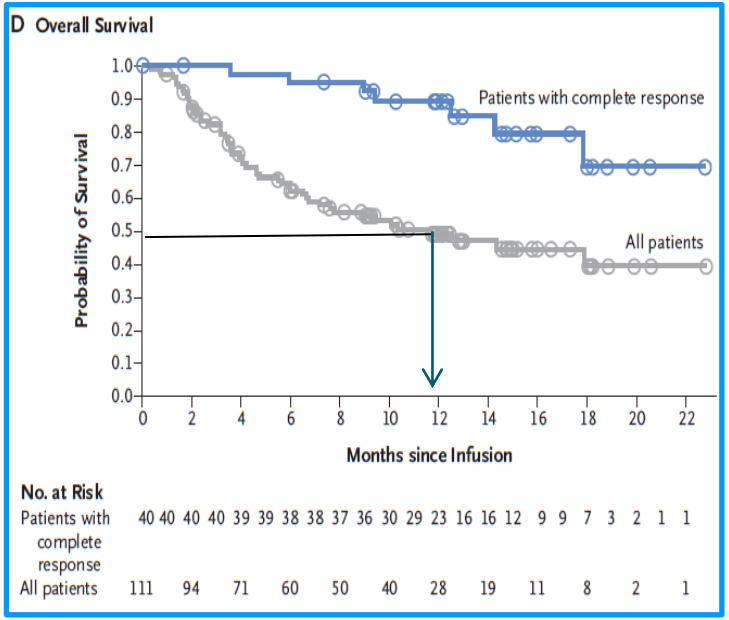
Indication	**R/R DLBCL**
HTA completed	September 2019
ICER	€ 197,119 per QALY
Cost per patient	€301,762
5 year net drug budget impact	€20.5 – 30.2 million

"Treatment with tisagenlecleucel is associated with particular institutional requirements, extremely high upfront costs and a limited evidence base. The HSE faces the possibility of huge unrecoverable costs should this treatment not prove to be as effective as suggested by this highly uncertain evaluation".

NCPE HTAs of tisa-cel: https://www.ncpe.ie/drugs/tisagenlecleucel-kymriah-for-dlbcl/

Clinical Evidence for Tisagenlecleucel

R/R DLBCL (Schuster et al NEJM 2019;380:45-56)



50% of treated patients did not survive beyond 12 months

Post HTA Negotiations/Reimbursement

- Sept 2019: NCPE recommended that tisa-cel not be considered for reimbursement unless cost-effectiveness be improved relative to existing treatments.
- NCPE evaluated impact of confidential commercial proposals on cost-effectiveness and budget impact.
- April 2021: HSE Drugs Group recommended reimbursement following commercial negotiations.
- July 2021: Reimbursement approved. The NCCP designated St James's Hospital as the initial National Adult CAR-T centre.
- December 2021: First patient administered CAR-T in St James's Hospital.

NCCP Chemotherapy Regimen

Tisagenlecleucel (Kymriah®) (CAR-T) DLBCL

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy	C83	00687a	ODMS 01/07/2021

HSE Drugs Group Minutes: April 2021

i. 20023 Tisagenlecleucel for the treatment of relapsed and/or refractory diffuse large B cell lymphoma (DLBCL)

Tisagenlecleucel for the treatment of r/r DLBCL was previously considered by the Drugs Group in November 2020. At that meeting the Drugs Group was unable to support reimbursement (in the majority) on the basis of the application submitted.

In response to the Drugs Group position on reimbursement in November 2020 the applicant submitted a revised commercial proposal for the DLBCL indication [redacted] Further efficacy data was also made available from the pivotal JULIET study. The commercial proposal improved the cost-effectiveness to a level that was considered acceptable by the Group for this application [redacted] Given the improved terms in the commercial offer, the unmet need, and potential for CAR-T to offer a prolonged response and survival in some patients the unanimous decision of the Drugs Group was to support a positive reimbursement recommendation for this indication.

Emerging Evidence: American Society of Haematology (ASH) December 2021

Bishop et al. NEJM 2022; 386: 629-639

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

M.R. Bishop, M. Dickinson, D. Purtill, P. Barba, A. Santoro, N. Hamad, K. Kato, A. Sureda, R. Greil, C. Thieblemont, F. Morschhauser, M. Janz, I. Flinn,

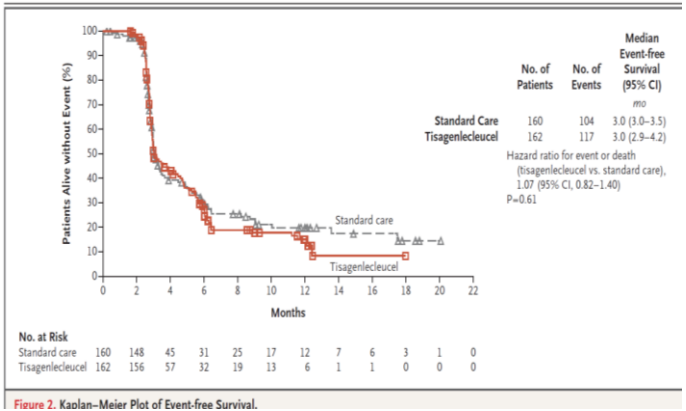


Figure 2. Kaplan–Meier Plot of Event-free Survival.

ASH December 2021:
"No Event Free Survival Benefit with Second Line Tisa-Cel in Relapsed/Refractory Non-Hodgkins Lymphoma".

FUTURE CHALLENGES

Performance Based Agreements in Practice

Future Challenges

- Trend towards accelerated approval of medicines with limited evidence
- High cost once-off treatments pose a substantial affordability challenge to the HSE
- Expect increase in requirement for performance linked reimbursement agreements
- Agility to assess impact of emerging clinical evidence and changing market dynamics
- Use of economic models to periodically evaluate impact of performance based agreements
- Performance linked reimbursement agreements are not a substitute for high quality RCTs.

Future of Value Based Healthcare in Ireland

10 March 2022

Lesley Tilson BSc (Pharm), Dip Stat, PhD

National Centre for Pharmacoeconomics
NCPE Ireland