Development, market authorization and market access of gene and cell-based therapies

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Colophon

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"If I have seen further it is by standing on the shoulders of giants".
Isaac Newton (1642–1727)

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General introduction

New biomedical discoveries are made every day providing us with more insights in the pathophysiology of disease. These insights are used to – amongst other purposes - develop new therapies to better our mental and physical health. In the beginning of the 21st century several discoveries occurred in synergy leading to a breakthrough in drug discovery and development. With the finalization of the Human Genome Project in 2003, the goal to map and understand the DNA sequence of all the genes of human beings was achieved.[1] Building on this finding, in 2011 Emmanuelle Charpentier and Jennifer Doudna developed a 'genetic scissor'-tool, by some better known as Clustered Regularly Interspaced Short Palindromic Repeats or CRISPR/Cas9.[2] This technique enabled simple and cheap, yet precise, editing of genomes. Shortly after its discovery Fen Zhang demonstrated applicability of CRISPR/Cas9 in mammalian cells.[3,4] Combined discovery and operationalisation of this genetic modification tool accelerated translation of gene transfer and gene modification for therapeutic use in humans.[5] The truly revolutionary nature of the gene editing technique was endorsed by the awarding of the 2020 Nobel Prize in Chemistry to Charpentier and Doudna.[6]

Advances in genetic modification techniques and gene therapy development are also an important part of the emergence of the novel field of regenerative medicine.[7] Regenerative medicines include therapeutic (stem) cell and tissue engineered products which have the potential to replace, repair or regrow tissues which are damaged by disease, trauma or age.[8] The origin of this discovery lays in the discovery of John Gurdon that specialisation of cells is reversible in 1962. This finding allowed Shinya Yamanaka more than 40 years later to uncover how mature murine cells can be reprogrammed to become pluripotent stem cells by introducing a specific gene combination.[9,10]

Translation of gene and cell-based therapies (GCTs) from the laboratory to early clinical settings resulted in new hopeful perspectives for patients and their caregivers in the late 1990's and early 2000s. This was especially the case for patients suffering from orphan diseases and those with high unmet need as the new and innovative technologies showed potential to unlock new treatment options for indications previously deemed untreatable.[11] Moreover, distinct types of GCTs showed potential to intervene with such precision that they could distinguish pathophysiological processes on an individual patient-level making them truly individualised medicines.[12,13] Hopes and expectations were further amplified by increasing development activity and promising results of early clinical studies.[14] Maciulaitis *et al.* estimated that clinical trials were performed for 250 different GCTs between 2004 and 2010.[15] A more recent technology forecast from 2019 shows 141 GCT clinical trials in advanced development stages (Phase III and IV).[16] And by 2025, it has been estimated that 10–20 cell and gene therapy products will be approved each year.[17] To continue, results from early clinical trials, such as an ex-vivo gene therapy intended to treat severe combined immune-deficiency in children, showed significant long-term effectiveness in diseases otherwise known to be fatal.[18,19] However, the occurrence of serious adverse events up to 2-7 years post-gene therapy admission abruptly halted the initial enthusiasm and investments.[20] Later is was found that improved gene transfer efficacy caused issues with insertion mutagenesis resulting in leukaemia and oncogene transactivation.[20,21] Learning from these serious adverse events led to the design of a new generation of vectors, manufacturing adjustments and further refined conditioning regimens.[20]

From previous studies it is known that instead of creating a revolutionary change overnight, historical advances in medical biotechnology show a slow but established pattern of incremental technology development and diffusion.[22,23] With early phases being characterised by "hypes and hopes", "myths of a revolution" or similar exclamations.[22,24,25] For example, monoclonal antibodies and proteins were once found highly innovative and had to overcome many development challenges resulting in slow initial development and uptake.[26–28] Yet, today they are overrepresented in the top of best-selling pharmaceutical product lists around the globe.[29] More so, in community pharmacies their dispensing is considered 'business as usual'.[30] This suggests that maturation, dissemination and implementation of radical innovations takes time and combined continuous efforts.[31,32] It has been reported that major technologies took up to 40-60 years before starting to yield direct or indirect benefits.[22] And even then, the pace may be dependent on complementary scientific, technical and organizational innovation as seen with the discovery of CRIPS/Cas9 and pluripotent stem cells.[9,33–35]

The translational challenges associated with innovation and biomedicines have also been described with regard to the development of GCTs. Authors have described translation of early discoveries into effective treatments for patients as time-consuming, costly, and often unsuccessful.[14,36,37] In the context of gene and cell-based technology it has been suggested that translational challenges stem from its novelty and a mismatch with existing regulation and policy frameworks and healthcare delivery systems that have been developed for conventional medicinal products.[38] For instance, following the enactment of the Advanced Therapy Medicinal Product (ATMP) regulation commentators raised concerns that only few products were submitted for market authorization.[15,38] The perception emerged that the expectations of GCTs were perhaps hyped and that developers faced difficulties to overcome development challenges.[39,40]

Innovation challenges have been extensively researched in biomedical science and in wider contexts outside of healthcare.[41,42] By drawing from these learnings and plotting them on the field of the development and uptake of GCTs, three domains have been formulated in which innovation challenges occur, being 1) clinical, 2) regulatory and, 3) health economic and technology assessment.[14,37] To assess GCT development more carefully, this thesis adopts these three domains in which GCTs currently predominantly face translational challenges and defines them as 1) translation from the laboratory to the clinic hereafter referred to as development, 2) regulation via centralized market authorization and 3) market access defined as health economics and health technology assessment towards implementation in healthcare services.

Development of gene and cell-based therapies

When biomedical inventions move from a laboratory setting towards clinical practice products have to cross the so-called "valley-of-death": a perceived gap between bench research and clinical application.[43] The valley of death-metaphor originated during the rise of molecular biology. This scientific advancement increased the need for highly specialized scientists to conduct the research.[36] Where medical research used to be conducted mostly by physicians (e.g. scientists who also treat patients), the physician-scientists quickly became outnumbered in the second half of the 20th century, causing researchers as well as products to venture away from the clinic.[36] Clinical and basic research started to diverge. In response to bridge the valley-of-death the field of translational

research emerged.[36] Translational researchers in the healthcare sector aim to increase the success of the *translation* of a novel technology into a viable product or service.[43,44]

It is often described that the characteristics of GCTs are considerably different from more conventional medicinal products such as small molecules or monoclonal anti-bodies, making the bridging of the valley of death a major challenge for GCT developers.[45–47] Differences are said to lay in their mechanism of action, raw materials, intended function and manufacturing.[45] GCTs consist mostly of live cell and tissue materials as opposed to small molecules or proteins in the case of early biotech products. Handling, manufacturing, manipulating and transporting these live materials requires extensive redesign of manufacturing and product supply chains.[47]

Developers need to build expertise and capabilities to develop and master the novel and highly specialized techniques.[48]

Similar to previous waves of biomedical technology, innovation leading to development of GCTs predominantly emerged from academia and small and medium-sized enterprises (SMEs).[49] It is known these developers have strong scientific and technical capabilities. However, previous research has described smaller (academic) developers experience more difficulties in development towards clinical practice. Described are challenges in clinical research such as trial design and the raising the resources needed conduct clinical trials.[50] But also, robust and reliable manufacturing and the ability to scale up (cost-)effective.[51] To add, GCT development needs to meet a variety of European and national (regulatory) requirements. Whereas previous research has also shown that regulatory and economic knowledge of small and academic is often less developed.[52] The regulatory and commercial capabilities as well as the resources needed to bring and keep products on the market are more often present within larger companies.[51]

To continue, the large heterogeneity of starting materials, manipulations and product characteristics adds to the complexity of manufacturing processes. Complexity is amplified by the fact that GCTs are regulated as medicinal products, which means that these processes ought to meet standardized Good-Manufacturing-Practices (GMP) and quality requirements.[53,54] This is not only a regulatory concern, as the choices made in early development manufacturing process design effect down-stream development.[55] To clarify, changes made in an existing manufacturing process often require (re)validation and reassessment by authorities, which may hamper and add costs in technology transfer or scaling-up. Additionally, GCTs come with high manufacturing costs which seem to dictate higher prices to be commercially viable.[56] These higher costs and prices are expected to influence health technology assessment and reimbursement.[46,57] This shows developers need to thoroughly understand the clinical, regulatory and commercial deployment of their product early on in development.[55] In a field where academic developers and SMEs are overrepresented, their regulatory and commercial capabilities are less developed, investments are substantial and early development choices can have a considerable effect on downstream development.[32,50]

Market authorization of gene and cell-based therapies

To facilitate the clinical development and market authorization of GCTs and regulate associated risks, the European Committee enforced regulations and created an assessment committee for the marketing authorization evaluation of advanced therapies in 2008 within the European Medicines Agency (EMA).[53] In doing so, the EU was the first jurisdiction globally to formally define a new medicinal product group: *Advanced Therapy Medicinal Products (ATMPs)*. ATMP is an umbrella term and includes gene therapy medicinal products (GTMPs), cell therapy medicinal products (CTMPs), tissue engineered products (TEPs), and combined-ATMPs (c-ATMPs). For the legal definition of the Advanced Therapy Medicinal Products see Box 1. Formalisation of GCTs as medicinal products had consequences for products in development or on the market.[45] Various human gene, cell and tissue therapies as well as blood products now had to demonstrate compliance to additional or different stringent quality requirements[58]. Additionally, the new regulation required manufacturers of GCTs to apply for centralized market authorization via the European Medicines Agency (EMA).[53] Before, especially blood products and human cell- and tissue therapies, did not need to be granted formal market authorization to achieve market access.[45] Additionally, for several products already on the market formal MA had to be granted before continuing clinical use.[59]

To facilitate implementation of the new regulation, the EMA allowed a two-year transition period. Developers, authorities, patients, physicians, and scientist awaited the approval of the first GCTs under this new regulation. However, the expected 'wave' of market authorization applications (± 20 products were known to be in late clinical development when the ATMP-regulation was invoked) was not observed.[49] The first cell therapy medicinal product was approved in November of 2009: ChondroCelect®, indicated for repair of cartilage defects in the knee. The first approved gene therapy, and second GCT overall, was Glybera®. This product, indicated for hyperlipidaemia, received a positive regulatory opinion in November 2012. In the following five years, seven more products received a positive opinion and were granted central market authorization. However, up until today widespread patient access in Europe to GCTs has not been observed yet.[46,63]

As already mentioned briefly, demonstration of adherence to GMP-requirements and specifications, quality assurance and risk minimisation by developers towards European regulators and national competent authorities were found challenging. Developers argued that acting (GMP-)guidelines did not suit GCTs.[46,47,64,65] Similarly, the application of the GMP-requirements to diverse and complex GCT manufacturing and supply chains were being flagged as troublesome and burdensome.[54] Difficulties in the assessment of quality, benefits and risks of GCTs were also described by regulators, both regarding the assessment process (i.e., roles and responsibilities between the European regulator and national competent authorities) as well as assessment standards. One example is that research with gene therapies requires an additional environmental risk assessment (ERA), in which possible shedding and transmission of genes to the environment is examined. Such assessments were previously predominantly conducted in the context of agricultural crops and therefore required inclusion and training of new stakeholders.[66] Regarding assessment standards, the specific product characteristics of GCTs – being live cells and tissues – were found to limit translation of preclinical safety and efficacy studies because they could often not accurately mimic human conditions.[67] Other issues described were, although not exhaustive, availability of less comprehensive clinical data due to orphan and novel indications, newly encountered safety concerns and irreversibility

of therapies.[19,67,68] Weighing of benefits and risks by regulators was extensively and discussed by stakeholders and described as a challenging endeavour by regulators.[67]

Market access of gene and cell-based therapies

To achieve patient access and allow for uptake in healthcare services medicinal products and services need to ensure reimbursement from payers. GCTs are facing several difficulties with respect to reimbursement from payers. In contrast to the centralized market authorization procedure, reimbursement decisions in the EU are mandated on a national level.[69] This makes HTA-bodies in Europe national gatekeepers for GCTs to achieve market access. However, Glybera®, the first approved gene therapy in Europe, was withdrawn from the market in 2017, after only one patient had been treated.[70] Reason given was that the developers were unsuccessful in achieving reimbursement. Following Glybera®, three more GCTs were withdrawn from the market for commercial reasons: Provenge® (2015), Zalmoxis® (2016) and ChrondroCelect® (2017).[71] The MA of MACI® was

- **Cell Therapy Medicinal Products** (CTMPs): A biological product which contains cells or tissue which has been subject to substantial manipulation which results in alteration of the biological characteristics, physiological functions, or structural properties relevant for the intended clinical use. The cells or tissue may not be used for the same essential function in the donor and recipient. The product presents properties or is used in or administered to humans and is intended to treat, prevent or diagnose a disease through the pharmacological, immunological or metabolic action of its cells or tissues.[53]

- **Tissue Engineered Products** (TEPs): A products which contain or consist of engineered cells or tissues, and are presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.[53,60]

- **Gene Therapy Medicinal Products** (GTMPs): A gene therapy contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence. The therapeutic, prophylactic, or diagnostic effects of the therapy relate directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. A gene therapy does not include vaccines against infectious disease.[53,60]

- **Combined-ATMPs**: Product must have incorporated one or more medical devices[61] within the meaning or one or more active implantable medical devices[62], and its cellular or tissue part must contain viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.[53,60]

Box 1. Definition of advanced therapy medicinal products (ATMPs) as described in European regulation 1394/2007.

suspended due to closing of the EU manufacturing site (2018).[72] With US prices reported to range between US $18,950 and $1,206,751 per single or short-term treatment, GCTs are expected to routinely be subjected to formal health technology assessment (HTA).[16,73,74] Additionally, these prices do not include procurement, purchase or management costs which significantly increase overall treatment cost.[74]

In addition to the high prices, HTA-bodies and payers have expressed concerns about the timing of payment.[75] The curative potential for chronic indications asks for an upfront payment of costs otherwise spread over multiple years. This may cause high upfront budget impact, even when cost-effectiveness over time is demonstrated.[56] In addition, the curative value claims of GCTs are accompanied by several uncertainties. Sustainability of effect has been mentioned, as the claimed effectiveness of marketed GCTs vastly extends the time horizon of the clinical trials supporting HTA-dossiers.[76,77] Although extrapolation of costs and effects are quite common in economic evaluations, little evidence and experience is available to substantiate treatment durability assumptions.[78] Even when biological plausibility suggests single or short-term treatment may provide (life-)long effect, evidence to support these claims may not or sparsely be available at the time of decision.[56] Additionally, it is reported that submitted GCT market authorisation applications are based on less evidence, such as Phase I or I/II clinical trials, with small patient sample size and limited follow-up.[79]

Thesis objective

Gene and cell-Based therapies are highly innovative therapies and hold great promise in the treatment and potential cure of high burden and chronic diseases. However, these products experience various development, regulatory and market access challenges towards becoming effective and safe treatments available to patients.

The aim of this thesis is therefore to assess gene and cell-based therapy development challenges and how these challenges play a role in marketing authorization and market access, as well as develop tools and methods to mitigate market access challenges for developers.

Thesis structure

In **Chapter 2** translational challenges of GCTs are examined from the developer perspective. First, we aim to explore the commercial GCT development landscape in the European Union in **Chapter 2.1**. We created a comprehensive overview of commercial developers of GCTs across Europe in 2017. Among these developers, challenges they experienced in the development of their products were queried in a survey. These challenges were categorised and described and scored in descriptive analysis. Additionally, an analysis was conducted in which differences in challenges were assessed between product types (gene and cell-based therapies) and company type.

To facilitate small-scale and academic CBT development, **Chapter 2.2** describes design and validation of a costing framework and methodology. This chapter provides a step-by-step guidance to estimate CBT manufacturing costs and includes a costing tool to allow direct adoption. In

literature the technical and scientific aspects of manufacturing design are shared, yet inclusion of cost components in these best-practices lags. **Chapter 2.3** explores feasibility of the costing framework and methodology to be applied in manufacturing development. Insight in these costs can help demonstrate required investments towards grant providers or payers. Additionally, **Chapter 2.3** may demonstrate wider applicability of the developed framework and methodology to accommodate cost-conscious decisions earlier on in development.

In the third chapter we examine how regulators and health technology assessment (HTA) bodies are involved in the assessment of GCTs. In **Chapter 3.1** we examine claims with regard to an assumed low number of regulatory marketing authorizations of GCTs. This is done by assessing and quantifying clinical and regulatory success of GCTs and by comparing this to past biomedical innovations. Next, in **Chapter 3.2** the key considerations formulated by three HTA-bodies (Scotland, the Netherlands and England) are examined using a multi-domain framework: the EUnetHTA core model®. Via identification of the key considerations in the HTA of GCTs the chapter aims to increase the understanding of difficulties and uncertainties experienced by HTA bodies when assessing GCTs and how these may be addressed.

Chapter 4 of this thesis examines cost-effectiveness, value, and affordability of gene therapies. Economic evaluations are of increasing importance when HTA-bodies evaluate GCTs for reimbursement. Previous studies question whether accepted methods are applicable to the evaluation of gene therapies. In **Chapter 4.1** a systematic literature review is conducted in which recent methodological considerations regarding the economic evaluations of gene therapies are identified. Additionally, a second review was conducted in this chapter of published economic evaluations of gene therapies to assess if recent methodological considerations were applied in literature and to explore their impact. **Chapter 4.2** aims to apply the learnings from **Chapter 4.1** in a cost-effectiveness analysis for a gene therapy that is in development for severe uncomplicated Haemophilia A. In this chapter, we also assess value-based pricing of the gene therapy and effect of payment models on budget impact and uncertainty.

References

1. Chial H. DNA sequencing technologies key to the Human Genome Project. *Nat Educ.* 2008;1(1):219.
2. Charpentier E, Doudna JA. Rewriting a genome. *Nature.* 2013;495(7439):50-51. doi:10.1038/495050a
3. Ran FA, Hsu PD, Wright J, Agarwala V, Scott DA, Zhang F. Genome engineering using the CRISPR-Cas9 system. *Nat Protoc.* 2013;8(11):2281-2308. doi:10.1038/nprot.2013.143
4. Cohen J. CRISPR, the revolutionary genetic 'scissors,' honored by Chemistry Nobel. Science. doi:10.1126/science.abf0540
5. Bak RO, Gomez-Ospina N, Porteus MH. Gene Editing on Center Stage. *Trends Genet.* 2018;34(8):600-611. doi:10.1016/j.tig.2018.05.004
6. Nobel Media AB. The Nobel Prize in Chemistry 2020. NobelPrize.org.
7. Nerem RM. Regenerative medicine: The emergence of an industry. *J R Soc Interface.* 2010;7(S6):S771-s775. doi:10.1098/rsif.2010.0348.focus
8. Mao AS, Mooney DJ. Regenerative medicine: Current therapies and future directions. *Proc Natl Acad Sci U S A.* 2015;112(47):14452-14459. doi:10.1073/pnas.1508520112
9. Gurdon JB. The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. *J Embryol Exp Morphol.* 1962;10:622-640.
10. Takahashi K, Yamanaka S. Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell.* 2006;126(4):663-676. doi:10.1016/j.cell.2006.07.024
11. Hollander AP. Cell therapies and regenerative medicine - the dawn of a new age or more hype than hope? *Clin Transl Med.* 2012;1(1):12. doi:10.1186/2001-1326-1-12
12. Faulkner E, Holtorf AP, Walton S, et al. Being Precise About Precision Medicine: What Should Value Frameworks Incorporate to Address Precision Medicine? A Report of the Personalized Precision Medicine Special Interest Group. *Value Heal.* 2020;23(5):529-539. doi:10.1016/j.jval.2019.11.010
13. Sahin U, Türeci Ö. Personalized vaccines for cancer immunotherapy. *Science.* 2018;359(6382):1355-1360. doi:10.1126/science.aar7112
14. Gardner J, Webster A. The social management of biomedical novelty: Facilitating translation in regenerative medicine. *Soc Sci Med.* 2016;156:90-97. doi:10.1016/j.socscimed.2016.03.025
15. Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical development of advanced therapy medicinal products in Europe: Evidence that regulators must be proactive. *Mol Ther.* 2012;20(3):479-482. doi:10.1038/mt.2012.13
16. Eder C, Wild C. Technology forecast : advanced therapies in late clinical research , EMA approval or clinical application via hospital exemption. *J Mark Access Heal Policy.* 2019;7(1). doi:10.1080/20016689.2019.1600939
17. Eichler H, Pignatti F, Schwarzer-Daum B, et al. Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth. *Clin Pharmacol Ther.* November 2020:cpt.2083. doi:10.1002/cpt.2083
18. Hacein-Bey-Abina S, Le Deist F, Carlier F, et al. Sustained Correction of X-Linked Severe Combined Immunodeficiency by ex Vivo Gene Therapy. *N Engl J Med.* 2002;346(16):1185-1193. doi:10.1056/NEJMoa012616

19. Williams DA, Baum C. Medicine. Gene therapy--new challenges ahead. *Science*. 2003;302(5644):400-401. doi:10.1126/science.1091258

20. Williams DA, Thrasher AJ. Concise Review: Lessons Learned From Clinical Trials of Gene Therapy in Monogenic Immunodeficiency Diseases. *Stem Cells Transl Med*. 2014;3(5):636-642. doi:10.5966/sctm.2013-0206

21. Howe SJ, Mansour MR, Schwarzwaelder K, et al. Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients. *J Clin Invest*. 2008;118(9):3143-3150. doi:10.1172/JCI35798

22. Nightingale P, Martin P. The myth of the biotech revolution. *Trends Biotechnol*. 2004;22(11):564-569. doi:10.1016/j.tibtech.2004.09.010

23. Kubinyi H. Drug research: myths, hype and reality. *Nat Rev Drug Discov*. 2003;2(8):665-668. doi:10.1038/nrd1156

24. Bluestone M. Hope and Hype in Biotechnology. *Nat Biotechnol*. 1992;10(9):946-946. doi:10.1038/nbt0992-946a

25. Hopkins MM, Martin PA, Nightingale P, Kraft A, Mahdi S. The myth of the biotech revolution: An assessment of technological, clinical and organisational change. Taylor T, ed. *Res Policy*. 2007;36(4):566-589. doi:10.1016/j.respol.2007.02.013

26. Shire SJ. Formulation and manufacturability of biologics. *Curr Opin Biotechnol*. 2009;20(6):708-714. doi:10.1016/j.copbio.2009.10.006

27. Shire SJ, Shahrokh Z, Liu J. Challenges in the development of high protein concentration formulations. *J Pharm Sci*. 2004;93(6):1390-1402. doi:10.1002/jps.20079

28. Zwart-van Rijkdom JEF. Assessment and diffusion of biotechnology drug. 2002. https://dspace.library.uu.nl/handle/1874/331.

29. Blankenship K. The top 20 drugs by global sales in 2019. Fierce Pharma. https://www.fiercepharma.com/special-report/top-20-drugs-by-global-sales-2019. Published 2020. Accessed October 5, 2020.

30. Shakeel S, Hassali MA, Rehman H, Rehman AU, Muneswarao J. Knowledge, Attitude, and Practice Towards Biosimilars and Interchangeable Products: A Prescriptive Insight by the Pharmacists. *Int J Gen Med*. 2020;13:1075-1082. doi:10.2147/IJGM.S266545

31. Sood A, Tellis GJ. Technological evolution and radical innovation. *J Mark*. 2005;69(3):152-168. doi:10.1509/jmkg.69.3.152.66361

32. Bayon Y, Vertès AA, Ronfard V, et al. Turning Regenerative Medicine Breakthrough Ideas and Innovations into Commercial Products. *Tissue Eng - Part B Rev*. 2015;21(6):560-571. doi:10.1089/ten.teb.2015.0068

33. Rake B. Determinants of pharmaceutical innovation: the role of technological opportunities revisited. *J Evol Econ*. 2017;27(4):691-727. doi:10.1007/s00191-017-0524-6

34. Petrova E. Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development. In: Ding M, ed. *Innovation and Marketing in the Pharmaceutical Industry*. 1stEdition ed. New York, NY: Springer-Verlag New York Inc.; 2016:768.

35. Turner M, Leslie S, Martin NG, et al. Toward the development of a global induced pluripotent stem cell library. *Cell Stem Cell*. 2013;13(4):382-384. doi:10.1016/j.stem.2013.08.003

36. Butler D. Crossing the valley of death. *Nature*. 2008;453(12):840-842. doi:10.1115/1.2017-dec-1

37. Gardner J, Faulkner A, Mahalatchimy A, Webster A. Are there specific translational challenges in regenerative medicine? Lessons from other fields. *Regen Med*. 2015;10(7):885-895. doi:10.2217/rme.15.50

38. Coppens DGM, de Wilde S, Guchelaar HJH, et al. A decade of marketing approval of gene and cell-based therapies in the United States, European Union and Japan: An evaluation of regulatory decision-making. *Cytotherapy*. 2018;20(6):769-779. doi:10.1016/j.jcyt.2018.03.038

39. Schutgens R. Gene Therapy in Hemophilia: From Hype to Hope. *HemaSphere*. 2018;2(2):e37. doi:10.1097/HS9.0000000000000037

40. Braude P, Minger SL, Warwick RM. Stem cell therapy: hope or hype? *BMJ*. 2005;330(7501):1159-1160. doi:10.1136/bmj.330.7501.1159

41. Goldman M. The Innovative Medicines Initiative: A European Response to the Innovation Challenge. *Clin Pharmacol Ther*. 2012;91(3):418-425. doi:10.1038/clpt.2011.321

42. Kayser V, Nehrke B, Zubovic D. *Data Science as an Innovation Challenge: From Big Data to Value Proposition*. Vol 8.; 2018.

43. Weggemans MM, van der Schaaf M, Kluijtmans M, Hafler JP, Rosenblum ND, Prakken BJ. Preventing translational scientists from extinction: The long-term impact of a personalized training program in translational medicine on the careers of translational scientists. *Front Med*. 2018;5(NOV):1-10. doi:10.3389/fmed.2018.00298

44. Barr S, Baker T, Markham S, Kingon A. Bridging the valley of death: Lessons learned from 14 years of commercialization of technology education. *Acad Manag Learn Educ*. 2009;8(3):370-388. doi:10.5465/AMLE.2009.44287937

45. Coppens DGM. Regulating gene and cell-based therapies as medicinal products. 2020. https://dspace.library.uu.nl/handle/1874/390654.

46. Morrow D, Ussi A, Migliaccio G. Addressing Pressing Needs in the Development of Advanced Therapies. *Front Bioeng Biotechnol*. 2017;5(9):1-6. doi:10.3389/fbioe.2017.00055

47. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. *Cell Stem Cell*. 2016;19(3):293-297. doi:10.1016/j.stem.2016.08.012

48. Cell and Gene Therapy Catapult. *UK Cell and Gene Therapy Skills Demand Report 2019*. London, UK; 2019. https://ct.catapult.org.uk/sites/default/files/publication/Catapult_01_UK Skills Demand Report 2019_published_v2.pdf.

49. de Wilde S, Guchelaar H-J, Zandvliet ML, Meij P. Clinical development of gene- and cell-based therapies: overview of the European landscape. *Mol Ther - Methods Clin Dev*. 2016;3(July):16073. doi:10.1038/mtm.2016.73

50. de Wilde S, Guchelaar HJ, Herberts C, et al. Development of cell therapy medicinal products by academic institutes. *Drug Discov Today*. 2016;21(8):1206-1212. doi:10.1016/j.drudis.2016.04.016

51. Catapult Cell and Gene Therapy. *Cell and Gene Therapy GMP Manufacturing in the UK: Capability and Capacity Analysis October 2017*. London, UK; 2017.

52. Clinical Trials Arena. Small players, big drugs – pharmaceutical SMEs take the innovative edge. https://www.clinicaltrialsarena.com/. https://www.clinicaltrialsarena.com/analysis/featuredrug-pharmaceutical-sme-big-pharma-innovation/. Published April 2012. Accessed January 29, 2021.

53. The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council. *Off J Eur Union*. 2007;324((EC)1394/2007):121-138. http://data.europa.eu/eli/reg/2007/1397/oj.

54. Abou-El-Enein M, Römhild A, Kaiser D, et al. Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: A novel tailored model for optimizing performance and estimating costs. *Cytotherapy*. 2013;15(3):362-383. doi:10.1016/j.jcyt.2012.09.006

55. Turner ML. ATMPs are at a starting point. *Regul Sci*. 2019:Edition 7. https://www.regulatoryscience.nl/editions/2019/07/interview-marc-turner.

56. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. *J Mark Access Heal Policy*. 2015;3(1):29321. doi:10.3402/jmahp.v3.29321

57. Hanna E, Tavella F, Rémuzat C, Auquier P, Toumi M. Market Access of Atmps: Overview and Expected Challenges. *Value Heal*. 2015;18(7):A518-A519. doi:10.1016/j.jval.2015.09.1580

58. Committee of Advanced Therapies. *Paper on Classification of Advanced Therapy Medicinal Products Table of Contents*. Vol 44.; 2015. doi:EMA/CAT/600280/2010

59. Coppens DGM, Hoekman J, De Bruin ML, et al. Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries. *Cytotherapy*. 2020;22(10):592-600. doi:10.1016/j.jcyt.2020.04.092

60. European Commission. Annex 1 to Directive 2001/83/EC on the Cummunity code relating to medicinal products for human use. *Off J Eur Communities*. 2000;L 269(September 2000):1-188. doi:2004R0726 - v.7 of 05.06.2013

61. European Parliament and of the Council. Council Directive 93/42/EEC. *Off J Eur Union*. 2007;(June 1993):1-60. doi:2004R0726 - v.7 of 05.06.2013

62. The European Parliament and the Council of the European Union. Council directive 90/385/EEC. *Off J Eur Communities*. 1990;(L):17-36.

63. Zech NH, Preisegger K-H, Hollands P. Stem cell therapeutics - reality versus hype and hope. *J Assist Reprod Genet*. 2011;28(4):287-290. doi:10.1007/s10815-010-9520-6

64. Rico-Sánchez L, Garzón I, González-Andrades M, et al. Successful development and clinical translation of a novel anterior lamellar artificial cornea. *J Tissue Eng Regen Med*. 2019;13(12):2142-2154. doi:10.1002/term.2951

65. Elsanhoury A, Sanzenbacher R, Reinke P, Abou-El-Enein M. Accelerating Patients' Access to Advanced Therapies in the EU. *Mol Ther - Methods Clin Dev*. 2017;7(December):15-19. doi:10.1016/j.omtm.2017.08.005

66. Iglesias-Lopez C, Obach M, Vallano A, Agustí A, Montané J. Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States. *Crit Rev Toxicol*. 2019;49(7):580-596. doi:10.1080/10408444.2019.1689380

67. Schneider CK, Celis P, Salmikangas P, et al. Challenges with advanced therapy medicinal products and how to meet them. *Nat Rev Drug Discov*. 2010;9(3):195-201. doi:10.1038/nrd3052

68. Celis P, Schüßler-lenz M. Advanced Therapy Medicinal Products : How to Bring Cell-Based Medicinal Products Successfully to the Market – Report from the CAT-DGTI-GSCN Workshop at the DGTI Annual Meeting 2014. 2015:194-199. doi:10.1159/000382107

69. Kleijnen S, George E, Goulden S, et al. Relative effectiveness assessment of pharmaceuticals: Similarities and differences in 29 jurisdictions. *Value Heal.* 2012;15(6):954-960. doi:10.1016/j.jval.2012.04.010

70. Yu TTL, Gupta P, Ronfard V, Vertès AA, Bayon Y. Recent Progress in European Advanced Therapy Medicinal Products and Beyond. *Front Bioeng Biotechnol.* 2018;6(September):1-8. doi:10.3389/fbioe.2018.00130

71. European Medicines Agency. Provenge Withdrawal of the marketing authorisation in the European Union. EMA/303072/2015. http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2015/05/WC500186950.pdf. Published 2015. Accessed December 22, 2020.

72. Hanna E, Rémuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. *J Mark Access Heal Policy.* 2016;4(1):31036. doi:10.3402/jmahp.v4.31036

73. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: An exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess (Rockv).* 2017;21(7):1-204. doi:10.3310/hta21070

74. Seoane-Vazquez E, Shukla V, Rodriguez-Monguio R, Seoane-Vazquez E, Shukla V, Rodriguez-Monguio R. Innovation and competition in advanced therapy medicinal products. *{EMBO} Mol Med.* 2019;11(3):e9992. doi:10.15252/emmm.201809992

75. Hollier-Hann G, Cork D, Ralston S, Curry A. Health Technology Assessment of Gene Therapies for Inherited Genetic Disorders in the US and Europe. *Value Heal.* 2018;21(2012):S210. doi:10.1016/j.jval.2018.04.1421

76. NICE, The National Institute for Health and Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166] | Guidance and guidelines | NICE. *NICE Guid.* 2019;(March):1-24. https://www.nice.org.uk/guidance/indevelopment/gid-ta10269.

77. Carr DR, Bradshaw SE. Gene therapies: The challenge of super-high-cost treatments and how to pay for them. *Regen Med.* 2016;11(4):381-393. doi:10.2217/rme-2016-0010

78. Coyle D, Durand-Zaleski I, Farrington J, et al. HTA methodology and value frameworks for evaluation and policy making for cell and gene therapies. *Eur J Heal Econ.* 2020;2:1421-1437. doi:10.1007/s10198-020-01212-w

79. Wilde S De, Coppens DGM, Hoekman J, et al. EU decision-making for marketing authorization of advanced therapy medicinal products: a case study. *Drug Discov Today.* 2018;23(7):1328-1333. doi:10.1016/j.drudis.2018.03.008

2

Challenges in the development of gene and cell-based therapies

2.1

Challenges in the development of gene and cell-based therapies among companies in Europe

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Abstract

Gene and cell-based therapies, hereafter called Advanced Therapy Medicinal Products (ATMPs), hold promise as treatments for previously untreatable and high-burden diseases. Expectations are high and active company pipelines are observed, yet only 10 market authorizations were approved in Europe. Our aim was to identify challenges experienced in European ATMP clinical development by companies.

A survey-based cohort study was conducted among commercial ATMP developers. Respondents shared challenges experienced during various development phases, as well as developer and product characteristics. Descriptions of challenges were grouped in domains (clinical, financial, human resource management, regulatory, scientific, technical, other) and further categorized using thematic content analysis.

A descriptive analysis was performed. We invited 271 commercial ATMP developers, of which 68 responded providing 243 challenges. Of products in development, 72% were in early clinical development and 40% were gene therapies. Most developers were small- or medium-sized enterprises (65%). The most often mentioned challenges were related to country-specific requirements (16%), manufacturing (15%), and clinical trial design (8%).

The European ATMP field is still in its early stages, and developers experience challenges on many levels. Challenges are multifactorial and a mix of ATMP-specific and generic development aspects, such as new and orphan indications, novel technologies, and inexperience, adding complexity to development efforts.

Introduction

Advancements in biomedical sciences are leading to new treatment options for disease with high unmet medical need and create possibilities to improve the quality of life in aging populations. Gene and cell-based therapies (GCTs) are medicines derived through these advancements and include genetic therapy medicinal products (GTMPs), cell-based therapy medicinal products (CTMPs), tissue-engineered products (TEPs), and products integrally combined with medical devices, in Europe known as advanced therapy medicinal products (ATMPs).[1] Recent reports show high development activity in the ATMP field that does not seem to match with the limited number of ATMPs currently available on the European market.[2]

Even though over 500 clinical trials were performed with ATMPs between 2009 and 2017, this led to only 19 market authorization applications to the European Medicines Agency (EMA).[2] Ten ATMPs received centralized marketing authorization (MA). Of these, three companies later withdrew the license and one discontinued product marketing, all for commercial reasons. Thorough understanding of stakeholder challenges experienced during development is needed to properly value the potential of ATMPs.

In the literature, no comprehensive overview of the challenges encountered by European-wide commercial ATMP developers is available. Given ATMP development occurs to a greater extent in the public domain compared with more traditional pharmaceutical development, the available literature of ATMPs and their development challenges mostly describes individual issues in academic and hospital settings.[3]

Difficulties described are complex manufacturing processes,[4–7] implementation of Good Manufacturing Practices (GMP) specifically for cell and gene products,[8–10] complex trial designs,[4,11] and heterogeneous national procedures at member state level.[12] The few reports on development by companies describe manufacturing difficulties, uncertain reimbursement perspectives, and the use of hospital exemption (HE).[13–15]

Plagnol et al. are the first to comprehensively describe industry commercialization barriers collected via interviews specifically for regenerative medicines in the United Kingdom.[16] Their study suggests that commercial ATMP developers encounter both ATMP-specific challenges and more general barriers similar to other emerging industries. Additionally, ATMPs also include a diverse set of technologies developed by a heterogeneous group of developers.[3,17] Challenges may be linked to certain product categories or developers. For example, biotech small- and medium-sized enterprises (SMEs) are known to have more difficulties in acquiring funds and addressing regulatory requirements compared with larger companies.[18] Also, manufacturers of biologicals encounter challenges specific for protein manufacturing and formulation.[19–21]

The aim of this study was to assess the challenges experienced by companies developing ATMPs in Europe. Experiences were collected via a survey distributed among identified ATMP developers active in Europe. The study contributes to a better understanding of the current European ATMP field and identifies issues impacting product development and patient access.

Materials and methods

We established a cohort of EU ATMP commercial developers. Identified ATMP commercial developers were invited to participate in a survey to systematically collect experienced challenges during clinical development, from first-in-human trials onward, as well as developer and product characteristics.

Cohort construction

We searched public-accessible databases for company names, EMA SME registry, EUDRACT, Clinicaltrials.gov (sponsor and/or collaborators), and Web of Science (funding agencies), using a comprehensive search query (Table S1). The search was limited to the years 2005–2015. Next, we collected member lists from the largest European (bio)pharmaceutical industry associations. We also searched speaker and attendee affiliations of EMA's Committee for Advanced Therapies (CAT) reports, ATMP-related conferences, EMA and Innovative Medicines Initiative (IMI) stakeholder meetings, and EMA and IMI public consultations from 2009 to 2016 (Table S2). Lastly, we invited ATMP companies to participate in our research by circulating an open call (Figure S1) on biotechnology associations and society websites in March 2017, as well as announcing the invitation in direct member communications.

Developers were added to the cohort if they met the following inclusion criteria: (1) involved in ATMP (GTMP, CTMP, TEP, or combined ATMP) development as defined by ATMP Regulation (EC) 1394/2007 from January 2005 onward, (2) developer is still active in January 2017, (3) develops ATMPs for human use, (4) is established in or developing for at least 1 of the 28 EU member states, (5) is a commercial entity, and (6) had ATMPs in development of which at least one was in clinical development.

Data collection

Public data (company websites, annual reports, literature, conference presentations) were used to collect basic cohort characteristics for the full cohort of companies, including company size, geographic location, and types of ATMP products under development. ATMP types were grouped into three categories: GTMP, cell-based medicinal products (combining CTMPs and TEPs), and combined ATMPs. After cohort construction, we collected contact details of individual employees via public association member lists, conference attendance lists, LinkedIn, and Google search. We targeted senior management officials linked to development in the organization. In large companies we targeted senior managers, department heads, or directors, whereas in SMEs we targeted (vice) presidents, CEOs (chief executive officers), CFOs (chief financial officers), or CMOs (chief marketing officers). Via the survey, detailed developer and product characteristics were collected, as well as challenge descriptions.

Survey design

The survey consisted of two parts. In the first part, developer and product characteristics were collected using multiple-choice questions. This part contained questions on developer location, number of employees, founding year, and expertise. It also included, for a maximum of three products, ATMP product-specific questions such as classification, intended indication, target

population, development stage and time, regulatory pathways used, and utilized regulatory and/or health technology assessment (HTA) body services. In the second part, we asked for experienced development challenges using open text boxes. Each respondent was asked to describe the two biggest challenges experienced per product and per development stage (early clinical development [phases I–II], late clinical development [phase III], regulatory approval, and product commercialization). The introduction to survey part two is included in Figure S2. Respondents were asked to classify challenges in pre-specified domains (clinical, financial, human resource management [HRM], regulatory, scientific, technical, and other challenges). Domain definitions are listed in Figure S2. Prior to survey distribution, content validity was checked by the European Federation of Pharmaceutical Industries and Associations/European Biopharmaceutical Enterprises (EFPIA/EBE) Advanced Therapies joint working group and via a face-to-face interview with a two-person panel consisting of a small CTMP developer and large GTMP developer. The working group and panel provided feedback about flow, question relevance, and missing topics. In March 2017, an e-mail invitation was subsequently distributed among the cohort via a SurveyMonkey link (https://www.surveymonkey.com/; Palo Alto, CA, USA). The invitation described study objectives, survey contents, and how the data would be handled to maintain the anonymity of respondents. The survey link could be forwarded internally in case multiple departments worked on product development. Recipients were reminded every 2 weeks via e-mail and finally once by telephone before the end of data collection in June 2017.

Data analysis

Characteristics and challenges were exported from the online survey environment into Microsoft Excel 2016. Missing developer and product characteristics of respondents, due to incomplete responses, were collected through a secondary public domain data search. All challenges (coded and non-coded) were checked for correct classification, according to definitions set in Figure S2 by two Utrecht University researchers (R.M.T.t.H. and A.M.H.). A challenge was assumed to fit only one domain. In ambiguous cases, challenges were added to domains most closely matching the underlying cause. Classification discrepancies were discussed until consensus.

Within each domain, challenges were further categorized into themes, using thematic content analysis methodology: after detailed data familiarization, emerging trends were labelled, reviewed, and eventually defined into mutually exclusive themes.[22]

The following themes were created within the domains: clinical (trial execution, patient recruitment, efficacy, and safety), financial (funding development, reimbursement perspectives), HRM (human resources, skilled resources), regulatory (process toward filing dossier, dossier compilation), scientific (trial design, preclinical translation, knowledge gap), technical (manufacturing, quality standards, starting materials, supply chain, admission), and others.

Results

The search for the European Union (EU) ATMP company cohort yielded 13,392 company names, which were checked for duplicates (n = 5,748). Thereafter we excluded non-commercial developers (n = 6,841), those not located in or developing for the EU (n = 208), non-ATMP developers (n = 98), non-developers (n = 14), and several developers for other reasons (n = 212), such as only non-human products, products in preclinical stages, bankrupt, or merged at time of data collection (January 1, 2017). This resulted in a cohort of 271 developers. In total, 38% (n = 101) responded to our survey request. Respondents returned 56 complete and 12 incomplete surveys resulting in 68 developer inputs and a corresponding response rate of 25%. The 33 remaining respondents indicated no interest in participation; reasons given were time constraints or unwillingness to share information. Table 1 displays characteristics of respondents compared with non-respondents. Table 1 shows respondent characteristics did not differ meaningfully from the non-responders, indicating that the responses are representative for the cohort. Detailed product information is included in Table 2. These characteristics were collected in part one of the survey.

Table 1. Respondent and non-respondent characteristics.

	Non-Respondents n (%)	**Respondents n (%)**
Response Rate	203	68
Respondent (Complete)	-	56 (55)
Respondent (Incomplete)	-	12 (12)
Not Interested Respondent	-	33 (32)
Company Size		
SME	149 (73)	44 (65)
Large company	54 (27)	24 (35)
Geography		
United Kingdom	36 (18)	16 (24)
Germany	33 (16)	11 (16)
United States	28 (14)	5 (7)
France	23 (11)	7 (10)
The Netherlands	16 (8)	8 (12)
Other (Europe)	64 (32)	19 (30)
Other (Rest of the World)	3 (1)	2 (3)
ATMP Type (total)		
GTMPs	80 (40)	31 (46)
Cell-Based Medicinal Products	121 (59)	36 (53)
Combined ATMP	2 (1)	1 (1)
Number of ATMPs in Development		
One	89 (44)	33 (49)
> One	114 (56)	35 (51)

GTMP: Gene Therapy Medicinal Product, CTMP: Cell Therapy Medicinal Product, TEP: Tissue Engineered Product, SME: Small Medium-Sized Enterprise (1-249 employees)[23]

Table 2. Survey respondent product characteristics

	Respondents n (%)
Product Development Stage	
Early Clinical (Phase I-II)	91 (72)
Late Clinical (Phase III)	16 (13)
Regulatory Approval	7 (6)
Commercialization	12 (10)
Intended Therapeutic Area	
Oncology	36 (29)
Ophthalmology	19 (15)
Hematology	18 (14)
Orthopedics & Skeletal	12 (10)
Immunology	9 (7)
Gastroenterology	8 (6)
Cardiovascular	8 (6)
Neurology	5 (4)
Dermatology	4 (3)
Other	7 (6)
Pediatric Indication	
Yes (< 18 years)	51 (40)
No (≥ 18 years)	75 (60)
Orphan Indication	
Yes	69 (55)
No	57 (45)

The survey yielded 243 challenge descriptions. After classification, the top three challenge domains were regulatory (34%), technical (30%), and scientific (10%). After further classification of the domains into themes, the top three themes were country-specific requirements (16%), manufacturing (15%), and trial design (8%). A detailed overview of challenge domains, themes, and frequencies is displayed in Table 3. In Figures 1A–1G, themes are presented per subgroup. The results will hereafter be reported per topic and placed into context with literature where possible.

European ATMP-field composition

Of companies that were active on the European market in January 2017, our survey shows 65% are small- and medium-sized enterprises (SMEs) (Table 1), which is higher compared with the small-molecule and biotechnology industry.[23]

Half of the respondents are located in Western Europe—United Kingdom (24%), Germany (16%), and France (10%)—which matches previous reports.[16] Companies primarily based in the United States, but also developing in and for the EU market, accounted for 7%. Most companies developed cell-based medicinal products (53%), followed by GTMPs (46%) and combined ATMPs (1%). Of

respondents, 35 (51%) reported developing more than one ATMP, and 10 developers worked on different ATMP types (e.g., GTMP, CTMP, TEP, or combined ATMP) simultaneously. Together, the 68 respondents were developing 126 ATMPs (Table 2). Acknowledging pharmaceutical development

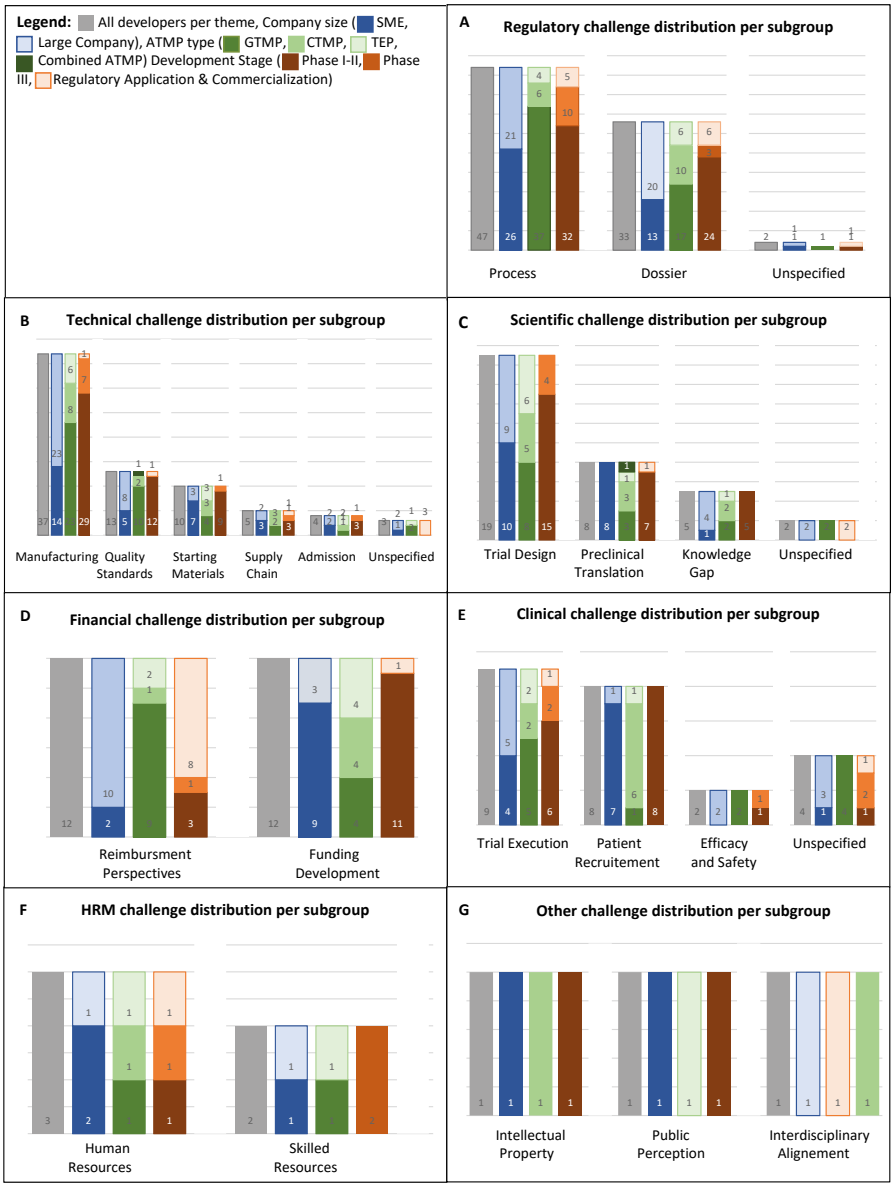

Figure 1A-G. Developer reported challenge domain and themes displayed per characteristic (company size, ATMP type and development stage).

Table 3. Developer reported challenges in European ATMP development Percentages are rounded off and displayed as fraction of total challenges (n=243). Challenge domains are bold. Only regulatory themes are split up in subthemes (italic).

	n (%)		n (%)
Regulatory Challenges	**82 (34)**	**Scientific Challenges**	**34 (14)**
Regulatory Process	47 (19)	Trial Design	19 (8)
Country specific requirements	40 (16)	Preclinical Translation	8 (3)
Submission Pathways	4 (2)	Knowledge Gap	5 (2)
Pre-submission interaction	2 (0)	Unspecified	2 (0)
Product Logistics	1 (0)	**Financial Challenges**	**24 (10)**
Regulatory Dossier	33 (14)	Reimbursement Perspectives	12 (5)
Content Uncertainty	16 (7)	Funding Development	12 (5)
Meeting Information Demand	9 (4)	**Clinical Challenges**	**23 (9)**
Information Relevance	5 (2)	Trial Execution	9 (4)
Post Approval Commitment	3 (1)	Patient Recruitment	8 (3)
Unspecified	2 (0)	Efficacy and Safety	2 (9)
Technical Challenges	**72 (30)**	Unspecified	4 (17)
Manufacturing	37 (15)	**HRM Challenges**	**5 (2)**
Quality Standards	13 (5)	Human Resource	3 (1)
Starting Materials	10 (4)	Skilled Resource	2 (0)
Supply Chain	5 (2)	**Other Challenges**	**3 (1)**
Product Admission	4 (2)	Intellectual Property	1 (0)
Unspecified	3 (1)	Public Perception	1 (0)
		Interdisciplinary Alignment	1 (0)

follows a funnel shape, Table 2 shows a higher (72%) percentage of respondent products in early clinical development (phases I–II) compared with non-advanced therapy products.[24]

Also, a high representation of orphan indications (55%) was reported. In line with previous findings, the top three indications were oncology (29%), ophthalmology (15%), and haematology (14%).[16] A new finding was the reported high number of paediatric indications (40%).

Multi-level regulations

Medicinal product regulations in Europe cover a variety of overlaying jurisdictions and authorities. To group challenges in the regulatory domain, we distinguished between two main themes: the process of working toward a European centralized marketing authorization, which accounted for 57% (n = 47) of the challenges, and composing regulatory dossiers, which are needed for authority approval (40%, n = 33). These themes were thereafter further divided into sub-themes. See Table 3 and Figure 1A for detailed theme and characteristics distribution.

On a European level, few direct references were made to EMA procedures such as pre-submission interactions and scientific advice. Companies mentioned more regulatory interactions with EMA

compared with non-ATMP product authorization to understand product nature, clinical trial endpoints, and technical specifications. Also, at day 120 of the MA process, a longer list of questions was mentioned. Meeting the regulators information requests was found to be difficult (n = 9, 11%). The data requested often led to more research and associated costs. The regulator interactions were said to be more frequent compared with non-ATMP development but did help in resolving described challenges. No specific regulatory pathways, such as PRIority MEdicines (PRIME) or protocol assistance in case of orphan drugs, were mentioned. European-level regulatory challenges were mentioned only by companies already involved in ATMP development prior to enforcement of Regulation (European Commission [EC]) 1394/2007.

Further, the majority of regulatory challenges were experienced on a member state level. Meeting country-specific requirements (n = 40, 49%) was the most occurring theme in our survey. GTMP developers reported proportionally more regulatory challenges. This was mainly driven by issues with the genetically modified organism (GMO) legislation (n = 27, 33%), affecting GTMPs the most. The GMO legislation was originally intended for the agri-food sector[25], established by the European Commission but interpreted and implemented on member state level. This local interpretation leads to a variety of national, or even local, responsible governing bodies and procedures. Developers experienced compliance to the GMO legislation as resource intensive and confusing, leading to duplicate applications and inspections resulting in time delays and extra resources without a perception of adding apparent patient or product benefit. For cell-based products, specific challenges with regard to customs and transporting of human tissue across member states were encountered (n = 9, 4%).

Multiple descriptions were given of varying levels of authority's ATMP familiarity and conflicting scientific advice between national competent authorities (NCAs). This was attributed to a lack of ATMP-specific knowledge and inexperience with this specific medicinal product group. Some developers indicated selecting trial locations based on local legislation interpretations and NCA experience with ATMPs. To address member state variance, one developer followed the EMAs Voluntary Harmonization Procedure (VHP) but experienced contradicting health authority feedback. Like the EU level, also on the member state level more frequent authority interactions took place, solving challenges in most cases. While compiling dossiers (clinical trial application or MA dossiers), uncertainty around desired information by authorities was reported most (n = 16, 20%). This was partially attributed to the lack of ATMP-specific guidelines.

Manufacturing and quality assurance

In the literature, complex manufacturing and difficulty in application of pharmaceutical quality control to ATMPs are frequently mentioned.[7,12,14]. In our survey, we have captured these challenges in the technical domain, which proved to be the second largest (n = 73, 30%). See Figure 1B for themes and characteristics distribution in this domain. Within the technical domain, manufacturing (n = 37, 51%) was the most occurring theme, mostly driven by process scale-up (n = 26, 36%). During scale-up, inconsistency issues were reported most, both in cell and gene therapy products. When seeking external help, finding experienced CMOs was difficult (n = 4, 6%). As with the GMO legislation, GMP legislation is interpreted differently across member states (n = 10, 14%). Additional to what the EMA's Committee for Advanced Therapies (CAT) may require, NCAs may also request

information. Additional information on quality standards (n = 13, 18%) was the most requested. This country variance led to confusion and was perceived to result in a patchwork of manufacturing and quality tests. GTMP developers expressed a need for quality guidance regarding potency, dosing, and impurities. A quality standard challenge mentioned specifically by two TEP developers was the need for high volumes of cell product for quality testing. These batches were thereafter unsuitable for patient use. This was found to be unethical because more donor material was needed.

To comply with GMP guidelines, products for medicinal use are required to be manufactured from appropriate level quality starting materials.[26] Suppliers providing certified appropriate quality starting materials were reported to be scarce, as well as expensive (n = 10, 14%). In response, some large ATMP developers expanded their in-house testing ability to certify raw materials, meet standards, and decrease supplier dependency. SMEs might not have the resources or means to copy this practice.

Supply chain challenges (n = 5, 7%) were described in the context of the highly personalized nature of ATMPs. Difficulties were caused by short product shelf-life requiring development of new shipping, preservation, and quality-control solutions. One cell therapy developer switched from an autologous to an allogenic product to overcome these issues. Technical challenges were experienced by both SMEs and large companies. Large companies mentioned that they profited from experience gained in non-ATMP development when addressing technical difficulties. The technical challenges were proportionally reported more in early clinical development, compared with late clinical development, and least in the combined regulatory and/or commercialization phase. No difference was noticed in the sub analyses of domains when distinguishing micro-, small-, and medium-sized enterprises within SMEs.

Translational uncertainties

To test efficacy and safety of any medicinal product, a rigorous scientific package needs to be built. All challenges associated with planning, design, and rationale of this package are captured in the scientific domain, which yielded 34 (14%) descriptions. ATMPs are currently most often developed for rare and previously untreated disease.[27] Developing medicinal products for these indications is associated with a specific set of challenges.[28] This was reflected in the most recurring scientific theme: trial design (n = 19, 56%). Descriptions revealed underlying issues such as low patient numbers because of the rare disease indication, little disease progression knowledge, as well as challenges associated with the creation and interpretation of endpoints for new indications. SMEs specifically described difficulties in preclinical translation (n = 8, 24%) mentioning the lack of relevant animal models available. In a few cases (n = 5, 15%), high uncertainty was also reflected by regulators' feedback, resulting in a request for additional fundamental research. More subgroup details are available in Figure 1C.

Financing and commercialization

Combining the developer-reported high development costs, reimbursement uncertainty, and the observation of ATMP market authorization holders withdrawing their products from the market for commercial reasons, one might expect the financial domain to be in the top of the challenges.[15,29]. Yet, the financial domain yielded 24 challenges, only 10% of all provided descriptions. This

domain equally covered two themes: uncertainty in reimbursement perspectives (n = 12, 50%) and funding (n = 12, 50%). Reimbursement uncertainty was mentioned most by large companies (n = 10, 42%), whereas SMEs experienced funding their clinical development most challenging (n = 9, 38%). Development stage also influenced experiencing financial challenges, with companies in late development (regulation/commercialization phase) reporting proportionally more financial challenges. See Figure 1D for all subgroup details.

Clinical implementation and acceptance

So far, we mostly discussed challenges experienced on a systems level. Although introduction of new treatments in the clinic is often accompanied by practical issues, these issues are included in the clinical domain (n = 23, 9%). Because of the limited penetration of ATMP in routine clinical care, this domain mostly includes challenges related to trial execution (n = 9, 4%). GTMPs reported proportionally more difficulties in executing trials (n = 5, 2%). At trial sites, additional training was needed in gene product handling, compounding, and admission. Also, trial site employees expressed hesitance toward handling GTMPs (n = 2, 1%). Cell-based products had more trouble reaching study enrolment rates than GTMPs, partially caused by orphan disease indications (n = 6, 2%). Subgroup details are displayed in Figure 1E. Practical issues were also mentioned in the context of employee recruitment in the human resource management (HRM) domain. HRM-related challenges (n = 5, 2%) were differentiated in recruiting personnel in general (n = 3, 1%) and recruiting skilled personnel with ATMP-specific knowledge (n = 2, 1%; see also Figure 1F). One SME reported having difficulty acquiring personnel with specific regulatory ATMP experience. Remaining challenges (n = 3, 1%) were included in the other domain (Figure 1G) and mentioned intellectual property (n = 1) and internal interdisciplinary alignment (n = 1).

Discussion

The aim of this research was to identify challenges experienced in European ATMP development by companies. Our survey shows that the European ATMP field is still in early stages of development with a high representation of SMEs (65%)[24,30], and 72% of reported products in the early clinical stages (phases I–II).[23] This is the first study in which the challenges of ATMP developers in the EU are systematically collected and quantified. High resemblance is observed between the challenges from our study and earlier literature, which has mainly focused on academic developers.[14,15]. Academic developers also experience difficulty with manufacturing processes[4–7], followed by the application of GMP requirements to cell and gene products[8–10], complex trial designs[4,11], heterogeneous national procedures[12], and reimbursement perspectives.[15] However, academia and hospitals produce ATMPs at a smaller scale, not for commercial purposes and for national use only, possibly explaining less of a focus on regulatory challenges. Comparing our findings with the few available papers focusing on companies, manufacturing[15], heterogeneous national procedures[14], and hospital exemption[13] are mentioned, which are also reflected in our study findings.

Although our study concentrated on developers active within the EU jurisdiction, some of our findings might also be applicable to other jurisdictions, with the exception of described regulatory challenges on multi-layered regulation, which are bound to jurisdictions. Non-authority-bound challenges

include technical, scientific, and clinical challenges, which are most likely to also be experienced outside of the EU. More research is needed to test this hypothesis.

Reimbursement of ATMPs is frequently mentioned as a major hurdle, both from a developer and health technology assessment (HTA) body point of view.[29,31,32] In our survey, financial challenges represented only 10% of responses, of which 5% specifically address reimbursement perspectives. It is likely that this low percentage can be explained by the early development stages of the ATMP field and high SME representation. Large companies experience more financial security and are therefore able to plan. They are also more likely to have experience in non-ATMP development and are aware of the preparations needed to acquire reimbursement[33]. On top of that, the manufacturing of ATMPs is considered to be more expensive by nature and is expected to pose pressure on healthcare budgets.[31] Combining the active ATMP pipelines with the prospect of healthcare budget constraints, sustainable ATMP reimbursement will become the next major challenge in this field if not already a reality. Companies should therefore address commercialization of their ATMP early in development. New payment models should be considered and their applicability to ATMPs explored. The potential curability of chronic diseases might shift from long-term and predictable treatment costs to one-off high upfront payments. To address this, a potential for annuity payment models is mentioned in the literature to alleviate these one-time budget constraints.[32]

Taking a closer look at the reported domains and company size, our survey suggests both SMEs and large companies experience multiple challenges with regard to ATMP-specific regulation and manufacturing. Interpreting the challenge descriptions, large companies seem to be more successful in bringing products to the market, probably by utilizing their non-ATMP development expertise and resources. From the literature it is known that SMEs in general face more challenges with manufacturing, regulatory requirements, and development funding than large companies.[34] SMEs are often considered to be highly innovative compared to large companies.[35] Most ATMPs on the market are products of large companies collaborating with SMEs or public partners. Examples of products from collaborations of large companies and smaller (public) partners are Strimvelis (autologous $CD34^+$ enriched cell fraction containing $CD34^+$ cells transduced with retroviral vector encoding for the human adenosine deaminase deficiency [ADA] cDNA sequence), Imlygic (talimogene laherparepvec), MACI (autologous cultured chondrocytes), and Holoclar (*ex vivo* expanded autologous human corneal epithelial cells containing stem cells). Collaborations between large companies and SMEs or academia are a way to move ATMP development forward, in which small partners develop innovative assets and large companies provide financial security and development experience.[36] Our study did not query the origin of companies or products, for example, academic spin-off, partnerships, or independent. No difference was observed when further subdividing the SME group into micro-, small-, and medium-sized enterprises in our challenge analyses, perhaps because of small sample size. It would be interesting to incorporate this information in future research because this may influence the challenges experienced.

A key initiative facilitating ATMP development was the adoption of European ATMP legislation (Regulation [EC] 1394/2007). This legislation was the first to define ATMPs and established the Committee for Advanced Therapies (CAT) within the EMA. The CAT is responsible for assessing

quality, safety, and efficacy of advanced therapy products. An active approach from European regulators was called for by Maciulaitis et al.[5] as early as 2012 describing several pro-active initiatives by the CAT, such as focus groups and workshops. Although most challenges in our survey were experienced in the regulatory domain, the EMA was only mentioned incidentally, and only by developers who have been active in the field before or around adoption of the (EC) 1397/2007 regulation. The majority of the regulatory challenges were experienced on member state level, often attributed to differences in experience and ATMP familiarity between NCAs. The diverse EU landscape was perceived as complex to navigate by both EU and non-EU companies, both in our survey as well as in the literature.[37] Several initiatives have started to address member state variance, such as efforts to harmonize GMP requirements and GMO legislation.[38] From the developers' perspective, respondents indicated that seeking frequent and early interactions with EU and NCAs helps attenuate regulatory challenges. Also, building internal ATMP regulatory and manufacturing expertise contributes to addressing challenges.

Taking a broader perspective and combining the high number of identified challenges in the regulatory and manufacturing domain with the high number of smaller and less experienced developers, the sketched situation seems to resemble the early days of biotechnology. This suggest that some of the identified challenges have a more generic character and are non-ATMP specific.[18,20] Similarly, the orphan drugs and new indication linked challenges in the scientific domain are also not ATMP specific. Each individual factor—developing new technologies, development for orphan indications, and new disease areas—adds complexity to the clinical development process. A lesson from early biotechnology innovations we could apply is that gaining experience with new technologies and societal adoption takes time. After the first biologicals entered clinical use, it took 20 to 30 years for these products to become widely available and viable.[39] Today, protein-based therapies represented 6 of the global top 10 pharmaceutical products.[40]

A similar finding is reported by Plagnol et al.[16], who investigated barriers in commercialization of regenerative medicine in the United Kingdom by interviewing leading industrialists. They claim that experienced barriers such as scaling up, lack of experienced people, and lack of business models are also experienced by entrepreneurs in other non-biotech sectors. Our survey was not designed to make a clear distinction between ATMP-specific issues and challenges correlated with an emerging field, new manufacturing techniques, or novel and orphan indications. However, it seems likely that developers active in the ATMP field do experience challenges due to a combination of factors of which not all are ATMP specific. A considerable proportion of challenges is driven by novelty of the field, new and orphan indications, and scientific and technical uncertainties. To test this statement, future research should include exploration of the root causes of the identified experienced challenges. Other considerations to include in future research are challenges experienced in preclinical development and how this may affect challenges downstream.

Our survey provides a snapshot of a rapidly changing commercial European ATMP field. The 271 developers we identified at the start of this study are very likely to change over time. Mergers, acquisitions, and bankruptcies may have occurred even in the short time after this cohort was compiled. Also, our cohort may not include 100% of active ATMP developers. By designing a comprehensive search strategy, we aimed to identify a clear majority of all ATMP developers

in Europe. Nonetheless, this is the first comprehensive overview of ATMP companies operating in Europe and identification of their challenges. Previous studies described either incidental challenges (e.g., manufacturing, GMP) or covered a single development phase.[13–15]

The high similarity between respondents and non-respondents, and the overlap of our findings with peer-reviewed literature, grey literature, conferences, and workshops[2,15,41–43] suggest the reported challenges are likely to be representative for the full cohort. However, we included only commercial developers currently involved in development. This may cause selection bias. Consequently, our results may underestimate developer-experienced challenges. Future analyses should include non-commercial and unsuccessful developers. Although our sample might be small, the quantification helps rank and prioritize identified challenges. Another future consideration is identification of factors that positively influenced ATMP development. Regulations also evolve over time: shortly after we completed data collection, a new ATMP-specific GMP guideline was released.[44] A renewed Clinical Trial Application guideline is expected in early 2019. With these new guidance's in place, this research can be considered as a baseline measure. It can be used for periodic (re)assessments of the ATMP landscape, following products as they advance through the medicine's life cycle, evaluating the influence of regulatory change, scientific advancement, and other factors.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgments

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References

1. The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council. *Off J Eur Union*. 2007;324([EC]1394/2007):121-138. http://data.europa.eu/eli/reg/2007/1397/oj.

2. Hidalgo-Simon A. The EMA view: Advanced Therapies in Europe. In: *6th EBE Annual Conference on ATMPs*. London: 5 December 2017; 2017. https://www.ebe-biopharma.eu/publication/ebe-annual-conference-on-atmps-speakers-presentations/.

3. Pearce KF, Hildebrandt M, Greinix H, et al. Regulation of advanced therapy medicinal products in Europe and the role of academia. *Cytotherapy*. 2014;16(3):289-297. doi:10.1016/j.jcyt.2013.08.003

4. Hanna E, Rémuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. *J Mark Access Heal Policy*. 2016;4(1):31036. doi:10.3402/jmahp.v4.31036

5. Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical development of advanced therapy medicinal products in Europe: Evidence that regulators must be proactive. *Mol Ther*. 2012;20(3):479-482. doi:10.1038/mt.2012.13

6. de Wilde S, Guchelaar H-J, Zandvliet ML, Meij P. Clinical development of gene- and cell-based therapies: overview of the European landscape. *Mol Ther - Methods Clin Dev*. 2016;3(July):16073. doi:10.1038/mtm.2016.73

7. Codinach M, Blanco M, Ortega I, et al. Design and validation of a consistent and reproducible manufacture process for the production of clinical-grade bone marrow–derived multipotent mesenchymal stromal cells. *Cytotherapy*. 2016;18(9):1197-1208. doi:10.1016/j.jcyt.2016.05.012

8. Viganò M, Giordano R, Lazzari L. Challenges of running a GMP facility for regenerative medicine in a public hospital. *Regen Med*. 2017;12(7):803-813. doi:10.2217/rme-2017-0051

9. Kitala D, Kawecki M, Klama-Baryła A, et al. The Isolation and Production of a Ready-to-Use Product (the Amniotic Stem Cell Culture) in Accordance with GMP Regulations. *Stem Cells Dev*. 2017;26(9):scd.2016.0198. doi:10.1089/scd.2016.0198

10. Galli M. ATMPs for Cancer Immunotherapy: A Regulatory Overview. In: Bondanza A, Casucci M, eds. *Tumor Immunology. Methods in Molecular Biology*. vol. 1393. New York, NY, NY; 2016.

11. Pignatti F, Aronsson B, Gate N, et al. The review of drug applications submitted to the European Medicines Evaluation Agency: frequently raised objections, and outcome. *Eur J Clin Pharmacol*. 2002;58(9):573-580. doi:10.1007/s00228-002-0532-8

12. de Wilde S, Veltrop-Duits L, Hoozemans-Strik M, et al. Hurdles in clinical implementation of academic advanced therapy medicinal products: A national evaluation. *Cytotherapy*. 2016;18(6):797-805. doi:10.1016/j.jcyt.2016.02.010

13. Alliance for Regenerative Medicine. *Position on Hospital Exemption*. Vol 28.; 2017. https://alliancerm.org/sites/default/files/ARM_position_on_HE_final.pdf.

14. Van Wilder P. Advanced therapy medicinal products and exemptions to the Regulation 1394/2007: How confident can we be? An exploratory analysis. *Front Pharmacol*. 2012;3 FEB(February):1-9. doi:10.3389/fphar.2012.00012

15. Morrow D, Ussi A, Migliaccio G. Addressing Pressing Needs in the Development of Advanced Therapies. *Front Bioeng Biotechnol*. 2017;5(9):1-6. doi:10.3389/fbioe.2017.00055

16. Plagnol AC, Rowley E, Martin P, Livesey F. Industry perceptions of barriers to commercialization of regenerative medicine products in the UK. *Regen Med.* 2009;4(4):549-559. doi:10.2217/rme.09.21

17. Bisson I, Green E, Sharpe M, Herbert C, Hyllner J, Mount N. Landscape of current and emerging cell therapy clinical trials in the UK: current status, comparison to global trends and future perspectives. *Regen Med.* 2015;10(2):169-179. doi:10.2217/rme.14.71

18. Tsiftsoglou AS, Ruiz S, Schneider CK. Development and regulation of biosimilars: Current status and future challenges. *BioDrugs.* 2013;27(3):203-211. doi:10.1007/s40259-013-0020-y

19. Shire SJ. Formulation and manufacturability of biologics. *Curr Opin Biotechnol.* 2009;20(6):708-714. doi:10.1016/j.copbio.2009.10.006

20. Singh SK, McAuley A, Rathore N, Rathore AS. *Best Practices for Formulation and Manufacturing of Biotech Drug Products Best Practices for Formulation and Manufacturing of Biotech Drug Products.* Vol 22.; 2009. https://www.biopharminternational.com/view/best-practices-formulation-and-manufacturing-biotech-drug-products.

21. Shi S. Biologics: An Update and Challenge of Their Pharmacokinetics. *Curr Drug Metab.* 2014;15(3):271-290. doi:10.2174/1389200215031404122129O5

22. Ajay Bailey, Hutter I. *Qualitative Research Methods.* 1st ed. (Hutter I, ed.). SAGE Publications, Inc.; 2010.

23. Stakeholders and Communication Division. *SME Office Annual Report 2017*. Vol 2017. London, UK; 2018. https://www.ema.europa.eu/en/documents/report/small-medium-sized-enterprise-sme-office-annual-report-2017_en.pdf.

24. Wong CHIH, Siah KWEI, Lo AW. Estimation of clinical trial success rates and related. 2018;(July):1-14. doi:10.1093/biostatistics/kxx069

25. EU. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. *Off J Eur Communities.* 2001;L 106(1):1-38. doi:2004R0726 - v.7 of 05.06.2013

26. Economic Community. Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use. *Off J.* 1991;L193(17.7.1991):30-33. http://data.europa.eu/eli/dir/1991/356/oj.

27. Abou-El-Enein M, Römhild A, Kaiser D, et al. Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: A novel tailored model for optimizing performance and estimating costs. *Cytotherapy.* 2013;15(3):362-383. doi:10.1016/j.jcyt.2012.09.006

28. Pariser AR, Gahl WA. Important role of translational science in rare disease innovation, discovery, and drug development. *J Gen Intern Med.* 2014;29(SUPPL. 3):804-807. doi:10.1007/s11606-014-2881-2

29. Marsden G, Towse A. *Exploring the Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: Is the NICE Approach Fit for Purpose?* London, UK; 2017. file:///Users/RensketenHam/Downloads/Final report NICE CAR T February 2017.pdf.

30. Clinical Trials Arena. Small players, big drugs – pharmaceutical SMEs take the innovative edge. https://www.clinicaltrialsarena.com/. https://www.clinicaltrialsarena.com/analysis/featuredrug-pharmaceutical-sme-big-pharma-innovation/. Published April 2012. Accessed January 29, 2021.

31. Hanna E, Tavella F, Rémuzat C, Auquier P, Toumi M. Market Access of Atmps: Overview and Expected Challenges. *Value Heal.* 2015;18(7):A518-A519. doi:10.1016/j.jval.2015.09.1580

32. Jørgensen J, Kefalas P. Annuity payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. *J Mark Access Heal Policy*. 2017;5(1):1355203. doi:10.1080/20016689.2017.1355203

33. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve RD productivity: The pharmaceutical industry's grand challenge. *Nat Rev Drug Discov*. 2010;9(3):203-214. doi:10.1038/nrd3078

34. OECD. Policy note: Improving the business environment for SMEs through effective regulation. In: *SME Ministerial Conference*. Mexico City, Mexico; 2018:1-11. https://www-oecd-org.proxy.library.uu.nl/cfe/smes/ministerial/documents/2018-SME-Ministerial-Conference-Parallel-Session-1.pdf.

35. Mengal P, Wubbolts M, Zika E, et al. Bio-based Industries Joint Undertaking: The catalyst for sustainable bio-based economic growth in Europe. *N Biotechnol*. 2018;40:31-39. doi:10.1016/j.nbt.2017.06.002

36. Mangematin V, Lemarié S, Boissin J, et al. Development of SMEs and heterogeneity of trajectories: the case of biotechnology in France. *Res Policy*. 2003;32(4):621-638. doi:10.1016/S0048-7333(02)00045-8

37. Coppens DGM, De Bruin ML, Leufkens HGM, Hoekman J. Global Regulatory Differences for Gene- and Cell-Based Therapies: Consequences and Implications for Patient Access and Therapeutic Innovation. *Clin Pharmacol Ther*. 2018;103(1):120-127. doi:10.1002/cpt.894

38. Salmikangas P, Schuessler-Lenz M, Ruiz S, et al. Marketing Regulatory Oversight of Advanced Therapy Medicinal Products (ATMPs) in Europe: The EMA/CAT Perspective. In: *Regulatory Aspects of Gene Therapy and Cell Therapy Products A Global Perspective*. Vol 871. ; 2015:235. doi:10.1007/978-3-319-18618-4_12

39. Hopkins MM, Martin PA, Nightingale P, Kraft A, Mahdi S. The myth of the biotech revolution: An assessment of technological, clinical and organisational change. Taylor T, ed. *Res Policy*. 2007;36(4):566-589. doi:10.1016/j.respol.2007.02.013

40. Mikulic M. Pharmaceutical sales worldwide 2017-2019, by region. Statistica.com. https://www.statista.com/statistics/272181/world-pharmaceutical-sales-by-region/. Published 2020. Accessed January 29, 2021.

41. European Medicines Agency. Committee for Advanced Therapies (CAT) Work Programme 2010 - 2015. 2010;44(June):18-21. http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2010/11/WC500099029.pdf.

42. Alliance for Regenerative Medicine, European biopharmaceutical Enterprises (EBE), European Federation of Pharmaceutical Industries and Associations (EFPIA), EuropaBio. *Position Paper: Possible Solutions to Improve the European Regulatory Procedures for Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms.*; 2017. https://www.ebe-biopharma.eu/wp-content/uploads/2017/09/Position_paper_ARM_EFPIA_EBE_EuropaBio_27Sept17_longversion.pdf.

43. Human Medicines Research and Development Support Division. *Issues Identified by Stakeholders: Follow- up from EMA's ATMP Workshop*. Vol 44. London, UK; 2017. https://www.ema.europa.eu/en/documents/other/issues-identified-stakeholders-workshop-multi-stakeholder-advanced-therapy-medicinal-products-atmps_en.pdf.

44. European Comission. *Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products*. Vol Volume 4. Brussels; 2017. doi:10.1093/oxfordhb/9780199546282.013.0024

Supplemental Materials

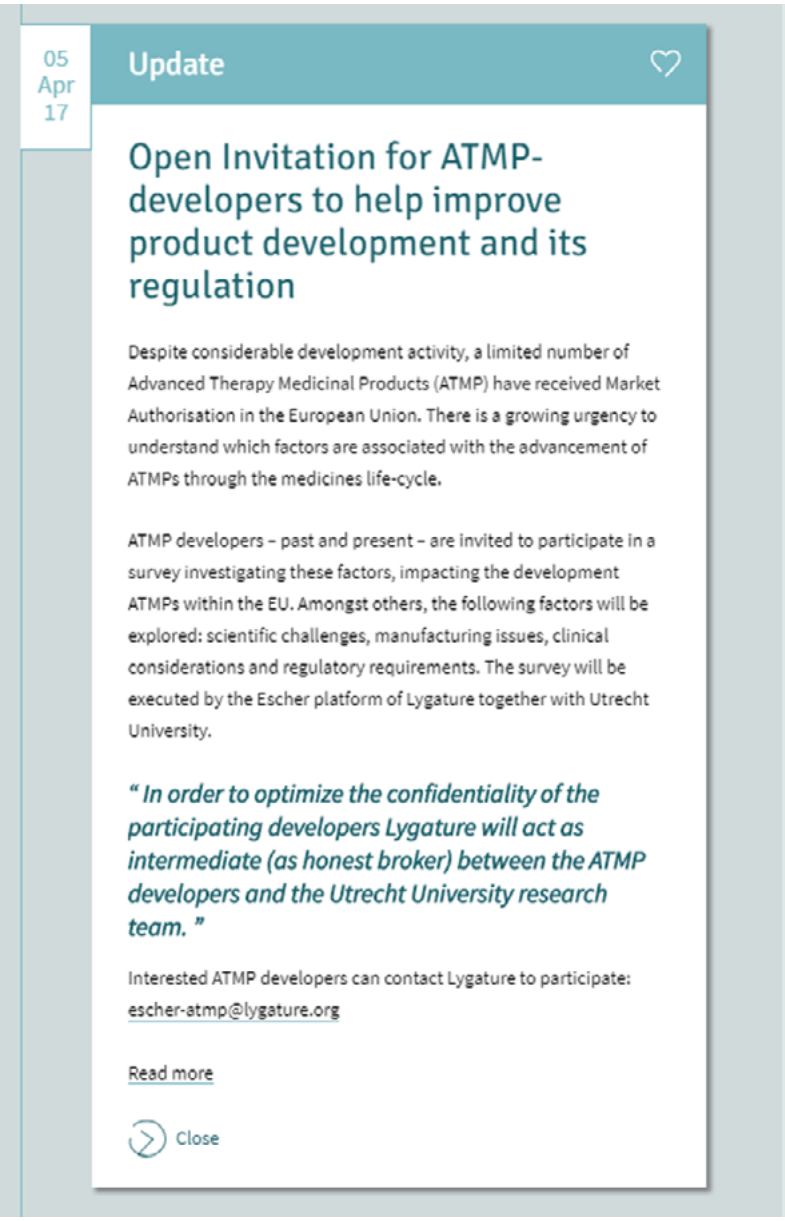

Figure S1. Open Call. Invitation to ATMP developers to participate in the survey as published on the website of www.lygature.org on April 5th, 2017.

Challenges - Product X - Introduction

You indicated your organization is currently involved in the development of MORE THAN THREE ATMPs.
Please visualize the three ATMPs furthest in development and/or most representative for your organization. These products will hereafter be referred to as **PRODUCT X**, **PRODUCT Y** and **PRODUCT Z**, starting with questions about **Product X**.

We are interested in the challenges your organization faced in the development (so far) of Product X. With challenges, we allude to hurdles or obstacles your organization has encountered, ranging from small and easy to solve to causing delay or even possible product discontinuation.

Figure 1: Simplified Overview of Different Stages in a Medicinal Product Life-cycle.
This research is interested in the clinical, regulatory and commercialization developmental phases (dark blue).

Looking at Figure 1, what development stage is **Product X** currently in?
When in doubt or stage overlap: Please select the stage furthest down in the product life-cycle.

[ ] Early Clinical Research (Phase I-II)
[ ] Late Clinical Research (Phase III)
[ ] Applying for Regulatory Approval
[ ] Product Commercialization

Challenges can occur in different domains. In this research, the domains are categorized as stated below. Please be aware that the given examples are not exhaustive!

Technical Challenge(s): For example, Quality Assurance, CMC, Product Consistency, Materials, Cell-Lines, Equipment, Specialized Technologies etc.

Scientific Challenge(s): For Example, Uncertainty on Mechanism of Action, Criteria for Proof of Concept, Dose vs Response Correlation, Targeted Delivery, Outcome Measures etc.

Clinical Challenge(s): For Example, Safety, Efficacy, Administration Requirements, and Delivery System etc.

Human Resource Challenge(s): For Example, Training, Skills, Knowledge, Recruitment, Support Functions, Collaboration, Contracting, Outsourcing etc.

Regulatory Challenge(s): For Example, Scientific Advice (National, European), Compliance, Guidance Documents, Dossier Requirements, and Medical Ethical Committees, Post-Approval Commitments, Periodic Safety Update Report etc.

Financial Challenge(s): For Example, Funding, Reimbursement Prospects, Development Cost, Investor Interest, Product Maintenance etc.

Other challenge(s): If you have encountered challenges in a different domain, please specify:_____

[NEXT]

Figure S2. Introduction to survey part two. CMC = Chemistry, Manufacturing and Control

Table S1. Search queries. Search terms used per source needed to co compose the European Advanced Therapy Medicinal Product (ATMP) developer cohort.

Source	Date	Search Query
EMA SME Registry	04-01-2017	((“Advanced therapy medicinal products” OR “Somatic cell therapy products OR “Tissue engineered products” OR “Gene therapy products” OR “Combined medical products and devices”) AND (Human”))
Glinicaltrials.gov	04-01-2017	ATMP OR “Advanced Therapy Medicinal Product” OR “Advanced Medicinal Product” OR “Advanced Therapy Product” OR “Advanced Therapy” OR “Advanced Medicinal Product” AND | Studies updated from 01/01/2005 to 12/31/2015)
	10-01-2017	“tissue engineered product” OR “tissue engineering” OR “engineered cell “OR “tissue engineered” OR “engineered product” | Studies updated from 01/01/2005 to 12/31/2015
	10-01-2017	“somatic cell therapy product” OR “somatic cell therapy” OR “cell therapy product” OR “somatic cell product” | Studies received from 01/01/2005 to 12/31/2015 | Studies updated from 01/01/2005 to 12/31/2015
	10-01-2017	“gene therapy medicinal products” OR “gene therapy product” OR “gene therapy” OR “gene therapy medicine” OR “DNA therapy” | Studies received from 01/01/2005 to 12/31/2015 | Studies updated from 01/01/2005 to 12/31/2015
	12-01-2017	(“cell therapy” OR “cord blood” OR “umbilical cord” OR “bone marrow” OR “cancer vaccine” OR “tissue engineering” OR “engineered cell” OR “tissue engineered” OR “mesenchymal cell” OR “somatic cell” OR “allogeneic cell” OR “viable cell” OR “gene therapy” OR “recombinant nucleic acid” OR “DNA therapy” OR “cDNA” OR “recombinant DNA” OR “nucleic acid therapy” OR “gene transfer” OR “virus delivery” OR “cancer immunotherapy” OR “RNA therapy” OR “tumour vaccine” OR “genetic therapy” OR “plasmid DNA” OR “oligonucleotides” OR “genetically modified microorganisms” OR “genetically modified organisms” OR “genetically modified cells”) | Studies updated from 01/01/2005 to 12/31/2015
EudraCT	12-01-2017	ATMP OR “Advanced Therapy Medicinal Product” OR “Advanced Medicinal Product” OR “Advanced Therapy Product” OR “Advanced Therapy” OR “Advanced Medicinal Product” | Date Range 01/01/2005 to 12/31/2015
	12-01-2017	“tissue engineered product” OR “tissue engineering” OR “engineered cell “OR “tissue engineered” OR “engineered product” | Date Range 01/01/2005 to 12/31/2015
	12-01-2017	“somatic cell therapy product” OR “somatic cell therapy” OR “cell therapy product” OR “somatic cell product” | Date Range 01/01/2005 to 12/31/2015
	12-01-2017	“gene therapy medicinal products” OR “gene therapy product” OR “gene therapy” OR “gene therapy medicine” OR “DNA therapy” | Date Range 01/01/2005 to 12/31/2015

Table S1. (continued)

Source	Date	Search Query
	12-01-2017	("cell therapy" OR "cord blood" OR "umbilical cord" OR "bone marrow" OR "cancer vaccine" OR "tissue engineering" OR "engineered cell" OR "tissue engineered" OR "mesenchymal cell" OR "somatic cell" OR "allogeneic cell" OR "viable cell" OR "gene therapy" OR "recombinant nucleic acid" OR "DNA therapy" OR "cDNA" OR "recombinant DNA" OR "nucleic acid therapy" OR "gene transfer" OR "virus delivery" OR "cancer immunotherapy" OR "RNA therapy" OR "tumour vaccine" OR "genetic therapy" OR "plasmid DNA" OR "oligonucleotides" OR "genetically modified microorganisms" OR "genetically modified organisms" OR "genetically modified cells") | Studies updated from 01/01/2005 to 12/31/2015
Web of science	28-02-2017	TOPIC: ATMP OR "Advanced Therapy Medicinal Product" OR "Advanced Medicinal Product" OR "Advanced Therapy Product" OR "Advanced Therapy" OR "Advanced Medicinal Product". AND "Human" Timespan: 2005-2015. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI. COUNTRIES/TERRITORIES: EU
	28-02-2017	TOPIC: ("tissue engineered product" OR "tissue engineering" OR "engineered cell "OR "tissue engineered" OR "engineered product") AND TOPIC: ("Gene Therapy") Timespan: 2005-2015. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI. COUNTRIES/TERRITORIES: EU
	28-02-2017	TOPIC: "somatic cell therapy product" OR "somatic cell therapy" OR "cell therapy product" OR "somatic cell product" AND "Human" | Timespan: 2005-2015. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI. COUNTRIES/TERRITORIES: EU
	28-02-2017	"gene therapy medicinal products" OR "gene therapy product" OR "gene therapy" OR "gene therapy medicine" OR "DNA therapy" | Studies received from 01/01/2005 to 12/31/2015 | Studies updated from 01/01/2005 to 12/31/2015
	28-02-2017	TOPIC: ("cancer vaccine" OR "engineered cell" OR "allogeneic cell" OR "gene therapy" OR "DNA therapy" OR "nucleic acid therapy" OR "gene transfer" OR "cancer immunotherapy" OR "RNA therapy" OR "tumour vaccine" OR "genetic therapy" OR "genetically modified cells") AND TOPIC: (Human) Refined by: COUNTRIES/TERRITORIES: EU. Timespan: 2005-2015. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.

Table S2. Industry associations and event list. European (bio)pharmaceutical industry association member lists, ATMP associated event attendee lists and an open call. EMA=European Medicines Agency, CAT=Committee for Advanced Therapies, ESGCT=European Society of Gene and Cell Therapy, IMI=Innovative Medicines Initiative.

Member Lists: • European Federation Pharmaceutical Industry and Associations (EFPIA) • European Biopharmaceutical Enterprises (EBE) • EuropaBio and European Confederation of Pharmaceutical Entrepreneurs (EUCOPE).
Event List: • EMA – CAT meetings minutes and reports (2009-2017) • EMA - European Medicines Agency's workshop on stem cell-based therapies (10-0-2010) • CAT/ESGCT - Satellite workshop: Advanced-therapy medicinal products (27-10-2011) • EMA - How to bring cell-based medicinal products successfully to the market (11-09-2013) • EMA – CAT hearing with interested parties (11-12-2014) • EMA - Workshop on development pathways for advanced-therapy medicinal products medicinal products (15-12-2014) • IMI – Pre-stakeholder Forum Consultation (26-07-2016) • IMI – Stakeholder forum (28/29-09-2016) • EMA/EBE - 5th Annual Regulatory Conference: Optimizing the development of ATMPs to meet patient needs (16-12-2017)
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2.2

A framework and methodology to facilitate costing of academic and small-scale cell therapy manufacturing

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Abstract

Recent technical and clinical advances with cell-based therapies (CBTs) hold great promise in the treatment of patients with rare diseases and those with high unmet medical need. Currently the majority of CBTs are developed and manufactured in specialized academic facilities. Due to small scale, unique characteristics and specific supply chain, CBT manufacturing is considered costly compared to more conventional medicinal products. As a result, biomedical researchers and clinicians are increasingly faced with cost considerations in CBT development and application. The objective of this research is to develop a costing framework and methodology for academic and other small-scale facilities which manufacture cell-based therapies.

We conducted an international multi-centre costing study in four different facilities in Europe using eight different CBTs as case-studies. This study covers the costs from cell or tissue procurement to release of final product for clinical use. First, via interviews with research scientists, clinicians, biomedical scientists, pharmacists, and technicians we designed a high-level costing framework. Next, we developed a more detailed uniform methodology to allocate cost items. Costs were divided into steps (tissue procurement, manufacturing, and fill-finish). The steps were each subdivided into cost categories (materials, equipment, personnel, and facility), and each category was broken down into facility running (fixed) costs and operational (variable) costs. The methodology was tested via the case studies and validated in developer interviews. Costs are expressed in 2018 Euros (€).

The framework and methodology were applicable across facilities and proved sensitive to differences in product and facility characteristics. Case study cost estimates ranged between €23,033 and €190,799 Euros per batch, with batch yield varying between 1 and 88 doses depending on type of CBT. The cost estimations revealed hidden costs to the developers and provided insights into cost drivers to help design manufacturing best-practices.

This framework and methodology provide a step-by-step guidance to estimate the manufacturing cost specifically for cell-based therapies manufactured in academic and other small-scale enterprises. The framework and methodology can be used to inform and plan cost-conscious strategies also for CBT in general.

Introduction

Recent technical and clinical advances with Cell-Based Therapies (CBTs) hold great promise in the treatment of patients with rare diseases and high those with high unmet medical need[1]. In Europe, CBTs include Cell Therapy Medicinal Products (excluding genetically modified Cell Therapy Medicinal Products) and Tissue Engineered Products (TEPs)[2]. These technologies are not new as they have been applied in a laboratory setting for many years[3,4]. Yet, their recent translation to medicinal products for human use is considered one of the major breakthroughs in biomedical history [5–7].

Although classified as medicinal product, CBTs differ significantly from more conventional pharmaceutical agents, such as small molecules or monoclonal antibodies. CBTs consist of live tissue or cells and therefore require specific manufacturing, quality control and supply chain solutions[8]. Recently large pharmaceutical companies are showing increasing interest in CBTs, although a majority of products are developed and manufactured in specialized academic and public facilities[9–11]. This is mainly driven by the personalized nature, science and advanced technologies required to develop CBTs. In these specialized centres the CBT specific supply chain – including tissue procurement, substantial manipulations, and administration - requires close collaboration between biomedical scientists, technicians, pharmacists, clinicians, and administrators. New collaborations incite (re) definition of roles and responsibilities, including novel cost allocations and payment considerations. Although costs in general are a topic of debate in healthcare, this is found more so for CBTs due to their perceived high cost compared to more conventional medicinal products[7]. The continued expansion of CBT applications will progressively stress budgets. As a result biomedical researchers and clinicians are increasingly faced with cost considerations, which generally is not a part of their routine activities [12].

Cost insights are of interest for multiple reasons. Accurate resource valuation helps determine budget allocation by administrators, payers, and investors. Yet perhaps most importantly, understanding of resource use and cost drivers facilitates product maturation and institutional readiness[13]. CBT manufacturing often involves multiple hospital units, introducing internal cost sharing questions. Additionally, CBTs are manufactured in facilities holding a Good Manufacturing Practice (GMP) license adding complexity[14]. Consequently, not just direct operational cost should be taken into account but also personnel, equipment and materials needed for maintenance, quality management and training purposes. Not including these so-called 'hidden expenses can result in substantial undervaluation of resources.

The literature provides several CBTs costing studies, however these are mainly cost-effectiveness analyses (CEAs) of cell-based products[15–17]. In these analyses the aggregate price of a product and overall treatment cost proportionate to its effect is compared to a standard of care. Although informative for pricing and reimbursement decisions, these CEAs provide little to no information on (in-house) manufacturing costs itself. Looking outside CBT literature a few more universal pharmaceutical frameworks are available, yet these focus heavily on pricing[18,19]. In 2013, Abou-EL-Enein et al. were the first to describe a Cleanroom Technology Assessment Technique (CTAT) in which the detailed manufacturing costs of two cell products were calculated[12]. Despite interesting insights, their complex approach shows low external validity which is confirmed by lack of its uptake in literature and

practice. More generalizable is a tool developed by Boeke et al. [14] which is specifically designed for dedicated large-scale vector production facilities[14].

Thus, the aim of this research was to develop a costing framework and methodology specifically for academic and other small-scale developers who manufacture in-house Cell-Based Therapies. To do so, an international multi-centre costing study was performed in which eight different CBTs from four different facilities acted as case-studies. The framework and underlying methodology will guide facilities to more accurately estimate CBT manufacturing costs to inform and plan cost-conscious strategies.

Methods

Study design

We conducted an international multi-centre costing study. First, we designed a costing framework. Thereafter, we developed a more detailed methodology to allocate specific cost items within this framework. The methodology was tested in eight case studies from four different facilities in Europe. Last, we validated our framework and methodology with research scientists, clinicians, biomedical researchers, pharmacists, technicians, and administrators (hereafter called developers). The starting point in this study is cell or tissue procurement, and the endpoint is release of end product for clinical use.

Development of framework

To design the framework, per case study we started with dissemination of the manufacturing process using flow charts and Investigational Medicinal Product Dossiers (IMPDs). The rationale for the bottom-up approach was to start with documents familiar to developers[20]. Across facilities and case studies, we identified three high-level and generalizable steps: *1) Procurement, 2) Manufacturing and 3) Fill & Finish*. Thereafter, we defined four cost categories across these steps: *Materials, Equipment, Personnel and Facility*. Within these categories, a distinction was made between fixed and variable costs[12,21–23]. Additionally, manufacturing steps and cost categories were required to be mutually exclusive preventing double counting or overlooking of costs[24]. The sum of costs acquired per step provides total manufacturing cost (or aggregated cost). To check internal validity, the aggregated cost should be equal to the sum of the cost categories.

Development of methodology

An accepted approach of identifying activities within an organization and assigning costs to each activity employed to produce a product or service is Activity Based Costing (ABC)[25]. The ABC-method is especially helpful in the identification of cost drivers and possible inefficiencies as well as in its applicability to manual and small scale processes[25]. In traditional cost accounting, resources are directly allocated to products or services[23]. With ABC, products and services are translated into activities (here manufacturing steps) and traced back to resource drivers (here cost categories)[25]. This makes ABC more accurate in comparison to direct cost allocation, especially when allocating indirect costs, which are thought to account for a considerable proportion of CBT manufacturing[10,26].

Per cost category, for both fixed and variable cost, we defined a method to best identify and allocate cost. These methods are based on the Campaign and Day rate model by Boeke et al. and Abou-El-Enein's manufacturing cost algorithm[12,14]. Our methodology ought to be applied for each manufacturing step defined in the framework.

This study takes the developer perspective. This means only costs incurred during the manufacturing process by the CBT developer are included[24]. Excluded are transportation costs, storage, and medical costs (e.g., patient pre-treatment, admission, or follow-up care). We assumed that in each of the case studies manufacturing took place on a routine basis in established facilities. Therefore, we did not include learning effects including product specific training of (new) employees, product development costs, and costs like IMPD or Standard Operating Procedure (SOP) writing or validation runs. The outcome is cost per batch. We assumed one batch yields one treatment. If this framework and methodology is applied for products who yield more than one treatment per batch or a different outcome (cost/dose, cost/treatment e.g.) is preferred, the outcome should be adjusted accordingly. Costs are reported in 2018 Euros (€), as this was the most recent full financial year at time of data collection. Our method is also applicable for other currencies (e.g., US dollars, Pounds, Yen etc.). Costs obtained in different years were adjusted for inflation to 2018 prices using price index numbers[27]. Purchasing Power Parity (PPP) was used to convert difference in currency by taking Gross Domestic Product-differences into account[28]. These adjustments are in line with the *Dutch Manual for Costing: Methods and Reference Prices for Economic Evaluations in Healthcare* [29].

Data collection and cost definitions

Data was collected within the facilities between June 2018 and September 2019. Sources used were IMPDs, manufacturing flowcharts, internal purchase-, payroll-, and contracting administration and developer interviews. We used material and equipment list prices. For personnel cost we used collective labour agreement wages.

Fixed cost

A cost is fixed if it does not increase as the number of products or services provided increases[14]. The sum of the fixed cost categories (fixed material, equipment, personnel and facility cost) is considered the facility running cost and calculated per year[12,22]. These facility running costs are consumed to ensure operability of the facility, independent of whether products are manufactured. The multi-layered and continuously monitored GMP-environment in which CBTs are manufactured makes allocating these shared costs to individual products impossible[9]. Therefore, we have chosen to divide the annual facility running cost by the annual number of batches (all products) manufactured in each facility, taking the same approach as the Campaign model described by Boeke et al.[14] In the equipment category we included all non-product specific equipment present in the facility (e.g. microscopes, pipettes, centrifuges, fridges, freezers, water baths).

Fixed equipment costs are calculated as the sum of annual depreciation cost plus annual maintenance fees[30]. The annual depreciation per apparatus is calculated by division of purchase price by an annuity factor[29]. This annuity factor takes into account the equipment life time and a 4.5% interest rate[29]. For example, using the formula provided by Kanter's et al., a pipette with a lifetime of 5 years is assigned an annuity factor of 4.39. For larger equipment (e.g. cell manufacturing platforms, flow

cytometers) we applied a 10 year life time (annuity factor 7.91)[29]. When an item is still in operation but has exceeded its life time it is removed from the costing template and considered amortized[29]. For fixed material cost we took a similar approach. In this study fixed material cost are defined as the sum of all non-product specific materials purchased per annum. Examples are stock materials and also consumables such as gloves, pipettes, pipette tips, tubes, and cleanroom suits, but also demi water, ethanol etc. Fixed personnel cost includes personnel with dedicated administrative, research, (project) management and quality positions (e.g., Quality Assurance [QA], Quality Person [QP], project managers). For personnel with hybrid responsibilities, we estimated (in %) their time spend on routine non-product specific (quality) duties such as GMP training and Quality Management (e.g., environmental monitoring, setting up and maintaining quality management system [QMS]). Their annual salary was adjusted proportionally to this estimate and added to the fixed personnel cost. Last, the fixed facility cost includes annual housing and maintenance cost - such as mortgage or lease, non-product specific cleaning, environment control contracts, storage, depreciation inventory - of the facility excluding the cleanrooms[29].

Variable cost

If a cost changes proportionally to the quantity of delivered good or services provided, the cost is considered variable[12]. When allocating variable cost items we have taken an opportunity cost approach[24]. This means we costed all time and resources which were spent manufacturing the product of interest, and which therefore could not be used for other purposes.

Variable materials include all consumables and (raw) materials directly used to manufacture a batch. To prevent double counting, these materials may not be part of the facility stock. The cost of these materials is identified and allocated per manufacturing step. Variable equipment cost includes specialized equipment only. This is equipment specifically purchased for production of the CBT of interest. We allowed equipment to be shared by multiple projects with a maximum of five (project share 20%). When equipment was shared by >5 products, it was considered fixed equipment. To translate equipment-purchase cost to a variable cost, the cost is translated to an annual cost using an annuity factor (similar to fixed equipment cost), adjusted for project share (in %) and corrected for annual production volume (APV). APV corresponds with the number of CBT batches manufactured per year.

Variable personnel and facility costs are calculated using the Day-rate model[14]. This implies cost is allocated based on time rather than share. Variable personnel cost includes all personnel directly involved in product manufacturing (e.g., technicians, QP, QA etc.). A day rate is calculated by correcting annual salary by full-time equivalent (FTE) and, if applicable, estimated time spent on QMS (as specified under fixed personnel cost). This day rate is multiplied by days spent on product manufacturing. Taking the opportunity cost approach this includes time spent on preparation, administration, in-process, and release testing. The variable facility day rate is determined by dividing the annual cleanroom specific cost – including maintenance, control, and cleaning expenses – by facility active days (FAD). FAD is defined as number of days the cleanroom can be used for manufacturing. This excludes days the cleanrooms are inoperable (e.g., due to recertification, inspections, maintenance, or non-product specific cleaning activities) or not in use (holidays and if applicable weekends). Similar to variable personnel cost, this facility day rate is multiplied by

the number of days cleanrooms were utilized for product manufacturing. Pro rata adjustment is needed when a facility has multiple cleanrooms and/or cleanrooms with multiple workstations.

Framework and methodology validation

We conducted multiple rounds of semi-structured interviews with developers. First, to understand the product manufacturing processes and the resources used. Second, the framework and underlying methodology were translated into a Microsoft Excel (Microsoft Corp. 2018) costing template and developers were asked to review and use the template and provide feedback. Changes were made accordingly. Last, within each facility, developers were asked to validate collected data, resource allocation and assumptions for each case study.

Facility and case study characteristics

The study was conducted in four specialized cell manufacturing facilities in the Netherlands (Facilities A & B) and Scotland (Facilities C & D). Facility A (case study 1-3) is an academic centre with a dedicated GMP Advanced Therapy Medicinal Products (ATMPs) development and production facility. The facility has an in-house chemical peptide synthesis facility and several cleanrooms of which one is dedicated to gene therapy production. Facility B is a dedicated GMP cell facility, which is integral part of the pharmacy department of a Dutch large academic centre. The GMP cell facility is considered an independent organizational unit. Costs of this facility are borne pro rata by two hospital departments developing cell therapies. Each department contributed one case study, in which the first department fully manufactures the product (case study 4) in the GMP facility and the other department conducts procurement and a few manufacturing steps in a JACIE (Joint Accreditation Committee ISCT-Europe & European Group for Blood and Marrow Transplantation[EBMT])[31] environment before moving to the hospital's GMP cell facility (case study 5). Facility C is a shared GMP cell therapy and tissue repair facility. This centre of excellence houses scientists and clinicians from a university and hospital and aims to facilitate scientific knowledge to the clinic and industry. Facility D is part of a large and recently opened (2016) blood transfusion, cell, and tissue centre. This facility contributed case study 8.

Case study inclusion criteria were:

1. products are manufactured under GMP conditions,
2. products are routinely manufactured at time of inclusion,
3. developer (academic group, facility, clinical researcher, biomedical scientist or other) can provide detailed manufacturing information,
4. developer can provide access to detailed financial information.

Table 1 provides case study characteristics. In case studies 1 to 7 one batch corresponds to one treatment. In case study 8, one batch yields 88 doses corresponding with 22 treatments. The included case studies are manufactured under Hospital Exemption, compassionate use program or in clinical trial setting.

Table 1. Case study characteristics.

Product ID	A-1	A-2	A-3
Product description	Peptide pulsed tolerogenic dendritic cells	pp65-specific T cells	Ex vivo expanded mesenchymal stromal cells
Indication	Type 1 diabetes mellitus	Refractory cytomegalovirus infection	Immunomodulation and tissue regeneration
Procurement	Apheresis	Apheresis	Bone marrow aspirate
Product Origin	Allogeneic peripheral blood	Allogeneic peripheral blood	Allogeneic bone marrow
Specialized equipment	Yes	Yes	Yes
Runtime	7 days	2 days	28 days (range 21-35)
Batches per year	2	6	14
Dose yield per batch	2	1	2
Dose per Treatment (avg/pt)	2	1	2
	B-4	**B-5**	**C-6**
Product description	Peptide-loaded natural dendritic cell vaccine	Stem cell-derived natural killer cells	Monocyte-derived macrophages
Indication	Stage III melanoma	Acute myeloid leukaemia, Ovarian carcinoma	Hepatic cirrhosis
Procurement	Apheresis	Apheresis	Apheresis
Product Origin	Autologous peripheral blood	Allogeneic umbilical cord blood	Autologous peripheral blood
Specialized equipment	Yes	Yes	Yes
Runtime	4 days	35 days	8 days
Batches per year	55	9	9
Dose yield per batch	9	1	1
Dose per Treatment (avg/pt)	9	1	1
	C-7	**D-8**	
Product description	Ex vivo expanded limbal stem cells	Anti-viral cytotoxic T lymphocytes	
Indication	Ocular surface disorders	Post-operative lymphoproliferative disease	
Procurement	Tissue extraction	Apheresis	
Product Origin	Allogeneic corneal tissue	Allogeneic peripheral blood	
Specialized equipment	Yes	Yes	
Runtime	15 days	21 days	
Batches per year	10	6	
Dose yield per batch	1	88	
Dose per Treatment (avg/pt)	1	4	

Pt-Patient

Results

Visualization of framework and methodology

The developed framework is visualized in Figure 1. This figure outlines high-level steps to calculate an aggregate per batch manufacturing cost as well as step- and category-specific costs. To start CBT costing, the manufacturing process of an individual product is categorized in mutually exclusive steps 1 to 3. For each step, we identified both fixed and variable costs for given resources and determined the quantities of consumed and associated cost for resources in each category.

After the framework is populated, the cost for each case study is calculated using the methodology as described in the materials and methods section' of this paper. This methodology is visualized in Figure 2 as a per step cross section of the framework shown in Figure 1. When manufacturing took place in one location/facility, steps 1-3 were bundled for the fixed costs. For the manufacturing taking place in multiple locations, facility running cost were determined for each location separately and combined as presented in Figure 1 and 2. Based on developer interviews we assumed a 5% failure rate (% failed batches) across case studies. This assumption is based on the average failure rate observed across facilities. We noticed failure rates were higher for manufacturing processes new to facilities and decreased over time. If cost estimation is made for processes with different failure rates this should be adjusted accordingly. If one batch yields multiple treatments or doses, post-hoc adjustment is needed to translate these costs into a desired output (e.g., cost/treatment, cost/dose).

Availability and use of costing template

We generated a costing template calculating form (in Microsoft Excel), which is available as Supplemental Material [Costing_Template_blanc.xls] accompanying the online version of this manuscript. The provided template by default applies the costing framework and methodology as described in this research and assumes that the full manufacturing process takes place in one facility.

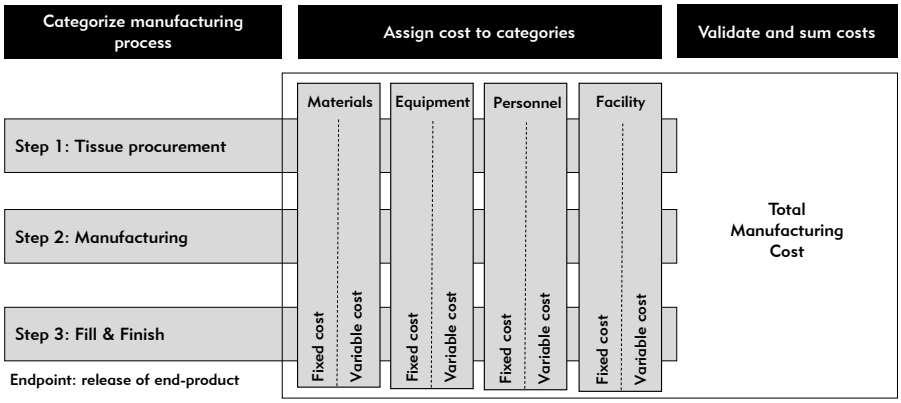

Figure 1. Cell-Based Therapy Manufacturing Costing Framework. Cost categories present both fixed and variable cost.

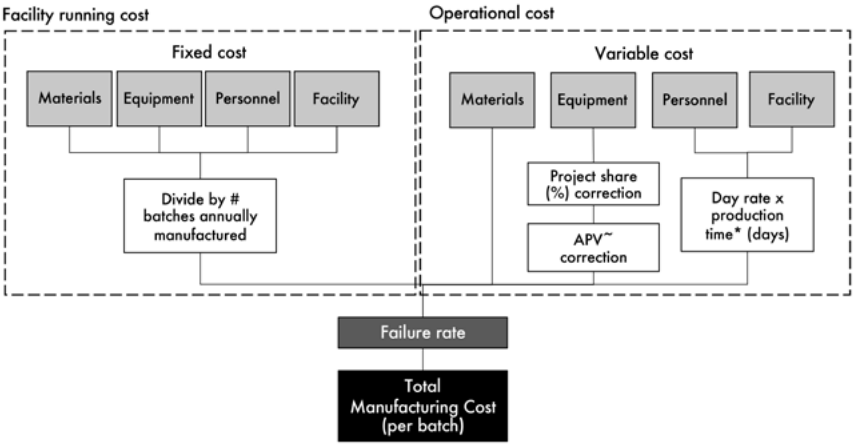

Figure 2. Costing methodology model of fixed and variable cost per cost-categories to calculate manufacturing cost per batch. This analysis ought to be applied for each step in the Cell-Based Therapy Manufacturing Costing Framework. ~APV – Annual Production Volume. * production time is corrected for Facility Active Days (FAD), number of days the facility is available for production. When a batch yields >1, post hoc adjustment is needed to calculate per treatment or per dosing cost.

The authors waive responsibility and liability for use, application, and maintenance of the provided costing tool.

Facility running cost

The sum of fixed cost categories per year was calculated as the annual facility running cost[12,21]. These resources are consumed regardless of whether CBTs are produced or not. Figure 3 shows fixed costs per facility stratified by category, as well as absolute costs and percentage of the cost category in comparison to total facility running costs. Although absolute facility running cost varied, cost category ratios showed similarities between facilities. Note that facility C did not show the fixed material or personnel cost because these could not be separated from the facility costs because of a lumpsum payment agreement between developers and facility C. In this agreement a fixed annual rate is payed and includes facility, materials, QMS, equipment and maintenance. Therefore, the proportional comparison of facility C gives somewhat of a distorted image compared to the other facilities. Across facilities, fixed material cost account for 8-10% of total facility costs. Equipment accounts for 6% of annual running cost of facility B (both departments) and D, with facilities A and C having higher proportional equipment cost of 21% and 23% respectively. Personnel cost is the main driver in Facilities A (41%), B-4 (46%) and B-5 (53%), but not in Facility D (4%).

A similar pattern is seen within the facility-category, where Facility A (30%), Facility B-4 (40%) and B-5 (33%) allocate similar percentage of resources to fixed facility cost. Facility D (80% fixed facility cost) is a more costly facility, both absolute and proportionally. This 80% facility cost however is similar to facility C (77%), but direct comparison between C and D cannot be made due to the specific payment agreement. The high fixed facility cost for facility D can partially be explained

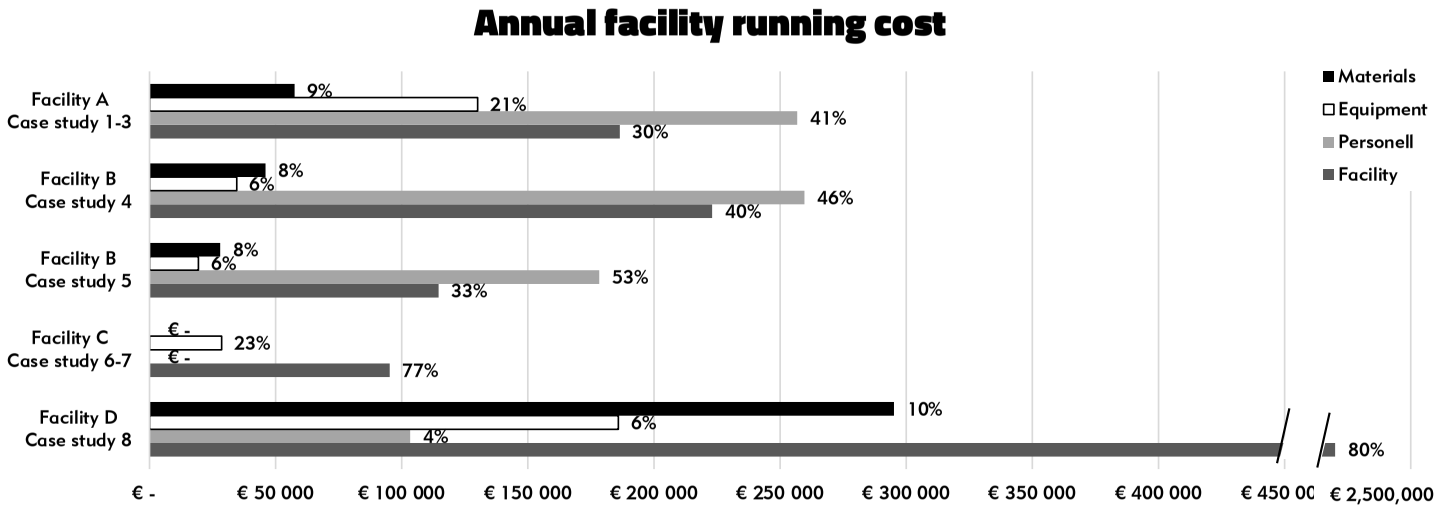

Figure 3. Annual facility running cost per facility. Percentages are proportion of total running cost per facility. Costs are presented in 2018 Euros. Numbers presented are direct measures, meaning they not adjusted for failure rate or doses/batch (post hoc adjustment).

by its novelty. The facility was built in 2016 which results in higher annual depreciation in the first few years after delivery. Also, facility D is the only stand-alone facility in this study. This means the cell facility is not part of a complex, but a detached building. When costing facility D, proportionally more square meters were allocated to office space, reception room, technical areas, and the cost, for example the cafeteria was included. Whereas facilities A, B-4 and B-5 are departments within a larger building complex. Facility A seemingly has lowest facility costs, but it should be pointed out that annual mortgage and utilities were not included as these costs are absorbed by the academic centre and not charged to the facility and developers. In Facility C only cleanrooms, supporting areas and a small office were included.

Operational cost

The sum of variable cost is the product specific operational cost per batch. Total operational and variable cost per category for each case study are shown in Figure 4.

Both absolute and proportional results in Figure 4 show large differences between case studies. This variance can partially be explained by product and facility characteristics. For example, case studies 1, 2, 4, 6 and 8 use specific antigenic peptides, which appear to be a major driver of material costs. Another emerging material cost driver is hypothesized to be the use of platforms (e.g., CliniMACS© or CliniMACS© Prodigy). Use of such platforms requires specific and costly consumables (e.g., cell selection reagents, tubing sets, bags) and buffers purchased from the platform provider. These buffers and consumables are more costly than generic or homemade buffer solutions. Use of these platforms and other specialized equipment (e.g., flow cytometer, closed system harvest device) were also cost drivers in the equipment section. Specialized equipment was used in all case studies with the exception of cost study 7 in which equipment cost accounted for 1% of operational cost respectively. Although costly, the impact of the purchase of such specialized equipment seems to be associated with Annual Product Volume (APV) and project share. It seems that sharing cost of expensive specialized equipment over multiple projects (or routine diagnostics and insured healthcare in case study 5) reduced the impact on the total operational costs. Another example is centre wide equipment sharing in Facility A. Here, departments have a fee-based arrangement to utilize flow cytometers of a centralized FACS unit. Whether project share or APV has more impact cannot be derived due to high case study and facility variability. Although purchasing a platform is a large investment for a small scale developer, it is also thought to reduce labour costs[32].

In the next category, personnel costs seem to correlate with both manufacturing time and the level of manipulations. Resource intensive products with longer manufacturing times (case studies 7 and 8) show higher personnel costs than products with shorter manufacturing timelines and little manual manipulations (case studies 2 and 4). Although caution is warranted in this comparison as 10-day runtime does not necessarily correspond with 10 cleanroom days. Whether sharing of specialized equipment or manufacturing time has more impact cannot be derived from these case studies because of high heterogeneity. In the facility cost category, the variable costs correlate mostly with manufacturing time. This is seen in Facility A with case studies 1, 2 and 3, where manufacturing time is 7, 2 and 28 days respectively. This result is not a surprise as variable facility and personnel costs are both based on a day rate model. Case study 8 from Facility D shows the highest absolute and proportional cost, similar to the fixed cost results. This facility is also the largest facility, both in absolute surface area and m^2 per cleanroom compared to other facilities.

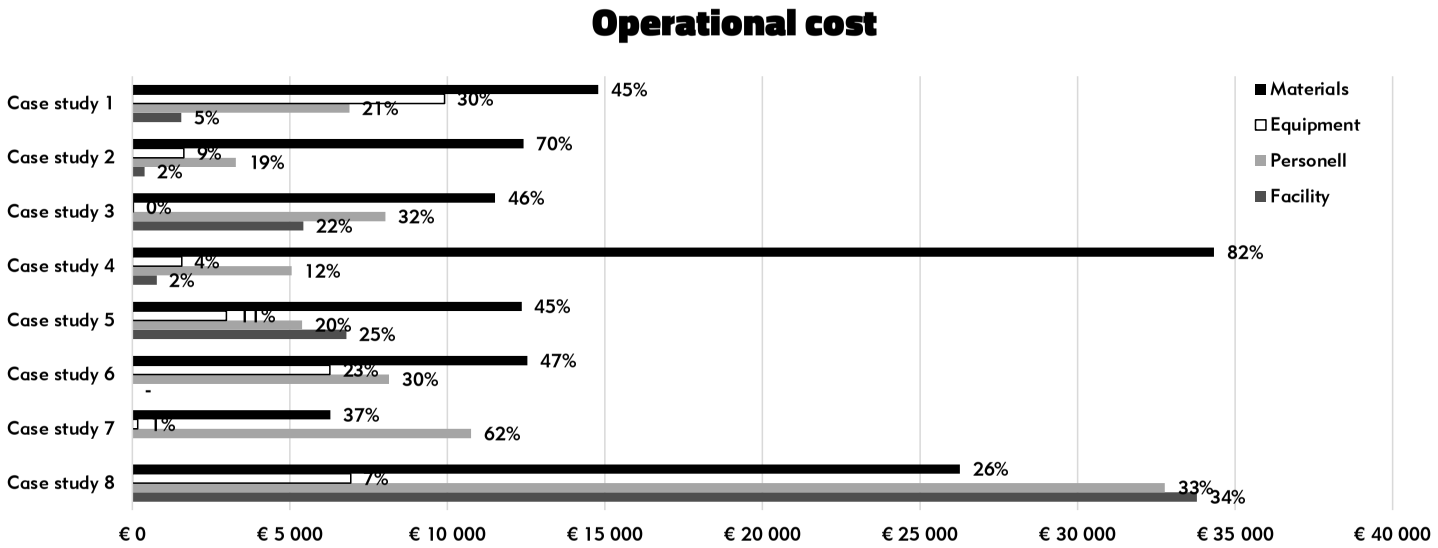

Figure 4. Operational cost presented per case study (per batch). Percentages are proportion of total running cost per facility. Costs are presented in 2018 Euros. Numbers presented are direct measures, meaning they are not adjusted for failure rate or dose/batch (post hoc adjustment).

Total batch cost and failure rate and post-hoc adjustments

Following the presented methodology in Figure 2, the sum of the fixed and variable category cost adjusted by failure rate results in the aggregated per batch manufacturing cost. Results of the application of the framework and methodology to the case studies are presented in Table 2. In case studies 1 to 7, batch cost is equal to per patient treatment cost, whilst case study 8 needs post-hoc adjustment as 1 batch yields 88 doses and can respectively treat 22 patients.

Batch cost is presented as total, fixed, and variable cost. Fixed cost in our case studies account on average for 24% (13-45%) of total cost and variable for 76% (55-87%) of total cost. Total batch costs varied between €21,936 and €181,713 Euros. When adjusted for failure rate and treatment yield cost varied between €8,673 and €53,683 Euros per treatment. Although facility D and case study 8 proved throughout the research to be most resource intensive, after post hoc adjustment the treatment cost result was one of the lowest. This may imply that increase of treatment yield per batch could reduce treatment costs, however this is not feasible for all products and indications (e.g., autologous products and rare indications).

Discussion

In this article, we describe the development of a uniform and transparent framework and methodology to facilitate costing of small-scale cell-based therapy manufacturing. This will help to advance the cell-based therapy field as this is the first method, to our knowledge, that shows demonstrable applicability for estimating costs of CBTs in different facilities with different products[12,14]. Our method showed sensitivity to differences in manufacturing time and resource use. The use and application of the framework and methodology was validated by developers in four different types of facilities across Europe. To facilitate the uptake or our framework and method, we provide a Microsoft Excel costing template as a supplemental document accompanying the online version of this research.

Although not exhaustive, we are confident that the types of facilities included in this study are representative of the majority of facilities currently manufacturing small scale CBTs in Europe[11,33]. Even in facilities where not all information was available, application of our method still yielded insights. For example, in Facility C a payment arrangement was in place which aggregates the fixed materials, personnel and facility costs. Such arrangements are not uncommon. Applying our methodology to this payment agreement, resulted in 'empty' cost categories meaning we have not been able to estimate the true breakdown of costs of CBT production in this facility. Moreover, our study takes the developer perspective. This resulted that for facility A partially and in facility C all overhead costs of the building are borne in full by the owner of the building. We have not been able to retrieve these costs, but it is likely that facilities A and C incur more facility cost than included in this analysis. This is confirmed when roughly comparing facility running costs of facilities A and C with Facility B. By applying our methodology, we were able to provide this insight to the developer and created awareness that if manufacturing of case studies 1-3, 6 and 7 were to be relocated a cost increase should be expected.

Table 2. Total cost per batch and treatment, adjusted for failure rate (assumed 5%) and treatment yield per batch (post hoc adjustment). Total costs are presented in fixed and variable cost, € (%). One treatment can consist of more than one dose.

	Facility A			Facility B		Facility C		
Case study	1	2	3	4	5	6	7	8
Materials	**€ 15,171 (46%)**	**€12,801 (58%)**	**€ 11,897 (41%)**	**€ 35,096 (69%)**	**€ 13,916 (30%)**	**€ 12,542 (39%)**	**€ 6,287 (28%)**	**€ 34,695 (19%)**
Equipment	**€ 5,862 (18%)**	**€ 2,506 (11%)**	**€ 904 (3%)**	**€2,150 (4%)**	**€ 4,063 (9%)**	**€ 7,521 (23%)**	**€ 1,604 (7%)**	**€ 12,247 (7%)**
Personnel	**€ 9,202 (28%)**	**€ 4,997 (23%)**	**€ 9,747 (33%)**	**€ 9,384 (18%)**	**€ 15,296 (33%)**	**€ 8,147 (25%)**	**€ 10,754 (47%)**	**€ 35,723 (20%)**
Facility	**€ 2,801 (8%)**	**€ 1,632 (7%)**	**€ 6,674 (23%)**	**€ 4,496 (9%)**	**€ 13,162 (28%)**	**€ 4,167 (13%)**	**€ 4,167(18%)**	**€ 99,047 (54%)**
Total/batch	**€ 33,036**	**€ 21,936**	**€29,221**	**€ 51,126**	**€ 46,437**	**€ 32,376**	**€ 22,812**	**€ 181,713**
Fixed	*€ 4,206 (13%)*	*€ 4,206 (19%)*	*€ 4,206 (14%)*	*€ 9,389 (18%*	*€ 18,908 (41%)*	*€ 5,419 (17%)*	*€ 5,598 (25%)*	*€ 81,958 (45%)*
Variable	*€ 28,830 (87%)*	*€ 17,730 (81%)*	*€ 25,016 (86%)*	*€ 41,738 (82%)*	*€ 27,529 (59%)*	*€ 26,957(83%)*	*€ 17,214 (75%)*	*€ 99,756 (55%)*
Failure rate adjustment								
Failure rate	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
Total/batch	**€ 34,688**	**€ 23,033**	**€ 30,682**	**€ 53,683**	**€ 48,759**	**€ 33,995**	**€ 23,952**	**€ 190,799**
Fixed	**€** *4,416 (13%)*	*€ 4,416 (19%)*	*€ 4,416 (14%)*	*€ 9,858 (18%)*	*€ 19,854 (41%)*	*€ 5,690 (17%)*	*€ 5,877 (25%)*	*€ 86,055 (45%)*
Variable	**€** *30,272 (87%)*	*€ 18,617 (81%)*	*€26,266 (86%)*	*€ 43,825 (82%)*	*€28,905 (59%)*	*€ 28,305 (83%)*	*€ 18,075 (75%)*	*€ 104,743 (55%)*
Post hoc adjustment								
Treatment yield/batch	1	1	1	1	1	1	1	22
Total/treatment	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	**€ 8,673**
Fixed	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*€ 3,912*
Variable	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*€ 4,761*

Specialized materials and equipment are an important driver of operational cost. Peptides are often custom made in low volume. The low demand corresponding with the novelty of the CBT field means that few vendors are active in the market[10]. Perhaps, when demand for specialized raw materials increases, the specialized material costs will reduce due to increase in competition and supply[23]. Regarding specialized equipment, the majority of the included facilities use platforms. Such platforms allow for partially automated material inputs and manipulations previously performed manually by technicians[34]. Additionally, the use of closed circuit platforms also allows for simultaneous manufacturing of multiple and different CBTs in the same room[9]. With the use of open systems, GMP regulation prohibits manufacturing of more than one CBTs in the same environment to avoid cross contamination[9]. Use of platforms could also decrease facility downtime. Therefore, although the capital investment in platform is significant, the impact on the aggregated manufacturing cost is suggested to decrease when project share and APV increased. To confirm this hypothesis, our framework and methodology can be used in future research to quantify the impact of factors such as platform use, project share and APV to inform best practices.

Another important cost driver we identified was personnel cost (18-47%). This observation is supported by findings in the literature[35,36]. Small batch sizes combined with manual manipulations make automation economically unattractive. Where possible, the development of modular approaches to CBT manufacturing, exploration of the possibility of allogenic material use instead of or in addition to autologous cells and the multi-purposing of existing specialized equipment within the facility could offer opportunities to increase volume throughput[34]. Another option would be to share facilities, equipment, and other resources (e.g., bioreactors) to reduce cleanroom down time, such as is done in facilities A and B. Facility A is available for all hospital departments and has access to a centralized FACS unit. Costs are primary borne by the hospital and pharmacy. Departments compensate for the services utilized. In Facility B, the GMP facility is shared between two departments which results in substantial cost and risk sharing. For case study 5 within Facility B, tissue procurement occurs in a large stem cell processing facility. Whether this substantially lowers costs cannot be concluded due to product and facility heterogeneity. But in general, when developing and planning manufacturing processes developers should strive to minimize equipment and facility down time.

It is important to realize that the timing of expenses and income differ substantially. The cost estimates presented in this research suggest that operational costs are incurred at time of production and that facility running costs are spread on an annual basis. However, a majority of costs are often incurred far before manufacturing in the form of substantial capital investments needed to build GMP facilities, purchase equipment and hire personnel. Also, the highly skilled personnel required to develop, and manufacture CBTs needs to be hired upfront and are most often not full-time occupied by product manufacturing or development. These high upfront investments are considerable, especially for small developers. While above mentioned, increasing production volume and batch yield could reduce costs considerably, not all products or indications allow or require upscaling. An example of a shared public-private facility with expertise is the Cell and Gene Therapy Catapult in the United Kingdom[37], providing infrastructure and expertise for translation and early-phase manufacture to help overcome development challenges (e.g. safety, effectiveness, scalability). Institutions like these could help small scale developers advance their products without having to make speculative and substantial high upfront investment.

Limitations of framework and methodology

Despite our best efforts, this study has limitations. First, by distributing the facility running costs over total batches manufactured per year we assume that all batches consume similar resources. This may overestimate the fixed costs for products requiring limited manufacturing time or minimal manipulation. Similarly, this may underestimate the fixed costs for resource intensive products. However, in a GMP environment the manifold or shared quality assurance measures cannot be segmented as all are required to manufacture a CBT. This, combined with the aim of designing a workable methodology may rationalize this approach[14]. Second, use of day-rates when estimating variable personnel and facility costs is known to somewhat underestimate resource use[14]. The day-rate approach assumes a facility is at full capacity, and any down-time is considered a loss. We partially corrected for this underestimation with an adjustment for facility active days (FADs). The developers mentioned in the interviews that facility downtime was expected to decrease when experience and predictability of manufacturing process increased. Nonetheless facility downtime should be minimized, as the fixed running and maintenance costs account for a large percentage of total costs (13-45%). Third, in our study we did not include the costs to recruit, hire and train personnel. Although out of scope of this research, one could argue that skills also experience some sort of depreciation which require continues training. Additionally, the most recent UK cell and gene therapy skills demand report foresees shortage of highly skilled individuals[38]. The report expresses high concerns around education, recruitment, and retention of skilled individuals, especially in process development and manufacturing. Fourth, in our framework we distinguish three manufacturing steps. We specifically defined these steps, as they may occur in different environments, at different time points or are paid out of different budgets. When the steps defined in our framework are not applicable the provided costing template can be modified to fit the end-users needs. The same applies to the applied perspective, which in this research is a developer perspective. To facilitate application of our framework and method, the template can be modified to reflect a hospital or departmental perspective. However, we do not encourage this practice as modifications decrease the comparability of estimates between facilities and products. Also, the current framework and method are validated for the context as described in this research. Last, the heterogeneity of the included case studies in different facilities impedes direct comparison between products and reduces our learnings of cost-drivers and best practices from this research. Ultimately, the main objective of this research was to develop a costing methodology. The heterogeneity of the case studies may reflect the large variety of CBTs currently applied in clinical practice. With our framework and methodology, future research may address identification of cost drivers and development of best practices across a broader range of examples. Other directions for future research could be exploration of the applicability of this framework and methodology towards (cell-based) gene therapies. Gene therapies are, together with CBTs, part of the Advance Therapy Medicinal Product group[2]. Expansion and validation of our framework and methodology would increase external validity.

We emphasize that the estimates given in our research only reflect manufacturing costs and under no circumstances should be confused with product price. We stress that this framework and methodology is designed and currently only validated for application in a routine manufacturing environment. Our estimates do not include costs incurred in other stages of medicinal product development such as Research & Development (R&D), manufacturing set-up, preclinical development, animal testing,

clinical development and if applicable regulatory costs of applying for Market Authorization as well as clinical cost of the treatment. The price of a product includes more than the manufacturing costs alone[18,39,40].

Strengths of framework and methodology

The heterogeneity of included facilities and case studies can also be seen as a strength of our study. Our framework and methodology were deemed applicable across facilities and products and was validated by experts increasing the generalizability and potential uptake of our work. Another strength is use of the ABC method. This bottom-up approach has proven particularly useful to estimate costs of the tailored, highly manual and small scale manufacturing processes[10], which reflects the current state of CBT manufacturing. Via co-creation with biomedical researchers and clinicians we aimed to develop a framework and methodology operable for developers with little or no experience in costing problems and also, we added a costing template to increase uptake. When using the template, it is important to realize that the cost estimate is a reflection of the manufacturing process at that point in time. This means, if changes occur in any of the cost-categories the cost estimate is outdated. However, the template allows the user to update items independently to address technical advances or change in the cost of goods without having to redo the complete analysis. Last, this research reiterates how developers and researchers can benefit from collaborations outside their specific field of research[14,41]. In this research collaboration between biomedical researchers with regulators and health economists resulted in the described framework and methodology. The costing template was found to provide step-by-step guidance to CBT developers to cost their manufacturing process, as well as gain insights in cost drivers and efficiency gains. We observed a majority of the developers undervalue their resources leading to too optimistic budgeting and low (external) setting. In the short term these unaccounted costs are likely to be absorbed in facility budgets or start-up subsidies. Long-term realistic costings are important to, for example, further facilitate sustainable translation of CBTs to the clinic, ensure financial stability of facilities. This latter is particularly relevant when quantity and volume of CBTs increase or when manufacturing locations are moved due to product scale-out or spin-off. Insights from this costing exercise have already been used by participating developers, for example in grant applications and adjustments in individual facility service and product cost settings.

Conclusion

To our knowledge, this is one of the first study aiming to develop a uniform and transparent framework and methodology to estimate the cost of cell-based therapies manufacturing. The framework and template have proven applicable in different facilities with different products and shown to be sensitive to capture differences in time and resources use. Developers found that the framework and methodology gave them step-by-step guidance in estimating the cost of CBTs. Manufacturing CBTs brings both technological and financial challenges. To advance the development and patient access to these promising products resources should be efficiently allocated, starting with gaining insights in cost drivers and increasing efficiency. This research contributes to more accurately estimate CBT manufacturing cost estimates in order to inform and plan cost-conscious strategies.

Declaration of competing interest

The NK cell product of case B-5 is manufactured according to a proprietary protocol. Other authors declare to have no commercial, proprietary, or financial interest in the products, companies or facilities described in this article.

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References

1. Burt RK, Balabanov R, Burman J, et al. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients with Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. *JAMA - J Am Med Assoc*. 2019;321(2):165-174. doi:10.1001/jama.2018.18743

2. The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council. *Off J Eur Union*. 2007;324((EC)1394/2007):121-138. http://data.europa.eu/eli/reg/2007/1397/oj.

3. Han W, She Q. *CRISPR History: Discovery, Characterization, and Prosperity*. Vol 152. Elsevier Inc.; 2017. doi:10.1016/bs.pmbts.2017.10.001

4. Wirth T, Parker N, Ylä-Herttuala S. History of gene therapy. *Gene*. 2013;525(2):162-169. doi:10.1016/j.gene.2013.03.137

5. Aiuti A, Roncarolo MG, Naldini L. Gene therapy for ADA-SCID, the first marketing approval of an ex vivo gene therapy in Europe: paving the road for the next generation of advanced therapy medicinal products. *EMBO Mol Med*. 2017;9(6):737-740. doi:10.15252/emmm.201707573

6. Soofiyani SR, Baradaran B, Lotfipour F, Kazemi T, Mohammadnejad L. Gene therapy, early promises, subsequent problems, and recent breakthroughs. *Adv Pharm Bull*. 2013;3(2):249-255. doi:10.5681/apb.2013.041

7. Hanna E, Toumi M, Dussart C, et al. Funding breakthrough therapies : A systematic review and recommendation. *Health Policy (New York)*. 2018;122(3):217-229. doi:10.1016/j.healthpol.2017.11.012

8. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. *Cell Stem Cell*. 2016;19(3):293-297. doi:10.1016/j.stem.2016.08.012

9. European Comission. *Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products*. Vol Volume 4. Brussels; 2017. doi:10.1093/oxfordhb/9780199546282.013.0024

10. ten Ham RMT, Hoekman J, Hövels AM, Broekmans AW, Leufkens HGM, Klungel OH. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Mol Ther - Methods Clin Dev*. 2018;11(December):121-130. doi:10.1016/j.omtm.2018.10.003

11. de Wilde S, Guchelaar H-J, Zandvliet ML, Meij P. Clinical development of gene- and cell-based therapies: overview of the European landscape. *Mol Ther - Methods Clin Dev*. 2016;3(July):16073. doi:10.1038/mtm.2016.73

12. Abou-El-Enein M, Römhild A, Kaiser D, et al. Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: A novel tailored model for optimizing performance and estimating costs. *Cytotherapy*. 2013;15(3):362-383. doi:10.1016/j.jcyt.2012.09.006

13. Gardner J, Webster A, Barry J. Anticipating the clinical adoption of regenerative medicine: Building institutional readiness in the UK. *Regen Med*. 2018;13(1):29-39. doi:10.2217/rme-2017-0121

14. Boeke A, Doumas P, Reeves L, et al. Vector Production in an Academic Environment: A Tool to Assess Production Costs. *Hum Gene Ther Methods*. 2013;24(1):49-57. doi:10.1089/hgtb.2012.213

15. Nagpal A, Milte R, Kim SW, et al. Economic Evaluation of Stem Cell Therapies in Neurological Diseases: A Systematic Review. *Value Heal*. 2019;22(2):254-262. doi:10.1016/j.jval.2018.07.878

16. Retèl VP, Steuten LMG, Geukes Foppen MH, et al. Early cost-effectiveness of tumor infiltrating lymphocytes (TIL) for second line treatment in advanced melanoma: A model-based economic evaluation 14 Economics 1402 Applied Economics. *BMC Cancer*. 2018;18(1):1-11. doi:10.1186/s12885-018-4788-5

17. Zimmermann M, Lubinga SJ, Banken R, et al. Cost Utility of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease. *Value Heal.* 2019;22(2):161-167. doi:10.1016/j.jval.2018.09.2841

18. Uyl-De Groot CA, Löwenberg B. Sustainability and affordability of cancer drugs: A novel pricing model. *Nat Rev Clin Oncol.* 2018;15(7):405-406. doi:10.1038/s41571-018-0027-x

19. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ.* 2016;47:20-33. doi:10.1016/j.jhealeco.2016.01.012

20. Tan SS, Rutten FFH, Van Ineveld BM, Redekop WK, Hakkaart-Van Roijen L. Comparing methodologies for the cost estimation of hospital services. *Eur J Heal Econ.* 2009;10(1):39-45. doi:10.1007/s10198-008-0101-x

21. Lennerts K, Diez K. A process-oriented analysis of facility management services in hospitals as a basis for strategic planning. *J Facil Manag.* 2009;7(1):52-60. doi:10.1108/14725960910929565

22. Roberts RR, Gussow LM, Kampe LM, et al. Distribution of variable vs fixed costs of hospital care. *J Am Med Assoc.* 1999;281(7):644-649. doi:10.1001/jama.281.7.644

23. Acemoglu D, Laibson D. *Economics.* Global 1st. (List J, ed.). London, UK: Pearson Education Limited; 2015.

24. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes.* Vol 2. 2nd ed. (Cartwright WS, ed.). Oxford University Press; 1999.

25. Arjmand MD, MMM, PhD EM, Hillegeist PhD SA, Caldwell JD HM, et al. Cost allocation can be as simple as A-B-C. *Physician Leadersh J.* 2018;5(4):34-38. https://search.proquest.com/docview/2069490216?accountid=10297%0Ahttp://resolver.ebscohost.com/openurl?ctx_ver=Z39.88-2004&ctx_enc=info:ofi/enc:UTF-8&rfr_id=info:sid/ProQ%3Aabiglobal&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rft.genre=article&rft.jtitle=Ph.

26. Misono AS, Oklu R, Prabhakar AM. Time-driven activity-based costing trumps traditional cost accounting for radiologists. *AJR Am J Roentgenol.* 2015;204(2):W217. doi:10.2214/AJR.14.13258

27. Centraal Bureau voor Statistiek (CBS). Statistics Netherlands. https://www.cbs.nl/. Published 2019. Accessed January 1, 2019.

28. OECD. Purchasing power pararities (PPP) (indicator). https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm. Published 2019. Accessed July 1, 2019.

29. Tan SS, Bouwmans CAM, Rutten FFH, Hakkaart-van Roijen L. Update of the Dutch Manual for Costing in Economic Evaluations. *Int J Technol Assess Health Care.* 2012;28(2):152-158. doi:10.1017/S0266462312000062

30. Van Nimwegen KJM, Van Soest RA, Veltman JA, et al. Is the 1000 genome as near as we think? A cost analysis of next-generation sequencing. *Clin Chem.* 2016;62(11):1458-1464. doi:10.1373/clinchem.2016.258632

31. Samson D, Slaper-Cortenbach I, Pamphilon D, McGrath E, McDonald F, Urbano Ispizua A. Current status of JACIE accreditation in Europe: A special report from the Joint Accreditation Committee of the ISCT and the EBMT (JACIE). *Bone Marrow Transplant.* 2007;39(3):133-141. doi:10.1038/sj.bmt.1705564

32. Hümmer C, Poppe C, Bunos M, et al. Automation of cellular therapy product manufacturing: Results of a split validation comparing CD34 selection of peripheral blood stem cell apheresis product with a semi-manual vs. an automatic procedure. *J Transl Med.* 2016;14(1):1-7. doi:10.1186/s12967-016-0826-8

33. de Wilde S, Guchelaar HJ, Herberts C, et al. Development of cell therapy medicinal products by academic institutes. *Drug Discov Today.* 2016;21(8):1206-1212. doi:10.1016/j.drudis.2016.04.016

34. Moutsatsou P, Ochs J, Schmitt RH, Hewitt CJ, Hanga MP. Automation in cell and gene therapy manufacturing: from past to future. *Biotechnol Lett.* 2019;41(11):1245-1253. doi:10.1007/s10529-019-02732-z

35. Gardner J, Faulkner A, Mahalatchimy A, Webster A. Are there specific translational challenges in regenerative medicine? Lessons from other fields. *Regen Med.* 2015;10(7):885-895. doi:10.2217/rme.15.50

36. Viganò M, Giordano R, Lazzari L. Challenges of running a GMP facility for regenerative medicine in a public hospital. *Regen Med.* 2017;12(7):803-813. doi:10.2217/rme-2017-0051

37. The catapult network by Innovate UK. Cell and Gene Therapy Catapult. ct.catapult.org.uk. https://ct.catapult.org.uk/. Published 2019. Accessed December 13, 2019.

38. Cell and Gene Therapy Catapult. *UK Cell and Gene Therapy Skills Demand Report 2019*. London, UK; 2019. https://ct.catapult.org.uk/sites/default/files/publication/Catapult_01_UK Skills Demand Report 2019_published_v2.pdf.

39. Ermisch M, Bucsics A, Bonanno PV, et al. Payers' views of the changes arising through the possible adoption of adaptive pathways. *Front Pharmacol.* 2016;7(SEP):1-9. doi:10.3389/fphar.2016.00305

40. Jørgensen J, Kefalas P. Annuity payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. *J Mark Access Heal Policy.* 2017;5(1):1355203. doi:10.1080/20016689.2017.1355203

41. Belardelli F, Rizza P, Moretti F, Carella C, Galli MC, Migliaccio G. Translational research on advanced therapies. *Ann Ist Super Sanita.* 2011;47(1):72-78. doi:10.4415/ANN_11_01_15

2.3

Estimation of manufacturing development cost of cell-based therapies

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Abstract

Cell-based therapies provide opportunities to treat rare and high burden diseases. Manufacturing development of these innovative products is said to be complex and costly. However little research is available providing insight into resource use and cost drivers. Therefore, this study aimed to assess feasibility of estimating cost of manufacturing development of two cell-based therapy case studies using a CBT-cost-framework specifically designed for small-scale cell-based therapies.

A retrospective costing study was conducted in which cost was estimated of development of an adoptive immunotherapy of Epstein-Barr Virus-specific cytotoxic T-lymphocytes (CTL) and a pluripotent stem cell (PSC) master cell bank. Manufacturing development was defined as products advancing from Technology Readiness Level (TRL) 3 to 6. The study was conducted in a Scottish facility. Development steps were recreated via developer focus groups. Data was collected from facility administrative and financial records and developer interviews.

Application of the manufacturing cost framework appeared feasible to retrospectively estimate cost of manufacturing design of two case studies in one Scottish facility. Manufacturing development cost was estimated at £1,201,016 for CTLs and £ 494,456 for PSC. Most cost were accrued in the facility domain (56% and 51% respectively), followed by personnel (20% and 32%), materials (19% and 15%) and equipment (4% and 2%).

Based on this study, it seems feasible to retrospectively estimate resources consumed in manufacturing development of cell-based therapies. This fosters for inclusion of cost in formulation and dissemination of best practices to facilitate early and sustainable patient access and inform future cost-conscious manufacturing design decisions.

Introduction

Cell-Based Therapies (CBTs) are promising products bringing new opportunities for treatment of rare and high burden diseases[1]. CBTs include cell therapy medicinal products and tissue engineered products, which are part of an innovative group of pharmaceuticals in Europe formally defined as Advanced Therapy Medicinal Products (ATMPs)[2]. CBTs contain autologous, allogeneic or xenogeneic cells and tissues, which have been substantially manipulated, resulting in a change of their biological characteristics[3]. Translation of CBTs from laboratory setting to effective and safe treatments is a breakthrough in both medicine and biomedical science[4,5].

Since CBTs are regulated as medicinal products they must comply with specific requirements set by regulatory bodies such as the European Medicines Agency (EMA) in Europe or Food and Drug Administration (FDA) in the United States of America [2,3]. Overall these regulations aim to ensure patient safety, product quality, data validity and reproducibility, and eventually effective medicinal products with a positive benefit-risk balance[6]. Like other medicinal products, CBTs are also required to be manufactured under Good Manufacturing Practice (GMP) conditions[7]. Translating conventional medicinal product GMP-requirements to CBTs is however challenging for both regulators and developers[8]. To facilitate development, European regulators have issued several guidelines and directives specifically for ATMPs (which include CBTs)[7].

Each CBT, as well as its manufacturing process, can be considered unique. Design of manufacturing processes is not routine practice and subject to rapid technical and scientific advancements[9,10]. In contrast to more conventional medicinal products, CBTs are more-often developed by public institutions (such as academic centres or hospitals) or Small and Medium-sized Enterprises (SMEs)[11]. This is attributed to the highly innovative and technologically complex characteristics of these products. In addition, batches of products are often personalized for individual patients. To advance product manufacturing, diverse strategies are explored, such as centralized manufacturing, up- and out-scaling, automation, use of platforms and bioreactors[12–14]. Public facilities and SMEs are known to have strong innovator capabilities but demonstrate less experience in structural incorporation of regulatory and economic considerations[15,16]. Additionally, these types of developers have lower reserves of finance and product development experience at their disposal compared to large established commercial companies.[17]

Recently, experiences and best-practices of CBT design and manufacturing are appearing in the literature[18–21]. So far, these best-practices are on a case-by case basis and focus mainly on technical and quality aspects[22,23]. Alongside the technical experiences and challenges, developers mention that the development is resource intensive and emphasize the importance of including development costs in the design process[24,25]. They describe that investments are substantial, risks high and materials costly. Yet, to our knowledge so far little or no literature is available which quantifies the cost of manufacturing development or apparent cost consequences of design decisions.

Due to the complex and highly regulated CBT environment, design decisions in manufacturing development can substantially affect downstream product development[26]. Consequently, cost considerations in manufacturing design, as well as insights into the financial consequences of

design decisions, are of importance to further facilitate translation of CBTs towards sustainable patient access to viable medicinal products[27]. Previous research does provide several models and frameworks to cost the manufacturing of CBTs, specifically in academic and small-scale settings[8,28,29]. Yet, it seems none describe costing of manufacturing development. Of the available frameworks two in particular are developed specifically for CBTs across multiple facilities[8,28]. One in particular has our interest, as it provides a ready to use costing tool[28]. Although the authors focus on costing of established manufacturing processes, exploration of applicability of this framework in manufacturing development could aid and cater to the need to include cost in the design of CBT manufacturing development.

Therefore, the primary objective of this study was to assess the feasibility of estimating cost of manufacturing development of two cell-based therapies in a publicly funded Cell and Tissue Centre in Scotland using a novel cost framework and methodology. The insights from these two case studies may be used to accommodate inclusion of cost in the design of CBT manufacturing development and inform cost-conscious decisions towards accelerated and sustainable clinical adoption.

Methods

Study design

A retrospective costing study was conducted in which resources consumed in manufacturing development of two cell-based therapy case studies were estimated. Manufacturing development was defined as products advancing from Technology Readiness Level (TRL) 3 to -and meeting all requirements of- TRL 6[30]. The study was conducted at the *Tissues, Cells and Advanced Therapeutics* (TCAT) department at the Scottish National Blood Transfusion Service in Edinburgh, Scotland. Cost estimates were obtained using a framework and methodology designed specifically for application in small-scale CBT manufacturing (hereafter referred to as *CBT manufacturing cost framework*). Detailed development and validation of this CBT manufacturing cost framework is described elsewhere[28]. Here, authors adhered to definitions and resources allocation guidance as depicted in the original CBT manufacturing cost framework publication[28].

Technology readiness levels

Technology Readiness Levels were first defined in the 1970s by the National Aeronautics and Space Administration (NASA) as an indicator for the maturity level of evolving innovative technologies during early operational development[31]. Since that time, this framework has increasingly been applied outside of aeronautics. From 2011 onwards, TRLs were implemented in European policies as a uniform measure to compare development maturity of different technology across sectors. An example is its use in the European framework program Horizon2020 (H2020)[30]. Figure 1 shows the TRL-framework translated to regenerative medicines[17,32]. This figure visualizes the context of TRLs and CBTs in comparison to more traditional drug development milestones as well as differences in developer types and main funders[32]. Individual TRLs are defined as a product hitting the level-specific development milestone[30]. If a product has successfully achieved the milestone(s), it will advance to the next TRL.

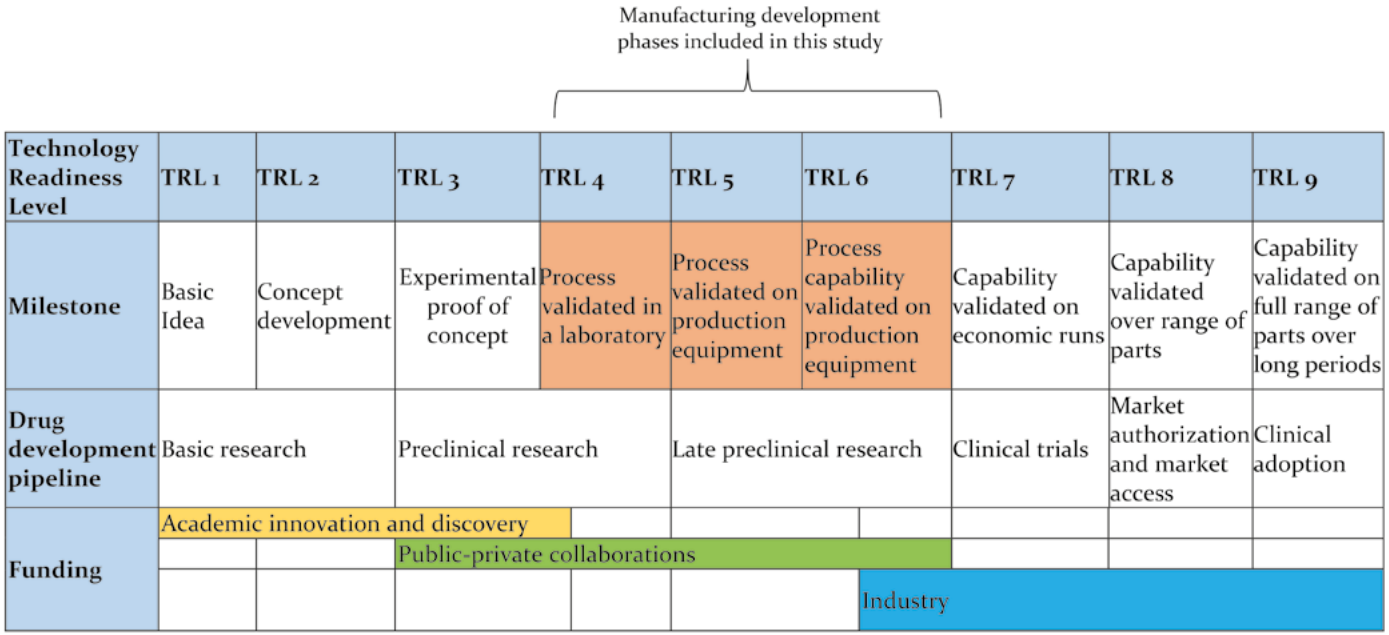

Figure 1. Technology Readiness Levels (TRLs) in cell-based therapy (CBT) manufacturing development. Figure adopted from written evidence by Prof. Chris Mason[17,32].

Facility and case study characteristics

Data was collected within the Tissues, Cell and Advanced Therapeutics (TCAT) department located at the Jack Copland Centre (JCC) in Edinburgh, Scotland[33]. TCAT is a specialized unit of the Scottish National Blood Transfusion Service (SNBTS) that have development facilities and Medicines and Healthcare products Regulatory Agency and Human Tissue Authority (MHRA/HTA) licensed GMP manufacturing facilities for cell and tissue products[33]. TCAT is one of several directorates of the SNBTS (e.g., blood manufacturing and testing), which is an NHS funded organization. TCAT performs internal research and development. They also offers expertise and development services to academics and early stage cell and gene therapy developers with the overall aim to develop safe, effective, scalable and affordable products[33,34]. This expertise includes scientific, analytics and process development, quality, regulatory and clinical expertise. Externally developed products have usually reached TRL 4 when brought to TCAT for further development and support.

Often the true origin of a research idea is difficult to trace back as many products are built on pre-existing techniques or theories. Combining this limitation with the normal practice of the JCC facility to undertake development of external products from TRL 4 onwards, resulted in exclusion of TRL 1-3 in this research. Continuing down the product pipeline, a product reaching TLR 6-7 will transition into pre-clinical testing, manufacturing, or will form the basis of an application for additional funding. The initial research and development phase is considered complete. At this point TCAT may be contracted to manufacture the product, or the processes is transferred. This results in products often leaving the JCC facilities and moving towards larger (commercial) facilities, Contract Manufacturing Organizations (CMOs) or the developer may opt for industry acquisition. We therefore excluded TRL 7 and above (i.e., animal studies, clinical trials etc).

Case studies were selected based on the following criteria:

- Manufacturing development (TRL 4-6) occurred at the SNTBS's Tissue, Cell and Advanced Therapeutics department, and
- Manufacturing steps and decisions are documented and available, and
- Cost associated with these manufacturing steps and decisions are documented and available, and
- People involved in the manufacturing development are still associated with JCC and/or were prepared to contribute to this research.

These criteria yielded two CBTs which acted as case studies:

1. adoptive immunotherapy of Epstein-Barr Virus-specific cytotoxic T-lymphocytes [35,36], and
2. pluripotent stem cell (PSC) master cell bank[37].

Case study i) is an adoptive immunotherapy of Epstein Barr Virus (EBV)-specific cytotoxic T-lymphocytes (CTLs) indicated for post-transplant lymphoproliferative disease (PTLD)[36]. EBV-specific CTLs are isolated from leukapheresis donations of healthy EBV-seropositive donors and subsequently expanded *in vitro* to generate multiple patient doses [35]. CTLs from multiple donors with different Human Leukocyte Antigen (HLA) types are manufactured as an allogeneic bank and are issued on-demand for one PTLD patient at a time on a partially HLA-matched basis. For this product TRL 7 and further costing data was retrievable. Yet, to increase comparability between case studies only TRL 4-6 were included in this study.

Case study ii) is a manufacturing intermediate master cell bank of pluripotent stem cells (PSC). PSC may be either embryonic or induced pluripotent and are expanded in the form of stable cell lines. From these established lines, seed lots or master cell banks can be established, enabling the PSCs to be transported to other facilities or companies for differentiation into various tissues.[37] The manufacturing process was developed for up to 400 vials. Table 1 shows case study characteristics. Non-proprietary technical and scientific details are described in detail elsewhere [21,35–38].

Data collection and analysis

Data was collected within the TCAT-department located at the JCC in Edinburgh, Scotland between February and July 2019. First, per case study a focus group was organized in which participants together aimed to reconstruct per product a timeline describing milestones and collectively recollect development decisions. Focus group participants were SNBTS-employees directly involved (current and past) in the manufacturing development of each product. The reconstructed timelines were drafted by an author (JN) based on the focus-group input and circulated amongst the developers to ensure content and face validity[39,40].

Next, costs were collected. In line with the CBT manufacturing cost framework, development activities were matched with resources consumed [28]. Costs were collected per TRL and divided into four domains (materials, equipment, personnel and facility) [28,41]. Cost and resource use were collected using the costing tool (excel template) provided by the CBT manufacturing cost framework. Utilized data sources were: manufacturing flowcharts, facility purchase-, payroll-, and contracting administration, quality management system (QMS) documentation, supplier catalogues, floor plans and billing documents. Additionally, data was collected via developer interviews. Historic versions of QMS-documents were used to trace back changes in manufacturing development activities and both refine and validate reconstructed product timelines.

For materials and equipment, list prices were used. Personnel costs were derived from SNBTS wage agreements. Facility costs were calculated using fixed and variable facility costs allocated per square meter[28]. In this study we applied an opportunity cost approach[42]. This means we costed all time and resources spent in developing the manufacturing process, which therefore could not be

Table 1. Case study characteristics.

	Case study 1	Case study 2
Product description	Anti-EBV cytotoxic T lymphocytes	Pluripotent Stem Cells (PCS)
Indication	Post-transplant lymphoproliferative disease	Source of cells for metabolic, degenerative, and inflammatory diseases
Cell/tissue procurement	Apheresis	-
Product origin	Allogeneic peripheral blood	Existing PSC lines
Manufacturing time	3 weeks	6 weeks + 2 months extended testing
Development time (TRL 4 to 6)	45 months	10 months
Product developer	Public developer	Public developer

EBV – Epstein Barr Virus, GMP – Good Manufacturing Practices.

used for other purposes. For example, cost of partially used materials with limited shelf-life which exceeded their expiration date was allocated fully to the case study. Although perhaps only partially used, this e.g., peptide or buffer had to be discarded.

Costs were expressed in 2019 Pound Sterling (£). Costs obtained in different years were adjusted for inflation to 2019 prices using price index numbers[43]. This adjustment is in line with guidelines for economic evaluation in healthcare[44,45].

Results

Product development and timelines

The focus groups yielded detailed product development roadmaps. Figure 2 shows a condensed summary of these roadmaps for case study 1 (Figure 2A) and case study 2 (Figure 2B).

In case study 1, initial research to generate EBV-specific CTLs using newer technology by way of IFNγ selection was done in-house (see Table 1 for product characteristics). The first step of manufacturing development in TRL 4 entailed a proof-of-principle of IFNγ isolation at small scale using buffy coats and development of flow cytometric QC assays. In TRL 5 platform technology (CliniMACS Prodigy™ by Miltenyi Biotec®, GatheRex™ and G-Rex flasks by Wilson-Wolf®) was introduced using multiple buffy coats mixed together as starting material to mimic full scale processes (instead of leukapheresis) to minimize the start material costs. Introduction of this platform automized isolation of virus-specific cells from starting material. In TRL 6 platform use and manufacturing were optimized using a commercial leukapheresis product. Since the final EBV CTL product is cryopreserved until issued to patient, many of the bagged doses generated are used not only in the final product quality release testing, but also at regular time-points in an ongoing stability program to ensure the frozen cell products are still viable and efficacious years after manufacture. Therefore, it was crucial to fully optimize the full-scale expansion such that a single manufacturing process could generate enough cells for all analytical testing as well as treating numerous patients, with final stage development typically generating 100-150 doses at $1.5x10^8$ CTLs/ dose.

Given the dosage regimen for PTLD is 4 doses over a monthly period per patient, and accounting for doses used in analytical testing, a single manufacturing process therefore would aim to treat 20-30 patients. In TRL 6 the development was moved from a research (non-GMP) laboratory to a development suite for the development of a process under GMP (closed system in a grade D environment). Additionally, in TRL 6 quality and regulatory experts were involved in the development process. These experts co-developed, among other things, standard operating procedures (SOPs), risk assessments, supply chain maps and microbial control strategies. At the end of TRL 6, case study 1 was considered 'GMP-ready', meaning the product was in accordance with GMP-guidance and ready to advance to TRL 7[7]. TRL 7 entails manufacturing process validation runs in a GMP environment, after which (TRL >7) routine manufacturing (e.g. clinical studies) can commence[17,32].

The manufacturing development time of case study 1 was approximately 42 months (Figure 2A). This was mainly driven by TRL 4. While previous iterations of the EBV-specific CTL products had

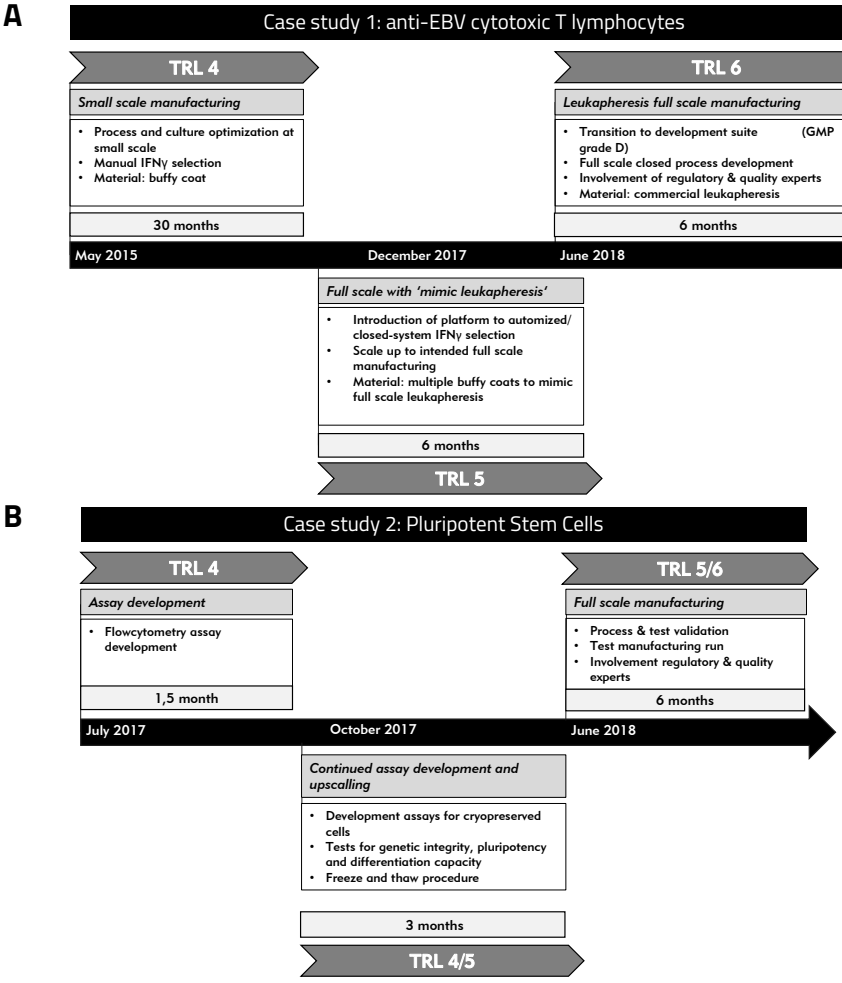

Figure 2. Product development timeline summary of anti-EBV cytotoxic T lymphocytes (figure 2A, case study 1) and Pluripotent Stem Cells (figure 2B, case study 2) displayed per Technology Readiness Level (TRL) EBV-Epstein-Barr virus; TRL- Technology Readiness Level; IFN – interferon; GMP – Good Manufacturing Practices.

been developed at SNBTS many years prior, introduction of new technology and comprehensive contemporary characterization assays to meet current regulatory requirements was time consuming and described as the main driver in the development time of this product. Additionally, between TRL-transitions developers changed starting materials (from buffy coat to mimic-leukapheresis product and commercial leukapheresis product) which required some adjustments. When composing the development timeline, it was possible to clearly distinguish when one TRL was complete and the next started because most of the development was done by one researcher.

In case study 2 manufacturing development in TRL 4 started with assay development (cell characterization and cell count). See Table 1 for product characteristics. Moving to TRL 5, assay development was continued (i.e., surface marker expression flow cytometry, stem cell differentiation, single-nucleotide polymorphism (SNP) analysis for genetic integrity). Also, the freeze and thaw process was designed. Similar as in case study 1, regulatory and quality experts were involved in TRL 6. Their involvement entailed process review, validation and documentation. TRL6 completion yields pluripotent stem cells which are an intermediate product. TRL 4-6 development took place in a research and development laboratory. Development was not dependent on specific equipment or conditions, so could thereafter go straight to cleanroom validation. Development in the research suite was not needed.

Manufacturing development time of case study 2 was considerably shorter (± 11 months) compared to case study 1. Although several assays needed to be developed, the time needed to do so was also shortened as multiple researchers worked simultaneously on the manufacturing development. Consequently, more people being involved in the development on concurrent workstreams, led to less clear distinction of TRLs over time, as can be seen in Figure 2B.

The case study 2 product is somewhat different to case study 1, as the manufactured product would be a Master Cell Bank (MCB) comprised of stocks of cells that will be used for further manufacturing not direct clinical use. This PSC product is therefore categorized as a manufacturing intermediate, but the level of process control is equivalent to that of a final product. Also, as the MCB may be used as starting material that may be used to treat large numbers of people the testing demands are high, requiring analysis for an extensive panel of human and animal viruses and other adventitious agents. Given the scope and specialist nature of this testing it would be outsourced to a contract laboratory rather than developed internally alongside other QC testing, costs for this testing are not incorporated here.

Manufacturing development cost estimates

Following the methods outlined by the CBT manufacturing cost framework, fixed and variable cost were collected and allocated across predefined domains: materials, equipment, personnel and facility. The estimates of consumed resources per domain to elevate case study 1 and 2 from TRL 4 (research grade) to TRL 6 (GMP-ready) are shown in Table 2.

Total estimated manufacturing development cost of case study 1 was £1,201,016, and of case study 2 £494,456. Cost estimate in case study 1 is considerable higher than in case study 2. Relative resource use per TRL is 54% (TRL4), 22% (TRL5), 24% (TRL6) and 12% (TRL4), 22%(TRL5) and 66% (TRL6) for case study 1 and 2 respectively. These are crude estimates taking no development variances into account. In case study 1 cost seems to decrease from TRL 4 to 6, while in case study 2 an opposite trend is seen. Taking time into account, we observe time per TRL decreases for case study 1 (Figure 2A) and an increase for case study 2 (Figure 2B). Besides time, other factors are likely to influence resource consumption, such as product characteristics, techniques applied, supplier choice, available techniques, costs of safety testing (in-house or contracted), scientific advances and many more. Because of high case study variance, effect of these characteristics could not be examined.

The relative distribution of consumed resources per cost domain are displayed in Figure 3. Although the case studies differ significantly, trends in relative resource consumption are observed. In both cases the facility is most resource intensive with 56% (38-71%) in case study 1 and 51% (46-62%) in case study 2. Equipment seems to consume least costs, with 4% (3-5%) of cost allocated to this domain in case study 1 and 2% (2-3%) in case study 2. In between were personnel costs, with an average of 20% (18-25%) for case study 1 and 32% (29-33%) in case study 2. This was followed by materials with 19% (8-33%) and 15% (7-19%) for case study 1 and 2 respectively.

Materials

The main cost driver in the material cost domain for case study 1 were tissue culture materials (88% of material cost) such as specialized reagents, peptides and media. This seemed partially to be influenced by the use of a (commercial) platform. To operate the platform specific buffers, but also consumables, had to be purchased from the platform-vendor. In case study 2 substantially less specialized materials were used in culture and the material cost driver were components for quality control (90% of material cost). Also, more assays needed to be developed for case study 2 resulting in more material consumption.

Another cost driver was thought to be material wastage. For CTL-development highly specialized materials were acquired. Due to short expiration dates and changes in manufacturing design, these materials could not be reused or allocated elsewhere. As mentioned before, CBTs differ widely as do their manufacturing process. Therefore, the opportunity to purchase specific reagents and proteins in bulk in general is often not possible. Partially, because bulk offerings of complex materials are not supplied by vendors but mostly because only little amounts are needed by developers. Non-platform consumables were bought in bulk. However, these materials were not found to be a cost driver.

Equipment

Equipment costs absorbs a relatively small percentage of manufacturing development costs (on average CTL=5%; iPSC=2%). In this domain a differentiation was made between product specific

Table 2. Cost estimates of manufacturing development of case study 1 (anti-EBV cytotoxic T-lymphocyte) and case study 2 (pluripotent stem cells). Cost estimates are reported per Technology Readiness Level (TRL) and cost domain in 2019 Pound Sterling.

Case study 1				Case study 2			
	TRL 4	**TRL5**	**TRL 6**		**TRL 4**	**TRL 5**	**TRL 6**
Materials	£ 48,527	£ 88,786	£ 94,523	Materials	£ 4,083	£10,893	£61,647
Equipment	£ 18,408	£ 13,326	£ 15,276	Equipment	£ 1,697	£ 2,399	£ 5,254
Personnel	£ 117,823	£ 53,897	£ 72,722	Personnel	£ 17,409	£ 31,594	£ 108,039
Facility	£ 458,444	£ 109,642	£ 109,642	Facility	£ 37,269	£ 62,992	£ 151,180
Total cost/TRL	**£ 643,202**	**£ 265,651**	**£ 292,163**	Total cost/TRL	**£ 60,458**	**£ 107,878**	**£ 326,120**
Total manufacturing development cost			**£1,201,016**	Total manufacturing development cost			**£ 494,456**

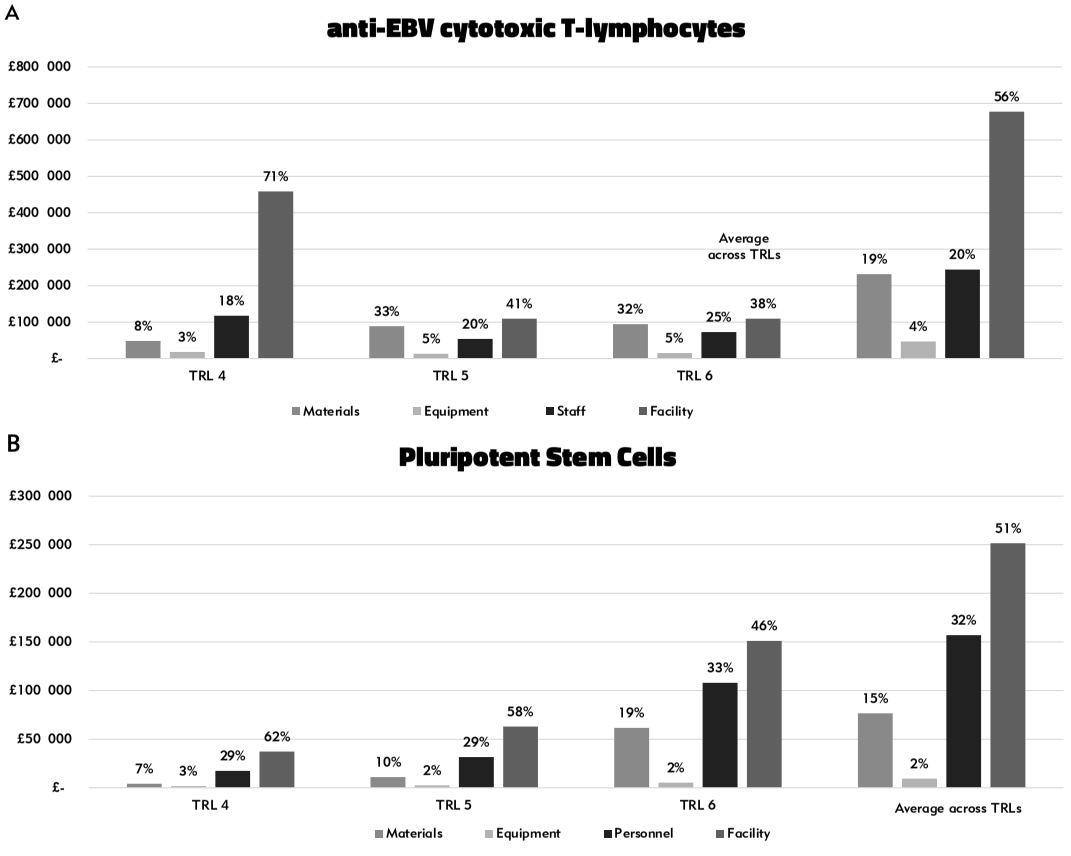

Figure 3. Relative distribution of consumed resources per cost domain for case study 1 (figure A) and case study 2 (figure B). TRL – Technology Readiness Level. EBV – Epstein-Barr Virus.

and non-product specific equipment. In line with the costing framework, equipment purchased specific for manufacturing and/or not shared with 5 or more other products, was deemed product specific. After introduction of a platform in case study 1 TRL 5, no clear increase in the absolute cost in the equipment domain was observed. Although, the aggregated equipment costs distribution seems constant across TRLs, the distribution between product specific and non-specific equipment within the cost domain does show a shift. Product specific costs are in case study 1: TRL 4; 11%, TRL 5; 72% and TRL 6; 63%. SNBTS already had the specialised equipment (i.e., Miltenyi Prodigy™ platform and GatheRex™) used in this study, and therefore the cost of purchase is not met only by this project, however, the initial capital outlay for such equipment would be a significant factor for example an SME developing a single product.

In case study 2 the equipment used were all non-product specific such as pipettes, microscope, refrigerators, freezer and incubators. Following the applied costing method, the equipment in case study 2 was shared between more than 5 products and was considered fixed cost. In both cases these low equipment costs reflect the relatively artisanal, hand-crafted nature of CBTs in contrast to the largely automated processes normal for e.g., small molecule drugs.

Personnel

Personnel cost was the second largest domain in manufacturing development (on average CTL=20%; iPSC=32%). Examining cost drivers within this domain, it was observed the main driver was developer salary followed by managers. From TRL 6 onwards quality and regulatory personnel were systematically involved. Regulatory and quality experts periodically allocated a few hours or days of their time while researchers and line managers often worked full time on development. Yet, the involvement of these experts accounted for 10% and 12% of personnel cost for CTL and PSC respectively due to higher wages or tariffs.

In these case studies, deployment of personnel seemed to influence development time. In case study 1, most work was done by one researcher. This results in sequential execution of development milestones. In case study 2, multiple researchers conducted development in parallel. Although not all products or assays allow parallel development, the results of this research may suggest allocating more full-time equivalents (FTEs) could help shorten development timelines which doesn't necessarily translate in lower cost due to high personnel time/time unit.

Facility

The facility domain absorbed most cost in manufacturing development for both case studies (on average CTL=56%; PSC=51%). As mentioned before, the facility cost seems to display a time dependent factor, with longer development time resulting in higher facility cost, as was expected. In compliance with GMP guidelines, manufacturing of medicinal products occurs under strictly controlled conditions[7]. Different levels of GMP environments and associated environmental control were found to be reflected in the facility costing. TRL 4 and 5 development of both case study 1 and 2 occurred in a research laboratory environment. In TRL 6 development was allocated to a development suite (GMP grade D environment). The research laboratory was estimated to cost 75% of the development suite. In turn in the grade D environment cost approximately 74% of the Grade C cleanroom and 69% of a grade B cleanroom. In line with the CBT manufacturing costing

framework, this converted cost/day included fixed facility running cost and variable operational cost. In the facility domain, approximately 70% of costs across TRLs were fixed facility running costs. This included building mortgage and lifecycle, utilities, and hard facility management costs. The JCC is a relatively new facility (opened in 2017), which may result in high depreciation cost in the first years after occupation in comparison to other facilities (here: a 30-year linear depreciation model). SNBTS is also sole occupier of the facility. This is also common in the private sector such as companies or contract manufacturing organizations (CMOs). However, in the public sector, such as hospitals or academic facilities, facilities are often shared resulting in facility (maintenance) costs or shared contributions. For example, here the overhead of the JCC facility is shared with other directorates within the organization. This may suggest facility cost for a stand-alone facility may be higher than estimated here.

Discussion

This study demonstrates the feasibility to retrospectively estimate cost of manufacturing development of two cell-based therapies using a CBT manufacturing cost framework. The original framework was designed and validated for use in small-scale routine manufacturing of cell-based therapies. By demonstrating feasibility of its use outside its initial context, broader application of this framework may be possible. Yet, it is highly recommended that extensive validation of this framework be undertaken before adoption in costing of CBT manufacturing development. Replication of this study in other facilities, across countries, prospectively and with different CBTs will provide more insights of its applicability and possible adjustments. Additionally, in general cost reduction should not be the primary objective when applying cost estimate frameworks. Their use lies in facilitating inclusion of cost considerations amongst quality and safety considerations in product development.

To be able to conduct this study access to (historic) administrative records, technical and cost data was a prerequisite. This was partially facilitated by development of manufacturing case studies occurring in one facility. The authors were able to extract the data from databases supplemented by interviews. It is not uncommon for medicinal products, especially during manufacturing development, to be relocated, outsourced, or acquired. This scatters data over multiple locations and owners. Meticulous record keeping may overcome some of these barriers to cost estimation. Additionally, the retrospective design of this study allowed reflection on past manufacturing design choices and their cost-consequences. These learnings can be applied in future cases.

Development costing could be conducted alongside development to manage budgets and spending. This can be useful for investors and funding bodies or help substantiate business models. An increase in a variety of publicly available costing models and tools is seen in literature[8,29,46,47]. Experience in costing of CBTs in any context will contribute to more accurate cost predictions. We therefore encourage others to explore the use of the here applied framework as well as others. Additionally, the authors stress that the cost estimates presented here strictly are the consumed resources and should not be confused with the prices of products or services. Also, our estimates represent the cost at a specific time-point and context. Also, if development of these case studies would have been started anew today, experience may shorten timelines. But additional cost can be expected in material and equipment cost as well as increase in wages. Costing of the included

case studies in other facilities and at a different timepoint will undeniably yield different estimates as CBT-development is subject to rapid technological and scientific advances.

From the aggregated cost estimate, in this study the facility domain absorbed most cost. Showing the development environment affected cost with more controlled environments being more costly. Therefore, developers tried to utilize lower grade environment as much as possible. Additionally, in this study developers had access to a Grade D research development suite. This was found helpful because the environment more closely replicated the equipment and processes used for manufacturing, as well as understanding the logistics of taking in process samples from controlled environment to accredited QC laboratories, and therefore tested suitability of the process to move to full GMP in the clean room. To continue, of the facility cost on average 70% were fixed. Fixed costs are resources consumed regardless of products or services being delivered[48]. In a CBT-context these fixed costs include air particle control, periodic cleaning, (re)certification etc. Therefore, it is recommended to reduce facility down time as much as possible[28]. This could be achieved by facility sharing, leasing vacant space, or considering the possibility for more developers to work in one space by adapting staff scheduling, and product or facility design.

Next, personnel consumed the largest part of the budget with 20% (CTL) and 32% (PSC). PSC manufacturing was developed as a mostly manual process. While in case study 1, a commercial cell processing platform was introduced. Commercial may not reduce cost during development but claim to reduce manual labour during manufacturing up to 70%, improving reproducibility and allowing scalability[49]. This may warrant investment, but on further investigation becomes more compelling[47]. To continue, the specialized manufacturing of CBTs require highly skilled personnel which are increasingly in high demand[34]. Allocation of these personnel elsewhere may contribute to more effective use of resources.

In both case studies regulatory and quality experts were involved from TRL 6 onwards. This point was considered by the developers to be optimal because processes were likely to change in TRL 4 and 5, however input was required sufficiently early to avoid the necessity to re-do critical and costly work if regulatory requirements were not met. Before TRL 6, developers managed quality requirements and reporting. It was mentioned timely involvement of regulatory and quality experts contributed greatly to development timelines. In the focus groups it was estimated timely involvement of regulatory and quality experts could shorten manufacturing development timelines up to 50%. In this research, we were not able to directly substantiate this claim as alternative strategies were not available for comparison. To continue, when addressing the regulatory requirements, the experts recommended to include local, national, and international guidance's early in the process development. Regulatory requirements may differ across jurisdictions. Developers were advised to be considerate of these variances keeping in mind the intended use of the product[50].

Scarcity and high cost of raw materials are often mentioned to be cost drivers in CBT development [50,51]. The case studies show an average of 19% (CTL) and 15% (PSC) of costs absorbed by the material domain. Cost drivers here were the specialized and low volume materials. In case study 1, developers intentionally used single buffy coat (TRL 4) and multiple buffy coats to mimic full scale leukapheresis (TRL 5) from internal sources (with ethical approval) during development. Not until

final full-scale development stage (TLR 6) was a commercially sourced leukapheresis product used due to the high cost of this starting material. In clinical manufacture (TLR 7 onwards) leukapheresis starting material was then procured from internally sourced donors (with ethical approval) which may have reduced upfront material cost but also incurred other costs due to extensive testing to determine suitability for clinical use. Another material domain cost driver appeared to be platform specific buffers and consumables. Also, essential reagents are usually platform-specific and can only be purchased via the platform vendor. To continue, in the literature it is suggested quality control and regulatory requirements are cost drivers[50]. In this study we aimed to categorize material cost in tissue culture and quality control categories. The large disparity between case studies did not allow in-depth inter- and intra-case study comparison. Further research is needed to explore this hypothesis. Additionally, resources consumed for regulatory, testing and quality proceedings may spill-over in personnel, facility and equipment cost domains.

The equipment domain consumed on average 5% (CTL) and 2% (PSC) with little variance per TRL. This was found surprising by the CTL-developers. It was expected that introduction of a platform would display a financial impact given purchase and maintenance of specialized equipment. Yet, platforms may also replace other machinery such as incubators and biological safety cabinets[49]. However, it cannot be concluded from a single case study whether equipment and cost substitution were equivalent. A reason for little relative consumption of equipment cost could be the size of the facility in which this study was conducted. JCC is a large blood and tissue establishment aimed at both production and development. This makes it possible to allocate multifunctional equipment cost to multiple projects. For a smaller facility purchase and maintenance of specialized equipment is likely to have bigger financial impact, this will be exacerbated by the proliferation of highly specialised new equipment that has been designed for individual products rather than flexible platform technologies. To add, similar as in the facility domain, specialized equipment downtime should be avoided as much as possible. Examples to achieve this could be via by equipment sharing or considering availability and flexibility of machinery during manufacturing development.

As previously mentioned, the CBTs field is very dynamic. With technologies and scientific advances occurring during manufacturing development of our case studies. Here we briefly discuss two trends mentioned by the developers which are thought to significantly impact the CBT-field. The first trend is more automation via increased uptake of platforms. Developers - and literature - mention a move towards automated and closed systems[24,47,52,53]. To address indication expansions, it is expected manufacturing processes are required to move from being open and manual to closed and automated. Early introduction of such systems may save time and costs downstream. Yet, if changes are made in a manufacturing process, revalidation and reporting to authorities is often required. With increased uptake of platforms, authorization of the platform could be a solution[7], which is a trend also described outside of the CBT field[54].

The second trend is use of centralized expert development centres. Combining technical, scientific, regulatory and quality expertise in one place, is expected to result in a more efficient use of resources which could decrease development timelines. Furthermore, the upfront investments that are substantial for SMEs and academic developers could be spread or mitigated in a shared facility.

Study Limitations

Despite best efforts, this study has limitations. First, our feasibility testing was limited to a small part of the CBT product life cycle. In this study we explored costing of products from TRL 4 to 6 only. Not included are early discovery research and (pre-)clinical research. The reason for this was that various aspects of the early R&D and preclinical testing may occur elsewhere. Therefore, the researchers did not have access to all of these data. For example, in the focus groups, developers mentioned CBT animal studies are highly resource intensive and were expected to contribute substantially to the development cost. Nevertheless, the highest costs are traditionally expected to be incurred in later phases of development (i.e., large-scale clinical grade manufacturing, clinical trials and regulatory procedures). Future costing studies could aim to include a broader spectrum of the CBT life cycle for more accurate estimates. Second, product timelines and data were collected in a retrospective interview setting. This may have caused information and recall bias, resulting in over- or underestimation. By combining triangulation (conducting interviews with multiple people asking the same questions) and focus groups we aimed to appeal to collective memory and increase validity of qualitatively collected data. Additionally, prospective data collection would increase accuracy.

Third, some developers may not be familiar with the Technology Readiness Level-Framework. Although use of TRL-classification is gaining traction in health and biomedical sciences, it is mostly used in the innovative technology and policy context[30]. However, benefit of this uniform classification system is that development stage and progress can be compared to other or (non-)health interventions. If researchers prefer to use other classifications, definitions of TRLs are publicly available and can be translated to preferred terminology. Last, this study included two case studies in one facility. This limits generalizability of the findings and learnings. However, the primary objective of this research was to test feasibility of the CBT manufacturing cost framework. Now that feasibility is demonstrated in one facility, we encourage exploration of its reproducibility and generalizability.

Conclusions

This study demonstrates feasibility for use of a novel costing framework and methodology, originally designed and validated for the costing of small-scale manufacturing of cell-based therapies, to estimate cost of CBT manufacturing development in two case studies. Next step is more widespread application and validation of this framework and methodology for use in CBT manufacturing development cost estimations. This can be done in multiple facilities, across jurisdictions, prospectively and should include different products. The results from this study should be considered a cross section in time and in context of this facility. The cost estimates revealed drivers and insights from which we aimed to derive learnings. Generalizability of these learnings remains to be examined. To do so we advise structural inclusion of cost-considerations in CBT manufacturing design. Costing can be done in retrospect to derive learnings and compose best-practices or prospectively alongside development to track spending. Additionally, more informal sharing of experiences amongst developers will contribute to knowledge dissemination and facilitate CBT-development.

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References

1. Burt RK, Balabanov R, Burman J, et al. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients with Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. *JAMA - J Am Med Assoc*. 2019;321(2):165-174. doi:10.1001/jama.2018.18743

2. The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council. *Off J Eur Union*. 2007;324((EC)1394/2007):121-138. http://data.europa.eu/eli/reg/2007/1397/oj.

3. Iglesias-López C, Agustí A, Obach M, Vallano A. Regulatory framework for advanced therapy medicinal products in Europe and United States. *Front Pharmacol*. 2019;10:1-14. doi:10.3389/fphar.2019.00921

4. Bayon Y, Vertès AA, Ronfard V, et al. Turning Regenerative Medicine Breakthrough Ideas and Innovations into Commercial Products. *Tissue Eng - Part B Rev*. 2015;21(6):560-571. doi:10.1089/ten.teb.2015.0068

5. Hanna E, Toumi M, Dussart C, et al. Funding breakthrough therapies : A systematic review and recommendation. *Health Policy (New York)*. 2018;122(3):217-229. doi:10.1016/j.healthpol.2017.11.012

6. Prat-Vidal C, Rodríguez-Gómez L, Aylagas M, et al. First-in-human PeriCord cardiac bioimplant: Scalability and GMP manufacturing of an allogeneic engineered tissue graft. *EBioMedicine*. 2020;54. doi:10.1016/j.ebiom.2020.102729

7. European Comission. *Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products*. Vol Volume 4. Brussels; 2017. doi:10.1093/oxfordhb/9780199546282.013.0024

8. Abou-El-Enein M, Römhild A, Kaiser D, et al. Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: A novel tailored model for optimizing performance and estimating costs. *Cytotherapy*. 2013;15(3):362-383. doi:10.1016/j.jcyt.2012.09.006

9. Campbell A, Brieva T, Raviv L, et al. Concise Review: Process Development Considerations for Cell Therapy. *Stem Cells Transl Med*. 2015;4(10):1155-1163. doi:10.5966/sctm.2014-0294

10. Rivière I, Roy K. Perspectives on Manufacturing of High-Quality Cell Therapies. *Mol Ther*. 2017;25(5):1067-1068. doi:10.1016/j.ymthe.2017.04.010

11. ten Ham RMT, Hövels AM, Klungel OH, Leufkens HGM, Broekmans AW, Hoekman J. Development and Regulation of Gene and Cell-Based Therapies in Europe: A Quantification and Reflection. *Trends Pharmacol Sci*. 2020;41(2):67-71. doi:10.1016/j.tips.2019.11.007

12. Grayson W, Stephenson M. Recent advances in bioreactors for cell-based therapies. *F1000Research*. 2018;7(0):1-9. doi:10.12688/f1000research.12533.1

13. Harrison RP, Ruck S, Medcalf N, Rafiq QA. Decentralized manufacturing of cell and gene therapies: Overcoming challenges and identifying opportunities. *Cytotherapy*. 2017;19(10):1140-1151. doi:10.1016/j.jcyt.2017.07.005

14. Smith D, Heathman TRJ, Klarer A, LeBlon C, Tada Y, Hampson B. Towards Automated Manufacturing for Cell Therapies. *Curr Hematol Malig Rep*. 2019;14(4):278-285. doi:10.1007/s11899-019-00522-y

15. Mangematin V, Lemarié S, Boissin J, et al. Development of SMEs and heterogeneity of trajectories: the case of biotechnology in France. *Res Policy*. 2003;32(4):621-638. doi:10.1016/S0048-7333(02)00045-8

16. OECD. Policy note: Improving the business environment for SMEs through effective regulation. In: *SME Ministerial Conference*. Mexico City, Mexico; 2018:1-11. https://www-oecd-org.proxy.library.uu.nl/cfe/smes/ministerial/documents/2018-SME-Ministerial-Conference-Parallel-Session-1.pdf.

17. Adopted from written evidence from Professor Chris Mason. Presentation outlining the vision for a Cell Therapy TIC, May 2011, US Department of Defence: Technology Readiness Assessment. In: *Strategy for Regenerative Medicine.* ; 2009.

18. Hourd P, Ginty P, Chandra A, Williams DJ. Manufacturing models permitting roll out/scale out of clinically led autologous cell therapies: Regulatory and scientific challenges for comparability. *Cytotherapy.* 2014;16(8):1033-1047. doi:10.1016/j.jcyt.2014.03.005

19. Kaiser AD, Assenmacher M, Schröder B, et al. Towards a commercial process for the manufacture of genetically modified T cells for therapy. *Cancer Gene Ther.* 2015;22(2):72-78. doi:10.1038/cgt.2014.78

20. Kirouac DC, Zandstra PW. The Systematic Production of Cells for Cell Therapies. *Cell Stem Cell.* 2008;3(4):369-381. doi:10.1016/j.stem.2008.09.001

21. Turner M, Leslie S, Martin NG, et al. Toward the development of a global induced pluripotent stem cell library. *Cell Stem Cell.* 2013;13(4):382-384. doi:10.1016/j.stem.2013.08.003

22. Rezvani K, Rouce R, Liu E, Shpall E. Engineering Natural Killer Cells for Cancer Immunotherapy. *Mol Ther.* 2017;25(8):1769-1781. doi:10.1016/j.ymthe.2017.06.012

23. Sediq AS, Klem R, Nejadnik MR, Meij P, Jiskoot W. Label-Free, Flow-Imaging Methods for Determination of Cell Concentration and Viability. *Pharm Res.* 2018;35(150):1-10. doi:10.1007/s11095-018-2422-5

24. Skorska A, Müller P, Gaebel R, et al. GMP-conformant on-site manufacturing of a CD133+ stem cell product for cardiovascular regeneration. *Stem Cell Res Ther.* 2017;8(1):1-15. doi:10.1186/s13287-016-0467-0

25. Shukla V, Seoane-Vazquez E, Fawaz S, Brown L, Rodriguez-Monguio R. The Landscape of Cellular and Gene Therapy Products: Authorization, Discontinuations, and Cost. *Hum Gene Ther Clin Dev.* 2019;30(3):102-113. doi:10.1089/humc.2018.201

26. Hassan S, Simaria AS, Varadaraju H, Gupta S, Warren K, Farid SS. Allogeneic cell therapy bioprocess economics and optimization: Downstream processing decisions. *Regen Med.* 2015;10(5):591-609. doi:10.2217/rme.15.29

27. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. *Cell Stem Cell.* 2016;19(3):293-297. doi:10.1016/j.stem.2016.08.012

28. ten Ham RMT, Hövels AM, Hoekman J, et al. What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings. *Cytotherapy.* 2020;22(7):388-397. doi:10.1016/j.jcyt.2020.03.432

29. Boeke A, Doumas P, Reeves L, et al. Vector Production in an Academic Environment: A Tool to Assess Production Costs. *Hum Gene Ther Methods.* 2013;24(1):49-57. doi:10.1089/hgtb.2012.213

30. Mankins JC. *Technology Readiness Levels.* Vol April 6. Washington, DC; 1995. http://www.artemisinnovation.com/images/TRL_White_Paper_2004-Edited.pdf.

31. National Aeronautics and Space Administration. NASA Official: Brian Dunbar. Technology Readiness Level. https://www.nasa.gov/directorates/heo/scan/engineering/technology/txt_accordion1.html. Accessed February 10, 2020.

32. House of Lords - Science and Technology Committee. *First Report: Regenerative Medicine.* London, UK; 2013. https://publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/2306.htm#note85.

33. Cell & Gene Therapy Catapult. *Cell and Gene Therapy GMP Manufacturing in the UK.* London, UK; 2019. https://ct.catapult.org.uk/sites/default/files/publication/GMP Manufacturing Report 2017 30_12_17 FINAL.pdf.

34. Cell and Gene Therapy Catapult. *UK Cell and Gene Therapy Skills Demand Report 2019*. London, UK; 2019. https://ct.catapult.org.uk/sites/default/files/publication/Catapult_01_UK Skills Demand Report 2019_published_v2.pdf.

35. Vickers MA, Wilkie GM, Robinson N, et al. Establishment and operation of a good manufacturing practice-compliant allogeneic Epstein-Barr virus (EBV)-specific cytotoxic cell bank for the treatment of EBV-associated lymphoproliferative disease. *Br J Haematol*. 2014;167(3):402-410. doi:10.1111/bjh.13051

36. Haque T, Wilkie GM, Jones MM, et al. Allogeneic cytotoxic T-cell therapy for EBV-positive posttransplantation lymphoproliferative disease: Results of a phase 2 multicenter clinical trial. *Blood*. 2007;110(4):1123-1131. doi:10.1182/blood-2006-12-063008

37. Barry J, Hyllner J, Stacey G, Taylor CJ, Turner M. Setting Up a Haplobank: Issues and Solutions. *Curr Stem Cell Reports*. 2015;1(2):110-117. doi:10.1007/s40778-015-0011-7

38. Vanhoutte VJ, McAulay KA, McCarrell E, Turner M, Crawford DH, Haque T. Cytolytic mechanisms and T-cell receptor Vβusage by ex vivo generated Epstein-Barr virus-specific cytotoxic T lymphocytes. *Immunology*. 2009;127(4):577-586. doi:10.1111/j.1365-2567.2008.03035.x

39. Markus BKA, Smith KM, Salkind NJ. Content validity. In: Salkind NJ, ed. *Encyclopedia of Research Design*. Thousand Oaks: SAGE Publications, Inc.; 2012:239-243. doi:https://dx.doi.org/10.4135/9781412961288

40. Johnson E. Face validity. In: Volkmar FR, ed. *Encyclopedia of Autism Spectrum Disorders*. New York, NY: Springer; 2013.

41. Héder M. From NASA to EU: The evolution of the TRL scale in Public Sector Innovation. *Innov J Public Sect Innov J*. 2017;22(2):1-23. https://core.ac.uk/download/pdf/94310086.pdf.

42. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Vol 2. 2nd ed. (Cartwright WS, ed.). Oxford University Press; 1999.

43. Centraal Bureau voor Statistiek (CBS). Statistics Netherlands. https://www.cbs.nl/. Published 2019. Accessed January 1, 2019.

44. Tan SS, Bouwmans CAM, Rutten FFH, Hakkaart-van Roijen L. Update of the Dutch Manual for Costing in Economic Evaluations. *Int J Technol Assess Health Care*. 2012;28(2):152-158. doi:10.1017/S0266462312000062

45. National Institute for Health and Care Excellence, NICE. *Guide to the Processes of Technology Appraisal*. Vol 26.; 2008. doi:10.2165/00019053-200826090-00002

46. Lipsitz YY, Milligan WD, Fitzpatrick I, et al. A roadmap for cost-of-goods planning to guide economic production of cell therapy products. *Cytotherapy*. 2017;19(12):1383-1391. doi:10.1016/j.jcyt.2017.06.009

47. Harrison RP, Medcalf N, Rafiq QA. Cell therapy-processing economics: Small-scale microfactories as a stepping stone toward large-scale macrofactories. *Regen Med*. 2018;13(2):159-173. doi:10.2217/rme-2017-0103

48. Roberts RR, Gussow LM, Kampe LM, et al. Distribution of variable vs fixed costs of hospital care. *J Am Med Assoc*. 1999;281(7):644-649. doi:10.1001/jama.281.7.644

49. Terumo BCT Inc. Automated cell culture: product confidence, process scalability. https://www.terumobct.com/quantum. Published 2020. Accessed May 29, 2020.

50. ten Ham RMT, Hoekman J, Hövels AM, Broekmans AW, Leufkens HGM, Klungel OH. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Mol Ther - Methods Clin Dev*. 2018;11(December):121-130. doi:10.1016/j.omtm.2018.10.003

51. Mount NM, Ward SJ, Kefalas P, Hyllner J. Cell-based therapy technology classifications and translational challenges. *Philos Trans R Soc B Biol Sci*. 2015;370(1680). doi:10.1098/rstb.2015.0017

52. Zhu F, Shah NN, Xu H, et al. CAR-T Cell Production Using the Clinimacs® Prodigy System. *Blood*. 2016;128(22):5724. doi:https://doi.org/10.1182/blood.V128.22.5724.5724

53. Roddie C, Reilly MO, Dias J, Pinto A, Vispute K, Lowdell M. Manufacturing chimeric antigen receptor T cells : issues and challenges. *Cytotherapy*. 2019;21(3):327-340. doi:10.1016/j.jcyt.2018.11.009

54. Schellekens H, Aldosari M, Talsma H, Mastrobattista E. Making individualized drugs a reality. *Nat Biotechnol*. 2017;35(6):507-513. doi:10.1038/nbt.3888

3

Assessment of gene and cell-based therapies by regulators and health technology assessment bodies

3.1

A quantification and reflection of development and regulation of gene and cell-based therapies

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Abstract

Gene and cell-based therapies (GCTs) are said to hold great promise as treatments for previously untreatable and high-burden diseases. Here, we provide insight into GCT development and regulation activities in Europe, quantify clinical and regulatory success, and compare these with other medicinal products in order to reflect on regulatory changes and challenges.

The European Gene and Cell-Based Therapy landscape

Gene and cell-based therapies (GCTs) are said to hold promise for previously untreatable and high-burden diseases. The development of GCTs, however, faces translational challenges due to their novelty and apparent misfit with existing healthcare delivery and regulatory systems. In Europe, the European Commission (EC), in close collaboration with the European Medicines Agency (EMA), has been active in mitigating these challenges by adapting the regulatory environment to accommodate and regulate GCTs as medicinal products. In 2008, the enactment of the advanced therapy medicinal product (ATMP) regulation[i] subjected GCT products to the EMA's centralized authorization procedure and a combined marketing authorization assessment by the Committee for Medicinal Products for Human Use (CHMP) and Committee for Advanced Therapies (CAT)[i]. Other examples of regulatory change include: the drafting of GCT-specific good manufacturing practice (GMP) guidelines[ii], a classification procedure for GCTs[iii], and enhanced possibilities for dialogue and deliberation between GCT developers and authorities[iv,v]. Additionally, non-GCT-specific regulatory pathways are in place, for which GCT developers are often eligible. These include conditional marketing authorisation[vi] and formal commitments between developers and authorities in the priority medicines (PRIME)[vii] scheme. Most GCT developers can also benefit from incentives provided for orphan[viii] and paediatric products[ix], and those for small and medium-sized enterprises (SMEs)[x]. Never before have so many incentives and schemes to facilitate medicinal product development in Europe coexisted.

Effects of new regulations

During the initial years of the implementation of new regulations, concerns among the stakeholders regarding the effect of regulatory change emerged, particularly after negative opinions and withdrawal of marketing authorization applications (MAAs) were noted and GCT marketing authorization holders withdrew four regulatory approved GCTs from the EU market (Figure 1)[1].

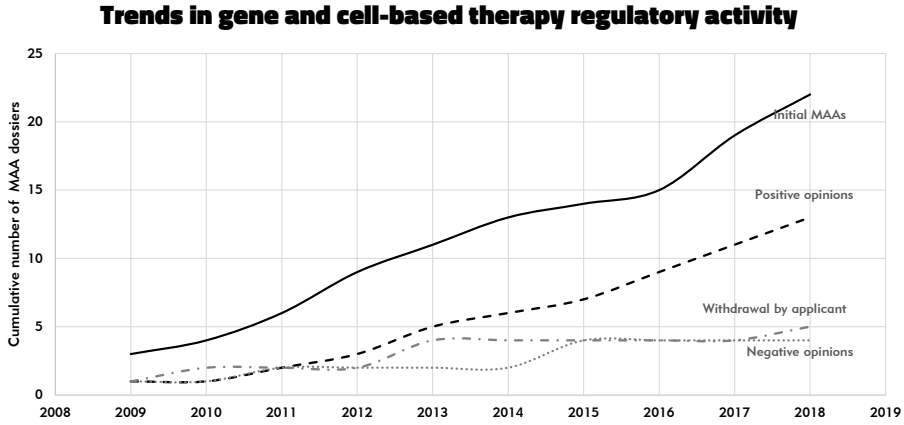

Figure 1. Trends in gene and cell-based therapy (gct) regulatory activity in the eu between 2009 and 2018.

The graph shows the cumulative number of initial marketing authorization applications (MAAs), positive and negative opinions by the Committee of Advanced Therapies (CAT) leading to approval or rejection of centralized marketing authorization by the European Commission (EC), and withdrawal by applicant from 2009, the year after regulatory policies were put in place in the EU, onwards. The numbers were obtained from 'the CAT monthly report of application procedures, guidelines, and related documents on advanced therapies' dated December 2018[xiii].

In response, several multistakeholder initiatives[xi,xii] were undertaken to inform and improve GCT development and discuss learnings with respect to the implementation of the regulatory instruments. Initiatives consisted, amongst others, of consultation and a concept paper[xi] by the Innovative Medicines Initiative (IMI) to facilitate translation of GCTs to patients in Europe as well as stakeholder workshops organized by the EMA and CAT[xii]. Regulatory challenges figured prominently in these meetings and stakeholders actively engaged with each other to exchange views and practices about GCT development in the new regulatory environment[xi].

If we look at the cumulative number of MAAs submitted from 2009 to 2018[xiii] (Figure 1), we roughly observe two phases of regulatory GCT activity. In the initial years following the enactment of the ATMP regulation (roughly 2009–2013), we not only observe an upward trend in GCT MAAs being submitted but also a similar upward trend in negative opinions and applicant withdrawals (Figure 1). This could have been caused by more developers entering the field (leading to more initial MAAs) and reaching regulatory milestones (probably leading to similar negative opinions and withdrawal by applicant). During these initial years we also see an overlap in the cumulative number of positive opinions, negative opinions, and withdrawals by applicants. However, from 2013 onwards, while the number of initial MAAs continues the upward trend, the number of negative opinions and applicant withdrawals does not follow similarly (Figure 1). This may imply that GCT developers started to benefit from the clarity provided by the new regulations and guidance, and might also signal a positive learning curve for CAT with regard to evaluation of submissions.

Factors influencing European GCT development

Literature and conference discussions on GCT development express concerns that the number of centrally marketed GCTs in Europe so far is disappointing when compared with clinical trial activity[2,3,xiv]; it is unclear whether such claims are supported by data. These concerns might also signal unrealistically high expectations surrounding GCT development and approval.

One way to decide whether expectations are too high for GCT therapies would be to compare the emergence of this field with previous waves of change in drug development, such as the emergence of biopharmaceuticals. A lesson we have learned from biopharmaceuticals is that although expectations are often high in early phases of emergence, 'revolutionary' models of innovation result in overestimation of the speed and extent of improvement in therapeutic value that can be reasonably expected[4]. Similar to the emergence of biopharmaceuticals, it is likely that the introduction of GCTs will follow an incremental pattern of technological and regulatory change, building on existing drug development and regulation heuristics and experiences[5]. As the medicinal product field is strictly regulated and GCTs have only recently been accommodated

within the regulatory medicinal product framework, it will take time for developers and authorities to learn how to bring these products to market.

We should also consider that complexities fand challenges described by developers are often not scientific and technical but arise from their lack of familiarity with both the regulatory frameworks as well as the development of products for indication areas where needs are challenging to serve. Key developers in the GCT field are not large pharmaceutical companies but SMEs, hospitals, and academic researchers[6]. These SMEs are often founded around a technology or product discovered in academic or hospital settings[7]. These parties cannot draw on resources, experiences, and capabilities from prior development trajectories, and experience more difficulties in navigating the regulatory landscape than pharmaceutical companies[8]. Moreover, most developers develop GCTs for niche areas where competition is limited and markets uncertain. Small patient populations and unfeasibility of large and repeated trials limit learning opportunities about the benefits and risks of GCTs in these patient populations.

Quantifying clinical trial and regulatory success of GCTs

In an effort to quantify whether expectations are high for GCTs, we provide insights into the development success of GCTs and where possible, make a comparison with other medicinal product groups. While reconstructing the success rates of GCT development is difficult because of limited historical data and small sample sizes, we are aware of two publications that give a useful overview of clinical GCT activity in the EU. Maciulaitis *et al.* found that between 2004 and 2010 clinical trials were performed for 250 different GCTs using the EU clinical trial database (EudraCT)[xv], 100 of which were privately sponsored[9]. de Wilde *et al.* identified 198 GCT products in clinical trials during the period from 2004 to 2014 using the EU Clinical Trials Register[xvi], 80 of which were conducted by private sponsors[10]. We evaluate the success of GCT drug development with two measures;

1. clinical trial success rate, obtained by dividing the number of products accepted by the EMA for initial MAA by the number of unique products in clinical trials (Table 1), and
2. regulatory success rate, obtained by dividing the number of products receiving an initial positive opinion by the EMA's CAT leading to approval by the EC, by the number of products submitted for initial MAA (Table 2).

Clinical success rate

As a benchmark for clinical trial success, we take the rule of thumb suggested by Mullard *et al.* who posit that globally around 10% of drug projects in Phase I clinical trials receive market authorization (MA)[11]. This number does not consider product, jurisdiction, or disease variability, and therefore provides a generic benchmark. Based on the EMA CAT report, we find that 22 initial MAA evaluations for GCTs received a positive opinion by the EMA as of December 2018[xiii]. Hence, we estimate that the overall clinical success rate of GCTs lies between 8.8 and 11.1% (22/250, based on Maciulaitis *et al.*[9]; 22/198, based on de Wilde *et al.*[10]) (Table 1, Figure 2A).

Our estimate assumes that all products observed by Maciulaitis *et al.*[9] and de Wilde *et al.*[10] could have been submitted for MAA. While GCT MAAs are reportedly submitted based on less evidence (such as a single Phase I or I/II clinical trial) than conventional medicinal products (such as small

Table 1. Estimated Clinical Success Rate per Medicinal Product Group[a]

	GCTs	GCTs	All products (non-GCTs)	NAS	Orphan products	Biologics
Time frame	2004–2010	2004–2014	2003–2011	2003–2011	2003–2011	2003–2011
Number of unique products in trial	250	198	–	–	–	–
Privately sponsored products	100	80	–	–	–	–
Number of unique initial MAAs[b]	22	22	–	–	–	–
% Clinical success rate (all)	8.8	11.1	12.5	9.8	40.6	16.4
% Clinical success rate private sector	22.0	27.5	–	–	–	–
Overall estimated clinical success rate (%)	8.8–22.0	11.1–27.5	12.5	9.8	40.6	16.4

[a] Clinical success rates of GCTs are estimated by dividing the number of unique products in clinical trials (obtained from [9,10]) by the number of GCTs submitted for initial MAAs[xiii]. Non-GCT clinical success rates were derived from [12] by multiplying phase success rates per clinical phase [(Phase I) × (Phase II) × (Phase III)]. [b] Denotes number of unique initial MAAs until December 2018. No distinction is made between indications.

Table 2. Estimated Regulatory Success Rate for GCTs and Non-GCTs[a]

	GCTs[xiii]		All products (non-GCTs)[xiv–xxiii]		NAS[b,xvii–xxvi]		Orphan products[xvii–xxvi]	
Year	**Initial MAAs**	**Positive opinions**	**Initial MAAs**	**Positive opinions**	**Initial MAAs**	**Positive opinions**	**Initial MAAs**	**Positive opinions**
2009	3	1	93	117	–	–	–	–
2010	1	0	90	51	34	20	12	4
2011	2	1	98	87	48	38	14	4
2012	3	0	93	59	47	30	19	8
2013	2	2	78	77	48	46	18	9
2014	2	1	98	81	37	40	21	17
2015	1	1	110	94	36	40	25	18
2016	1	2	113	79	40	28	27	16
2017	4	2	86	90	32	30	19	15
2018	3	3	81	80	31	31	17	18
Total	22	13	940	815	353	303	172	109
Regulatory success rate (%)	–	59.1	–	86.7	–	85.8	–	63.4

[a] Regulatory success rate is estimated by dividing positive opinions by the number of initial MAAs. [B] Excludes orphan products. No distinction is made between indications.

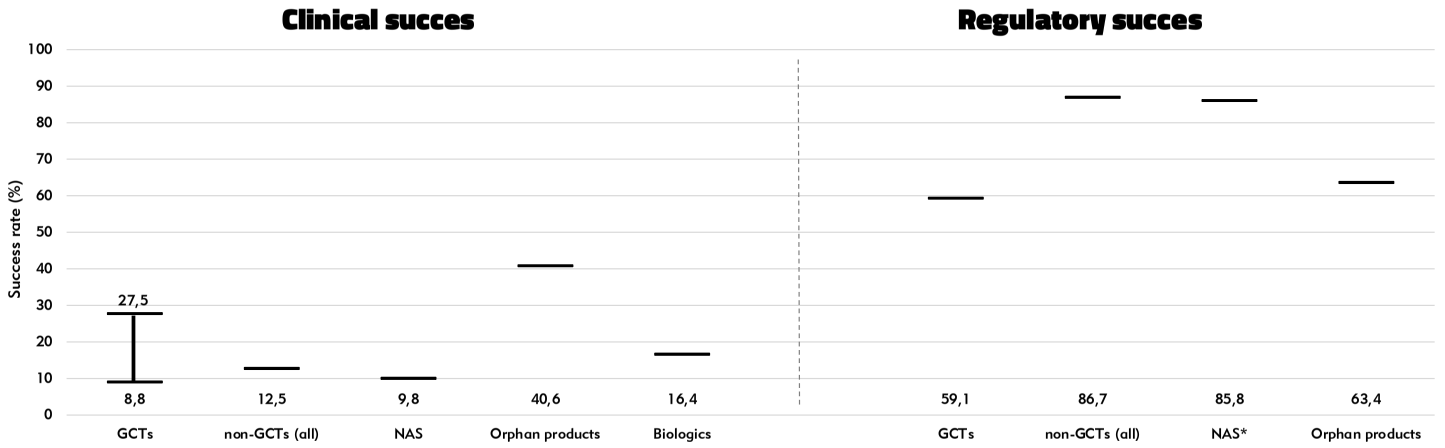

Figure 2. Comparison of success rates between gene and cell-based therapies (gcts) and non-gcts. (a) clinical success rate of gcts compared with non-gcts, new active substances (nas), orphan products, and biologics. (b) regulatory success rate of gcts compared to non-gcts, nas, and orphan products. the estimate of regulatory success rate of nas* includes orphan products that are a nas. no distinction is made between indications.

molecules or biologics), we realize that our estimation might be an overestimation. Our analysis also assumes that all GCT developers aim to apply for MA. Yet, it is known that a substantial number of nonprivate developers do not aspire formal MA[6]. Only including trials that have private sponsors increases the success rate to 22.0–27.5% (22/100, based on Maciulaitis *et al.*[9]; 22/80, based on de Wilde *et al.*[10]) (Figure 2A). Thus, combining the available data and considering the earlier assumptions, we estimate that the overall GCT clinical success rate is in the range of 8.8 to 27.5% (Table 1, Figure 2A).

To compare GCT clinical success rates with other medicinal products developed by companies, we relied on Hay *et al.*[12]. Although Hay's numbers are based on the US market, they are representative of European trends[13]. Without distinguishing between indications or different medicinal products, we derive a clinical success rate of 12.5% from this research tracking clinical trials between 2003 and 2011 (Table 1, Figure 2A). However, the success rates vary per indication and product type. Here, we focus merely on product types and disregard variance per indication due to lack of data to support this analysis. Analysing the different product types, Hay *et al.* shows a success rate of 9.8% from Phase I to FDA submission for small molecule new active substances (NAS) [known as new molecular entities (NMEs) in the USA], 40.6% for orphan products, and 16.4% for biologics (Table 1, Figure 2A). The range reported by Hay *et al.* for clinical success of non-GCTs (9.8–40.6%) thus largely overlaps with our estimates for GCTs (8.8–27.5%) (Table 1, Figure 2A).

Regulatory success rate

To estimate regulatory success rates of GCTs, all non-GCT medicinal products, NAS, and orphan products, we collated the number of initial MAAs and positive opinions for each group from the EMA annual[xvii] and CAT reports from 2009 to 2018[xiii] (Table 2). These reports did not include specific information for biologics; hence they were excluded from further analysis. Regulatory success rate was calculated by dividing the total number of positive opinions by the number of submitted initial MAAs. We found that the regulatory success rate for GCTs (59.1%) was lower than for non-GCTs (86.7%) (Table 2, Figure 2B). However, regulatory success rates varied by product type, with NAS (85.8%) having similar rates to non-GCTs (86.7%) and orphan products (63.4%) having similar rates to GCTs (Figure 2B).

Ultimately, we obtained an overall estimate of GCT development success in the EU (obtained by multiplying clinical success rate with regulatory success rate) as ranging between 5.2 and 16.3% [(8.8–27.5%) × 59.1%]. This estimate falls within Mullard's 10% rule of thumb, suggesting no indication of lower success rates for GCTs compared with other medicinal products.

Concluding remarks

A decade of GCT development and regulatory approval in Europe demonstrates that constructive engagement of stakeholders and an active approach towards policy learning is crucial in making implementation of regulation a success. Even in the short time period where GCTs have been regulated as medicinal products in Europe, it is encouraging to observe, as is clear from our analysis, that the implementation of the regulatory policies has not slowed the development and

success rates of GCTs compared with conventional medicinal products. It is likely that this can be, at least partially, attributed to the active approach to regulatory change taken by the EMA and EC, although mitigation of other translational challenges might also play a role, such as a reduction in technological and scientific uncertainties and an increase in clinical adoption and experience. Continued success is dependent on regulation and regulators being adaptive to rapid technological advancement and new information about benefits and risks accruing over the drug life cycle. In so doing, regulation can simultaneously contribute to minimizing risks for patients, balancing the values and interests of stakeholders, and enabling further GCT innovation.

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Resources

i. https://eur-lex-europa-eu.proxy.library.uu.nl/legal-content/EN/ALL/?uri=CELEX%3A32007R1394

ii. https://ec-europa-eu.proxy.library.uu.nl/health/documents/eudralex/vol-4_en

iii. www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification

iv. www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/support-advanced-therapy-developers

v. www.imi.europa.eu/news-events/press-releases/outcomes-imi-consultation-advanced-therapies

vi. www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation

vii. www.ema.europa.eu/en/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime_en.pdf

viii. www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

ix. www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation

x. www.ema.europa.eu/en/human-regulatory/overview/supporting-smes

xi. www.imi.europa.eu/news-events/press-releases/outcomes-imi-consultation-advanced-therapies

xii. www.ema.europa.eu/en/human-regulatory/overview/advanced-therapies/meetings-stakeholders-other-organisations

xiii. www.ema.europa.eu/en/documents/committee-report/cat-monthly-report-application-procedures-guidelines-related-documents-advanced-therapies-december_en-5.pdf

xiv. www.ema.europa.eu/en/about-us/annual-reports-work-programmes

xv. https://eudract-ema-europa-eu.proxy.library.uu.nl

xvi. www.clinicaltrialsregister.eu

xvii. https://www-ema-europa-eu.proxy.library.uu.nl/en/documents/work-programme/committee-advanced-therapies-cat-work-programme-2010-2015_en.pdf

xviii. www.ema.europa.eu/en/documents/annual-report/annual-report-european-medicines-agency-2010_en.pdf

xix. www.ema.europa.eu/en/documents/annual-report/annual-report-european-medicines-agency-2011_en.pdf

xx. www.ema.europa.eu/en/documents/annual-report/annual-report-european-medicines-agency-2012_en.pdf

xxi. www.ema.europa.eu/en/documents/annual-report/annual-report-european-medicines-agency-2013_en.pdf

xxii. www.ema.europa.eu/en/documents/annual-report/annual-report-european-medicines-agency-2014_en.pdf

xxiii. www.ema.europa.eu/en/documents/annual-report/2015-annual-report-european-medicines-agency_en.pdf

xxiv. www.ema.europa.eu/en/documents/annual-report/2016-annual-report-european-medicines-agency_en.pdf

xxv. www.ema.europa.eu/en/documents/annual-report/2017-annual-report-european-medicines-agency_en.pdf

xxvi. www.ema.europa.eu/en/documents/annual-report/2018-annual-report-european-medicines-agency_en.pdf

References

1. Coppens DGM, de Wilde S, Guchelaar HJH, et al. A decade of marketing approval of gene and cell-based therapies in the United States, European Union and Japan: An evaluation of regulatory decision-making. *Cytotherapy*. 2018;20(6):769-779. doi:10.1016/j.jcyt.2018.03.038

2. Hanna E, Rémuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. *J Mark Access Heal Policy*. 2016;4(1):31036. doi:10.3402/jmahp.v4.31036

3. Morrow D, Ussi A, Migliaccio G. Addressing Pressing Needs in the Development of Advanced Therapies. *Front Bioeng Biotechnol*. 2017;5(9):1-6. doi:10.3389/fbioe.2017.00055

4. Hopkins MM, Martin PA, Nightingale P, Kraft A, Mahdi S. The myth of the biotech revolution: An assessment of technological, clinical and organisational change. Taylor T, ed. *Res Policy*. 2007;36(4):566-589. doi:10.1016/j.respol.2007.02.013

5. Salter B, Zhou Y, Datta S. Hegemony in the marketplace of biomedical innovation: Consumer demand and stem cell science. *Soc Sci Med*. 2015;131:156-163. doi:10.1016/j.socscimed.2015.03.015

6. de Wilde S, Guchelaar HJ, Herberts C, et al. Development of cell therapy medicinal products by academic institutes. *Drug Discov Today*. 2016;21(8):1206-1212. doi:10.1016/j.drudis.2016.04.016

7. Sampat BN, Lichtenberg FR. What Are The Respective Roles Of The Public And Private Sectors In Pharmaceutical Innovation? *Heal Aff*. 2011;30(2):332-339. doi:10.1377/hlthaff.2009.0917

8. Regnstrom J, Koenig F, Aronsson B, et al. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur J Clin Pharmacol*. 2010;66(39). doi:0.1007/s00228-009-0756-y

9. Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical development of advanced therapy medicinal products in Europe: Evidence that regulators must be proactive. *Mol Ther*. 2012;20(3):479-482. doi:10.1038/mt.2012.13

10. de Wilde S, Guchelaar H-J, Zandvliet ML, Meij P. Clinical development of gene- and cell-based therapies: overview of the European landscape. *Mol Ther - Methods Clin Dev*. 2016;3(July):16073. doi:10.1038/mtm.2016.73

11. Mullard A. Parsing clinical success rates. *Nat Rev Drug Discov*. 2016;15(7):447. doi:10.1038/nrd.2016.136

12. Michael Hay, David W Thomas, John L Craighead, Celia Economides, Jesse Rosenthal. Clinical development success rates for investigational drugs. *Nat Biotechnol*. 2014;32(1):40-51. doi:doi:10.1038/nbt.2786

13. Barker RW, Scannell JW. The Life Sciences Translational Challenge: The European Perspective. *Ther Innov Regul Sci*. 2015;49(3):415-424. doi:10.1177/2168479014561340

3.2

Key considerations in the health technology assessment of gene and cell-based therapies in Scotland, the Netherlands, and England

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Abstract

Gene and cell-based therapies, defined in EU regulation as Advanced Therapy Medicinal Products (ATMPs), are highly innovative therapies. While their high costs and uncertain value claims have raised concerns amongst Health Technology Assessment (HTA) bodies and payers, little is known about their experiences with HTA of ATMPs so far. The aim of this research is therefore to provide insight into the key considerations that played a role in the HTA of ATMPs in three European countries and reimbursement recommendations.

A review of HTA-reports was conducted of authorized ATMPs in Scotland, the Netherlands and England. Considerations were extracted from HTA-reports and categorized into EUnetHTA Core Model®-domains. Per jurisdiction considerations were aggregated and key considerations identified as occurring in more than one assessment per jurisdiction. A descriptive comparison was made between jurisdictions, and between positive, restricted, and negative recommendations.

Our search yielded 15 ATMPs for 16 indications being assessed in 18 HTA-reports (Scotland: n=5, Netherlands: n=5, England: n=8). In the Netherlands and England most, key consideration were identified in the clinical effectiveness (EFF) and cost and economic effectiveness (ECO-) domains (Netherlands: 37% and 16%, England: 37% and 25% respectively). In Scotland the social aspects-domain yielded most key considerations (26%), followed by ECO- and EFF-domains (22% and 19%). It was observed more uncertainty was accepted when orphan- or end-of-life criteria were applied. Last, a trend was seen in the ratio of enabling and hindering key considerations

This is the first empirical review of HTA assessment that using the EUnetHTA Core Model to identify and structure key considerations in HTA of ATMPs. This structured overview of pro- and contra (key) considerations provides insight in HTA of individual products as well as on a Member State level. More research is needed to understand weighing of key considerations as well as allow comparison with other medicinal product groups and jurisdictions.

Introduction

Advances in biomedical science have resulted in the translation of gene and cell-based technologies into effective and safe therapies authorised by regulatory authorities.[1] In European Union regulation, the diverse group of Gene Therapy Medicinal Products (GTMPs), Cell Therapy Medicinal Products (CTMPs), Tissue Engineered Products (TEPs) and combined-advanced therapies were formally defined in 2007 as a medicinal product group: Advanced Therapy Medicinal Products (ATMPs).[2] ATMPs are expected to provide opportunities for previously untreatable indications with current development efforts targeting diseases with high unmet medical need and orphan indications in particular. To date, 15 ATMPs have received market authorization in Europe with full development pipelines suggesting that more ATMPs will reach the market in the next few years.[1,3]

For access to treatment, patients in Europe are dependent on the inclusion of ATMPs in public health care funding. Because ATMPs are associated with high costs, they are subject to formal Health Technology Assessments (HTAs) to be considered for reimbursement. HTA-bodies and payers have however been expressing concerns how to assess and appraise ATMPs[1], as an increased number of ATMPs is expected to enter the market in the coming decade. In particular the novel and uncertain value claims in combination with high (upfront) payments are deemed challenging.[4–6] Time horizons of the sustained and curative value claims exceed available clinical evidence[7], resulting in a need to extrapolate evidence to model treatment benefits despite little experience to interpret and substantiate retreatment, treatment waning and disease progression assumptions. Also, a majority of ATMPs has been authorized through expedited pathways which has downstream effects as less comprehensive data is available at time of authorization.[8,9] Finally, ATMPs are administered in single or short-term courses while claiming curative or sustained benefits. Consequently, treatment discontinuation is not possible when desired benefits are not accomplished, and cost of the failed treatment cannot be recouped.[10]

Available literature on HTA in the context of ATMPs provides several assessment of and recommendations for adjusting specific HTA components to increase the fit with ATMP characteristics.[7,11] Adjustments proposed are introduction of novel value elements, cost-effectiveness methodology, lowering budget impact, ethical considerations and ways to deal with evidentiary uncertainties at time of decision making.[7,11–15] Novel payment models are also proposed in response to the high uncertainty around (sustained) effectiveness together with high upfront payments.[16–18] Coyle et al and Angelis et al. colleagues take a more holistic approach and propose adjustments to HTA-frameworks and policies to accommodate HTA assessment of ATMPs.[7,11] HTA has also been studied from the developer perspective describing challenges and strategies in acquiring reimbursement.[5,19,20]

So far, studies that have provided empirical insights into the practice of HTA of ATMPs are limited. HTA is a multi-domain assessment comprising of more than (relative) effectiveness and cost and affordability considerations.[21] Especially in the case of ATMPs incorporation of or redefinition of novel elements are thought to be relevant.[15] Studying early experiences with HTA is useful to help shape how HTAs should be conducted.

In this study we therefore conduct a review of HTA-reports of authorized ATMPs in three European countries (Scotland, the Netherlands, and England). The aim of the review is to provide insight into key considerations that played a role in the Health Technology Assessment (HTA) of Advanced Therapy Medicinal Products (ATMPs) underlying the reimbursement recommendations. We also examined whether considerations differed between positive, restricted, and negative, recommendations were explored.

Methods

Study design

A review was conducted of HTA-reports of ATMPs published by HTA-bodies in Scotland, the Netherlands, and England. Included were all ATMPs who received a positive opinion for marketing authorization by the European Medicines Agency (EMA) up until 1 June 2020.[3] After identification of all HTA-reports of authorized ATMPs, considerations were extracted, and key considerations were identified. A consideration was defined as: "*a value judgement of the HTA-body on the presented dossier by the developer*". This definition includes considerations that may contribute to a positive recommendation as well as issues or concerns that may contribute to a restricted, or negative recommendation.

Medicinal products and jurisdictions

ATMPs were identified via a search of the EMA's Committee of Advanced Therapy (CAT) monthly reports from March 2009 (first available public report after committee establishment) until June 2020.[3] CAT reports provide a summary of all ATMP related regulatory activity in Europe, including market authorization opinions. Products who received a positive market authorization (MA) opinion were included.

Similar to previous research, eligibility of HTA-bodies in this research was assessed by applying five inclusion criteria[8]: (i) HTA-body is linked to an European jurisdiction, (ii) HTA-jurisdiction is part of the European Union at time of data collection (June 2020), (iii) the HTA body is the primary institute with legal remits within the jurisdiction, (iv) the HTA-body systematically published HTA-reports in the public domain, and (v) the published reports are written in a language understood by the researchers (i.e., English or Dutch).

This resulted in the inclusion of three HTA bodies: Scottish Medicine Consortium (SMC) from Scotland, National Health Care Institute (ZIN) from the Netherlands and the National Institute of Health and Care Excellence (NICE) from England.

Per jurisdiction HTA-reports were identified which we found to best reflect the considerations of the assessment: SMC; Detailed advice document, ZIN; Final recommendation document[in Dutch], NICE; Final appraisal document (FAD). Per jurisdiction the reports were retrieved via the HTA-bodies' website by searching the products branded and generic name.[22] If products were authorized for multiple indications, HTA reports describing the assessment for each indication were included separately[8]. Additionally, only reports describing the initial assessments were included.[23]

This excluded resubmissions, withdrawals or ongoing assessment and resulted in inclusions of one HTA-report per indication per jurisdiction.

Data extraction

Considerations were extracted from the HTA-reports using a predefined data extraction form constructed in Microsoft Excel (Microsoft Corporation, 2018, Redmond, Washington, USA). This form included a product-section (e.g., proprietary name, generic name, indication and HTA-report number), a considerations section and the reimbursement recommendation. In line with previous research, reimbursement recommendations were classified as a positive, restricted (positive with conditions) or negative.[24]

Per report considerations categorized into predefined domains after removing duplicates. The domains were derived from an existing data extraction framework: the EUnetHTA JA2 – HTA core modelv3.0®[25] (hereafter referred to as EUnetHTA core model). The EUnetHTA core model is a methodological framework for both creation as well as sharing of HTA information in a European context.[25–27] The EUnetHTA core model defines the following domains: Health problem and current use of technology (CUR), Description and technical characteristics (TEC), Clinical Effectiveness (EFF), Safety (SAF), Cost- and economic effectiveness (ECO), Ethical analysis (ETH), Organizational aspects (ORG), Patient and social aspects (SOC) and Legal aspects (LEG). Additionally, we added an 'Other (OTH)'-domain to capture any considerations not covered by the predefined domains. More information about the EUnetHTA core model®, domain definitions and a description how to categorize information (here considerations) into domains is described in detail elsewhere[25,28]. **Figure 1** provides a schematic overview of the applied data extraction form and domains.

Each consideration was labelled as a judgement supporting (pro) or opposing (contra) a positive recommendation. Both domain categorisation as well as pro-/contra-labels were mutually exclusive.

Data analysis

Extracted considerations were aggregated to a jurisdiction level. To identify key considerations, per jurisdiction considerations were merged within the domains, and indication, disease and product specific terminology generalized (e.g., intervention, disease, survival, standard of care). Using thematic content analysis, similar value judgements were grouped together and scored.[29,30] A consideration was considered key if it was mentioned more than once across HTA-reports within the same jurisdiction. Consequently, considerations which were identified once were excluded and deemed incidental or product- or disease-specific.

To illustrate key considerations, a descriptive analysis was performed of key considerations between jurisdictions.[29,30] Also, differences in key considerations products who received positive, restricted and negative recommendations were described. Data extraction and analysis was conducted by one author (RtH). A second author (JH) validated data extraction and analyses by processing of a representative sample. Inconsistencies were discussed until consensus was reached.

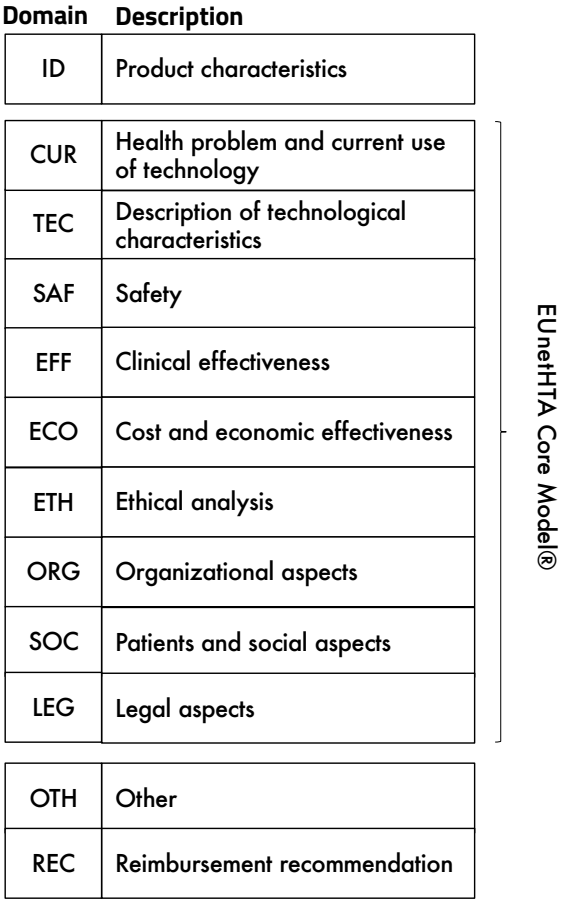

Figure 1. Schematic overview of data extraction form and domain based on the EUnetHTA Core Model® (JA2 – HTA core modelv3.0.)[25]

Results

Identified ATMPs and HTA-reports

The search of CAT monthly reports yielded 15 ATMPs for 16 indications see **Table 1.** Following initial MA, four ATMPs were withdrawn from the market by the developer. The MA of one product was suspended by the EMA.[3] Next, 18 HTA-report were identified (Scotland: n=5, Netherlands: n=5, England: n=8). Of these, 3 issued a positive recommendation (Scotland: n=0, Netherlands: n=1, England: n=2), 10 a restricted recommendation (Scotland: n=3, Netherlands: n=2, England: n=5) and 5 negative (Scotland: n=2, Netherlands: n=2, England: n=1). Table 1 shows that 6 ATMPs were not assessed by any of the included HTA bodies, 5 ATMPs by one included HTA body and 3 by all included HTA bodies. An overview of the identified reports per HTA-body is provided in **Supplemental Table S1**.

Table 1. Identified health technology assessment reports and initial reimbursement recommendations of advanced therapy medicinal products in Europe who received a positive opinion for centralized market authorization by the European Medicines Agency to date (June 2020).

Product	Indication	Market Authorization	Scotland (SMC)	The Netherlands (ZIN)	England (NICE)
ChondroCelect®*	Cartilage defect in the knee	November 2009	N/A	Negative recommendation	N/A
Glybera®*	Hyperlipo-proteinemia	November 2012	N/A	N/A	N/A
MACI®*	Cartilage defect in the knee	June 2013	N/A	N/A	N/A
Provenge®*	Prostate cancer	October 2013	N/A	N/A	N/A
Holoclar®	Limbal stem cell deficiency	December 2014	N/A	N/A	Restricted recommendation
Imlyglic®	Metastatic melanoma	December 2015	N/A	N/A	Restricted recommendation
Strimvelis®	ADA-SCID	June 2016	N/A	N/A	Positive recommendation
Zalmoxis®*	Adjuvant to HSCT in hematologic malignancies	September 2016	N/A	N/A	N/A
Spherox®	Cartilage defects in knee	July 2017	N/A	N/A	Positive recommendation
Alofisel®	Crohn's disease	March 2018	Negative Recommendation	N/A	Negative Recommendation
Yescarta®	DLBCL	Augustus 2018	Restricted recommendation	Positive recommendation	Restricted recommendation
Kymriah®	ALL	August 2018	Restricted recommendation	Restricted recommendation	Restricted recommendation
	DLBCL	August 2018	Negative recommendation	Negative recommendation	Restricted recommendation
Luxturna®	Inherited retinal dystrophy	November 2018	Restricted recommendation	Restricted recommendation	N/A
Zynteglo®	b-thalassaemia	June 2019	N/A	N/A	N/A
Zolgensma®	SMA type 1	March 2020	N/A	N/A	N/A

NA – No HTA-report identified meaning not assessed or assessment ongoing. * - market authorization withdrawn or suspended. ADA-SCID - Adenosine deaminase-severe combined immunodeficiency. HSCT – Hematopoietic Stem Cell Transplant. DLBCL – Diffuse Large B-cell Lymphoma. ALL – Acute Lymphoblastic Leukaemia. SMA – Spinal muscular Atrophy. SMC - Scottish Medicines Consortium. ZIN - Dutch National Healthcare institute. NICE - National Institute for Health and Care Excellence.

Identification of (key) consideration

Figure 2 shows a flow chart visualizing data extraction and analysis leading to identification of key considerations. In total, *557* considerations (Scotland: n=196, Netherlands: n=153, England: n=208,) were extracted from which 188 key considerations were identified (Scotland: n=69, Netherlands: n=*57*, England: n=62). A comprehensive listing of the key considerations per jurisdiction is provided in Figure S1: Scotland, Figure S2: Netherlands and Figure S3: England. The aggregate of key considerations distributed as pro- and contra-considerations is shown in **Figure 3**.

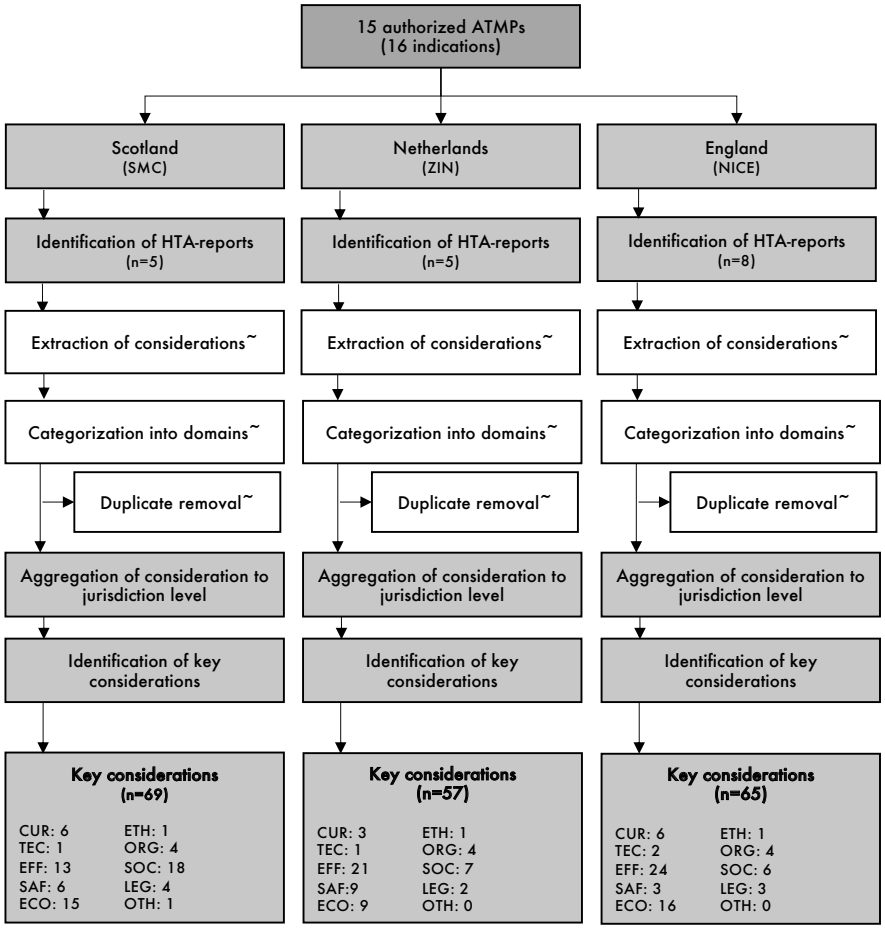

Figure 2. Flow diagram of data extraction and analysis of (key) considerations. ATMP – Advanced Therapy Medicinal Product, SMC-Scottish Medicines Consortium, ZIN-Dutch National healthcare institute, NICE-National Institute for Health and Care Excellence, CUR-Health problem and current use of technology, TEC-Description and technical characteristics, EFF-Clinical Effectiveness, SAF-Safety, ECO-Cost- and economic effectiveness, ETH-Ethical analysis, ORG-Organizational aspects, SOC-Patient and social aspects, and LEG-Legal aspects. ~These data extraction steps were conducted on a product level.

Figure 3 shows an overview of key considerations per jurisdiction. In the Netherlands and England, the Clinical effectiveness (EFF)-domain yielded most key considerations (both 37%). In Scotland the EFF-domain covered 19% of considerations and was less often considered than Patients and Social aspects (SOC-domain, 26%) and Cost and economic effectiveness (ECO-domain, 22%).

Regarding Clinical effectiveness (EFF)-domain, the pro-considerations domain describe (relative) effectiveness (See **Figures S1-S3**). In the description and valuation of (relative) effectiveness, the Netherlands distinguished between statistically significant and clinically relevant improvements. England described demonstration of clinical effectiveness together with incremental relative clinical effectiveness. Scotland describes demonstration of significant benefit which was seemingly linked to societal partaking (i.e., patients resuming work, self-care, and social activities). A supporting key consideration mentioned by all jurisdictions was awaited clinical data. This data was expected as part of market authorization conditions or (ongoing) clinical trials. The contra-considerations described evidentiary uncertainties. Uncertainties were said to be introduced due to single-arm studies (Scotland and England) and lack of direct comparative data (the Netherlands and England). The Netherlands specifically mentioned uncertainty in effect due to low data quality, while England described the lack of comparative data as challenging in the same context.

The cost and economic effectiveness (ECO)-domain covered 19%, 16% and 25% of key considerations for Scotland, Netherlands, and England respectively **(Figure 3)**. In Scotland 2 supporting considerations were identified both concerning sensitivity analysis. The majority of Scottish ECO-consideration were contra reimbursement (13 of 15) describing uncertainties due to data (primary outcome in CEA differs from trial, use of proxy data), assumptions (cure and survival assumptions) and methods (indirect comparison, extrapolation, insufficient robust analysis, utility measurement). The SMC was the only HTA-body who also described service implications and financial risk due to high upfront cost. In the Netherlands supporting considerations (4 of 9) were limited increase of budget impact, while opposing considerations (5 of 9) discussed expected increase of budget impact, insufficient methodological quality of analyses as well as uncertainty associated with cure assumptions. Albeit small, England was the only jurisdiction where more enabling than hindering key consideration were identified in the ECO domain (9 of 16**)**. Appreciation was expressed when compliance to guidance's and if as developers responded to consultation by provision of additional data or (sensitivity) analyses. Also, overlap in developer and external review group (ERG) approaches were classified as enabling. In the assessment of Holoclar® and Strimvelis® it explicitly reads that more uncertainty was accepted in the CEA given the small patient sample size. Hindering key considerations (7 of 16) showed similarities with other jurisdictions, describing high ICER (higher than considered plausible) and uncertainties in survival extrapolation, cost, and cure assumptions. Drug price and budget impact information were not disclosed in Scottish and English HTA-reports due to confidentiality agreements.

The SOC-domain yielded most key considerations in Scotland (26%). All Scottish HTAs included a section describing considerations from Patient and Clinical Engagement (PACE) meetings[31] **(Figure S1)**. A PACE-meeting can be requested by a submitting party for medicines treating (ultra-) orphan and end-of-life indications, aiming to give patient groups and clinicians a stronger voice in SMC decision making. The enabling key considerations in these assessments included impact of

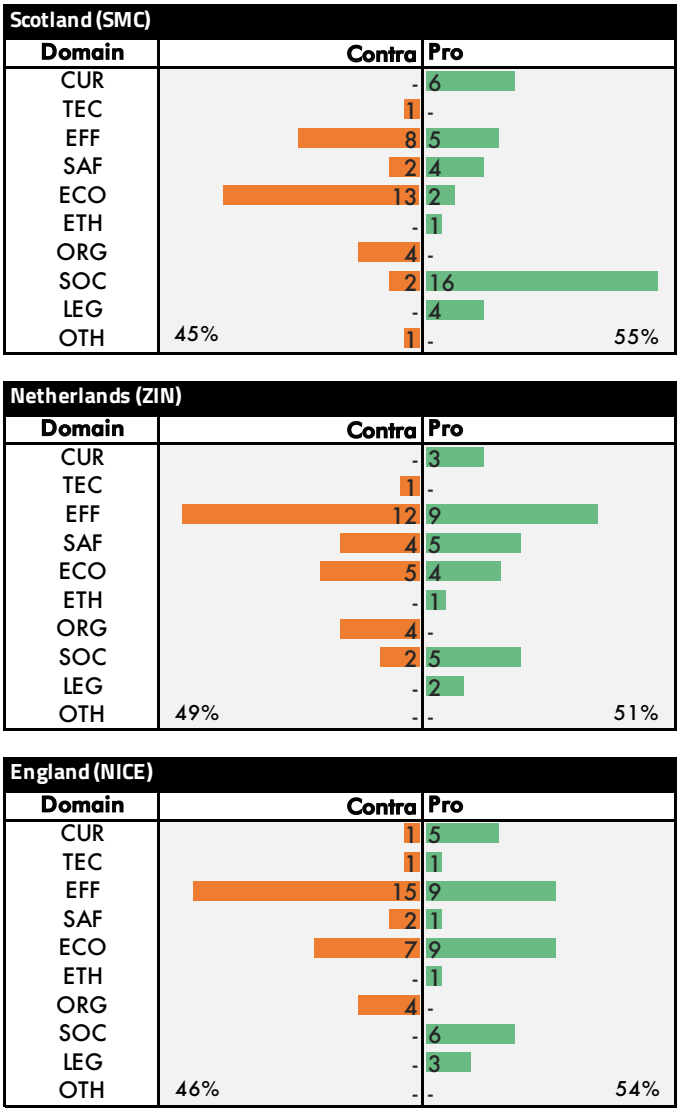

Figure 3. Distribution of identified key pro- and contra- consideration aggregated on a jurisdiction level.

the intervention as well as standard of care, the patient and carer perspective, physical and mental wellbeing, and societal partaking. Two hindering key considerations mention unknown long-term effect and significant initial monitoring after treatment. In the Dutch HTAs 12% of key considerations were identified in the SOC-domain **(Figure S2)** and some products include discussions from the Insured Package Committee (Adviescomissie Pakket: ACP). The ACP supports the Dutch HTA-body in considerations that may affect society. The enabling key value judgements included ease of use, single administration and halting of disease progression. For four products ease of use

was weighed less with increasing disease severity, in two products ease of use was even found irrelevant in the context of the life-threatening disease. In England, 5 of the 6 (9%) key considerations describe the impact of the condition on different aspects of the patient life **(Figure S3)**. No hindering key considerations in the SOC-domain were identified.

In the LEG-domain rules and regulations were included which may have implication on the HTA process, such as binding assessments or designations issued by the EMA. The ETH-domain includes health equity and ethical considerations. Scottish and English HTAs showed no specific section addressing ethical issues. In Dutch HTAs ethical considerations were described in the advice of ACP, in which an ethicist holds a position. The advice of the ACP can inform by consultation of relevant parties such as patients, physicians among them. Considerations described in the ACP meeting summary were included in the ETH-domain (**Figure S3**). It was observed that the Health problem and current use of technology (CUR-domain), legal aspects (LEG-domain) domain and Ethical analysis (ETH-domain) combined determined the conditions of an HTA. To illustrate, in Scottish HTAs where an unmet medical need was described in the disease description (CUR domain), in the ETH-domain it was made explicit that the EMA had granted an orphan designation. Accordingly, the HTA-reports mentioned that products with an orphan designation were eligible for SMC orphan criteria and assessment under the orphan framework (LEG-domain). This framework described to allow for greater uncertainty in the economic domain. Additionally, the SMC also exerts end-of-life criteria. What this meant for the assessment could not be derived from the HTA-reports.

In the Netherlands mention of unmet medical need and high disease burden in CUR-domain was often mentioned in the context of orphan indication (ETH-domain) by the ACP. Additionally, in the two most recent HTAs design of an orphan drug agreement (addressing pricing and data collection) was advised (LEG-domain). In England a similar observation was made where unmet medical need was described alongside limited treatment options (CUR-domain). Two ATMPs in England were classified as ultra-orphan conditions (ETH-domain) which seemed to have implications for acceptance of uncertainty in the assessment (LEG-domain). Also, end-of life-criteria were applied in HTA of three products. The final section of these three HTA-report reads that the ICER estimates are highly uncertain and often higher than what NICE considers acceptable. Therefore, these products could not be recommended for use in the national health services (NHS). However, the HTA-body considered that the uncertainties could be addressed with additional collection of specific data. Therefore the products were recommended for use under the Cancer Drug Fund (CDF) which is an interim funded Manged Access Agreement and the products received a restricted recommendation[32]. To add, whether use of the CDF would also have been granted to non or different oncologic agents or to oncologic agents wo did not meet end-of-life criteria could not be derived from this sample.

The ORG-domain covered 6%, 7% and 6% of total key considerations in Scotland, the Netherlands and England respectively and were all labelled as contra arguments. In the Netherlands limited experience and administration in specialized centres was emphasized, while in Scotland a need for appropriate centres with experienced staff was considered. In the England a '*great*' need was expressed for staff training to treat and handle adverse events (AEs). Also, administration in specialist centres was considered. It seemed this domain did not bare much weight in the assessment. This is based on the observation that organizational consideration were to a lesser extent reiterated in the HTA-report conclusions or summaries compared to considerations identified in other domains.

Positive, restricted, and negative recommendations

The HTAs identified in this research were categorized in positive, restricted, or negative recommendations (**Table 1**). Acknowledging limited sample size, the authors aimed to identify trends by comparing key consideration-figures between these three recommendations (**Figure 4**). The percentage of enabling key consideration of products resulting in a positive recommendation in the Netherlands was 53%. This percentage is similar to product who received a restricted recommendation (52%), but higher when compared to the negative recommendations (41%). A stronger pattern was seen in England: positive 77%, restricted 51% and negative 43%. In Scotland no positive recommendations were identified. Amongst the restricted recommendations 55% of key considerations was enabling, this was 53% in the negative group. This suggest that the weight of individual consideration or domains plays a role in the recommendation. Our sample was too small to substantiate this trend.

We did observe that in the HTAs of the ATMPs with a negative recommendation (Scotland: n=2, the Netherlands: n=2, England: n=1) the ICER estimates exceeded willingness to pay thresholds combined with a large confidence interval, described as highly uncertain estimates. Additionally, these HTA-reports described less satisfaction in mitigation of factors contributing to uncertainties. HTAs in which identified uncertainties were addressed by the developer seemed more likely to receive a positive or restricted recommendation. A hindering key considerations seemed to be weighed less if the issue was addressed or demonstrated little impact. A measure or clarification of a hindering consideration was often classified as enabling (**Figures S1-S3**) as it were to outweigh the issue. Hindering considerations were addressed via quantification (additional sensitivity analyses in CEA), providing context for choice of methods (no or little data available) or inclusion of alternative (e.g., historic, real-world, literature) evidence. Additionally, if addressed uncertainties demonstrated high impact on the ICER, additional measures were put in place or requested. Examples were risk mitigation plans, additional trials, trainings, and development of materials for clinicians and patients. The additional clinical trials could be company initiated or mandated by the EMA (e.g., conditional marketing authorization or post-authorisation safety studies). Recommended studies by the HTA-bodies included set-up of registries or addition of country specific effectiveness and quality of life measures to existing trials or registries. Not all uncertainties could be addressed at time of the assessments. For example, lack of long-term effectiveness and safety evidence or re-treatment data were described as weighty. Merely the prospect of additional clinical evidence seemed to contribute to the acceptance of uncertainties regarding long-term effectiveness, safety, and re-treatment. Addressing residuary uncertainties were found to appear in the conditions of restricted recommendations.

Discussion

In this review of HTA report, key considerations were identified in the assessment of ATMPs in three European jurisdictions: Scotland, the Netherlands, and England. Considerations were categorized using the EUnetHTA Core Model[25]. In the Netherlands, and England most key consideration were identified in the EFF- and ECO- domains (Netherlands: 37% and 16%, England: 37% and 25% respectively). In Scotland the SOC-domain yielded most key considerations (26%), followed by

Scotland (SMC)	Restricted (n=3)		Negative (n=2)	
Domain	Contra	Pro	Contra	Pro
CUR	-	6	-	4
TEC	1	-	1	-
EFF	7	5	7	4
SAF	2	4	2	2
ECO	13	2	13	2
ETH	-	1	-	1
ORG	4		4	-
SOC	2	14	-	15
LEG	-	4	-	4
OTH	45% 1	- 55%	47% 1	- 53%

Netherlands (ZIN)	Positive (n=1)		Restricted (n=2)		Negative (n=2)	
Domain	Contra	Pro	Contra	Pro	Contra	Pro
CUR	-	2	-	3	-	3
TEC	1	-	1	-	1	-
EFF	7	7	11	7	11	2
SAF	3	5	3	3	3	4
ECO	4	1	4	4	2	1
ETH	-	1	-	1	-	1
ORG	3	-	3	-	4	-
SOC	1	4	1	5	2	4
LEG	-	1	-	2	-	1
OTH	48% -	- 53%	48% -	- 52%	59% -	- 41%

England (NICE)	Positive (n=2)		Restricted (n=5)		Negative (n=1)	
Domain	Contra	Pro	Contra	Pro	Contra	Pro
CUR		3	1	5	1	2
TEC	1	1		1	1	1
EFF	5	7	14	7	10	3
SAF	-	1	2	1	-	-
ECO	1	6	7	8	3	2
ETH	-	1		1	-	-
ORG	-	-	4	-	1	-
SOC	-	3	-	3	-	4
LEG	-	2	-	3	-	-
OTH	23% -	- 77%	49% -	- 51%	57% -	- 43%

Figure 4. Key considerations stratified by reimbursement recommendation. In Scotland no positive recommendations were identified.

ECO- and EFF-domain (22% and 19%). We also observed that the LEG-, CUR- and ETH-domain imposed assessment conditions via orphan- or end-of-life criteria which, among other conditions, allowed for acceptance of more uncertainty in decision-making. Last, a trend was observed in the ratio between key considerations supporting and opposing a positive recommendation and observed recommendation outcomes, with a higher percentage supporting key considerations identified in positive recommendations and lower percentages in restricted and negative recommendations.

In literature some argue that ATMPs are considerable different from more established medicinal products such as small molecules or biologicals.[33,34] This is to some extent reflected in the key considerations regarding the technical and organisational domain describing impact of lengthy

manufacturing processes and measures needed for proper transportation and admission. Additionally, only Scotland described service implications and financial risk due to high upfront cost in the ECO-domain. In other domains, identified key considerations show overlap with challenges previously also described in the assessment of orphan products increased advancement of statistical methods and non-randomized evidence.[35–37] In line, NICE mentioned in the HTA of Holoclar® a collaboration with the Centre for Reviews and Dissemination and Centre for Health Economics, University of York.[38] This collaboration yielded a report that investigated whether NICE's assessment and appraisal methods were fit for purpose for regenerative medicines and cell therapies. It concluded that the appraisal methods and decision framework was largely applicable but individual elements may need adjustment. Several studies describe similar findings.[7,11,12,17]

While prior studies have identified key considerations from HTA reports, they have not focused specifically on ATMPs. However, similarities are observed with findings of research addressing assessments of orphan products and conditional marketing authorization. First, Vreman et al. found that based on similar evidence HTA-agencies from different countries may formulate different recommendations.[8] This is described previously and is said to be caused by application of different HTA frameworks and conditions.[24,26] Although our sample is small, we did observe different recommendations for same products between jurisdictions. Additionally, applications of country specific conditions (e.g., end-of-life, orphan criteria) affected weighing of evidence in specific domains. Next, the same authors suggests that demonstrated statistical or clinical significant benefit of orphan indicated products may positively drive assessment of relative effectiveness in the HTA.[39] This is in line with our observation that if (unmet) medical need is demonstrated more uncertainty may be accepted in the assessment.

We used the EUnetHTA model to categorize key considerations. Application of the EUnetHTA model in HTA research is not new.[40–42] Although technologies, jurisdictions and purpose differ between studies, use of similar terminology and definitions increases transferability and dissemination. Additionally, Radaelli et al describes that issues (here contra key indications) identified by following the EUnetHTA workflow represented the questions that need to be addressed in the assessment.[41] As a result, application of the model allowed for breakdown of the assessment in smaller units which could be assigned to experts.[41] In our research these smaller units and provided insight in the content of discussions underlying the reimbursement recommendations. When categorizing considerations into EUnetHTA domains overlap in domain descriptions was experienced, especially in the ETH-, SOC- and CUR-domain. This has previously been described in literature.[21] Also, by using a framework (EUnetHTA Core Model®) well-known amongst HTA-bodies, it was aimed to increase the understanding and transferability of our insights to policy makers and researchers. The OTH-domain, which was added by the authors to capture considerations not captured by the EUnetHTA framework, yields one key consideration in Scotland and none in the Netherlands and England. This may suggest our approach has a sufficient fit and may be appropriate for its intended purpose within this research.

Taking a wider perspective, in ATMP-literature payment models have been discussed as solution to address both high cost and evidentiary uncertainties.[17,18,43] The innovative payment models proposed in literature such as annuity payment, outcome based payment or coverage with evidence

development were not widely discussed in the included assessments.[43,44] However, application of the CDF in England and the orphan drug agreement in the Netherlands can be seen as payment agreements allowing for early patient access while additional data is collected. Application of novel and more advanced statistical methods were not observed, neither were novel value elements considered.[45,46]

Our research has several limitations. First, the reports represent a written summary of the HTAs and discussions. We realize that not all considerations were included in the reports and detail may be lost including an understanding of the weight of individual arguments. Second, the used definitions of considerations may be subject of discussion. It is also important to realize that our approach is sensitive to time as policies change over time. Additionally, the high incidence of CAR-T products (9 of 18) may have yielded identification of key considerations reflecting benefits and hinderances mainly for these therapies and less for ATMPs in general. The results of this study should therefore be considered as a snapshot of assessments within a rapidly evolving field. Next, analysis and interpretation of qualitative research is sensitive to bias.[30] This is a limitation inherent to the type of research. To decrease bias and increase external validity, data extraction and analysis was conducted by two authors. This approach is highly recommended and considered good research practice in qualitative research.[30,47] To continua, the included HTA-bodies are known to be quite advanced and similar in their approach.[26,48] Therefore, replication of this research in jurisdictions with less alike HTA-processes could result in poorer fit or adjustment of methodology. Last, our study does not include a comparator cohort, which impedes interpretation of our results. For example, if alternative assessment conditions were not applied would the recommendations outcomes been different? At time this analysis was conducted, little empirical evidence is available to contextualize our findings. Although this can be seen as a limitation, it also demonstrates the novelty of the approach and the need for future research. It would be of interest to contextualize the findings in future research and apply the analyses to different jurisdictions. Additionally, more in-depth qualitative research could be conducted via interview-based studies within an HTA-bodies. This may derive learnings of how HTA-agencies accommodated to novel technologies and accumulation of uncertainties. This could contribute to assessment of so-called *organizational learning* and *organizational readiness*.[49,50]

To conclude, this study used the EUnetHTA Core Model to identify and structure key consideration in health technology assessment of ATMPs in 3 European jurisdictions. We found some ATMP-specific considerations, but most identified key considerations overlapped with known considerations for orphan medicines and conditional approved products. We found that considerations outside the common described effectiveness and cost-effectiveness domains may bare considerable weight in formulation of the recommendation including ethical and legal aspects. Also, specific criteria (e.g., orphan or end-of-life) may alter conditions of the assessment. Additional research is needed to explain consideration and recommendation variances in more detail as well as allow for comparison with other medicinal product groups and jurisdictions.

Conflicts of interest

The authors have no conflicts of interest to declare.

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References

1. Eder C, Wild C. Technology forecast : advanced therapies in late clinical research , EMA approval or clinical application via hospital exemption. *J Mark Access Heal Policy*. 2019;7(1). doi:10.1080/20016689.2019.1600939

2. The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council. *Off J Eur Union*. 2007;324((EC)1394/2007):121-138. http://data.europa.eu/eli/reg/2007/1397/oj.

3. European Medicines Agency. *CAT Monthly Report of Application Procedures, Guidelines and Related Documents on Advanced Therapies - June 2020 Meeting*. Vol EMA/CAT/34.; 2020.

4. Hanna E, Tavella F, Rémuzat C, Auquier P, Toumi M. Market Access of Atmps: Overview and Expected Challenges. *Value Heal*. 2015;18(7):A518-A519. doi:10.1016/j.jval.2015.09.1580

5. Morrow D, Ussi A, Migliaccio G. Addressing Pressing Needs in the Development of Advanced Therapies. *Front Bioeng Biotechnol*. 2017;5(9):1-6. doi:10.3389/fbioe.2017.00055

6. Ermisch M, Bucsics A, Bonanno PV, et al. Payers' views of the changes arising through the possible adoption of adaptive pathways. *Front Pharmacol*. 2016;7(SEP):1-9. doi:10.3389/fphar.2016.00305

7. Coyle D, Durand-Zaleski I, Farrington J, et al. HTA methodology and value frameworks for evaluation and policy making for cell and gene therapies. *Eur J Heal Econ*. 2020;2:1421-1437. doi:10.1007/s10198-020-01212-w

8. Vreman RA, Bouvy JC, Bloem LT, et al. Weighing of Evidence by Health Technology Assessment Bodies: Retrospective Study of Reimbursement Recommendations for Conditionally Approved Drugs. *Clin Pharmacol Ther*. 2018;105(3). doi:10.1002/cpt.1251

9. Vreman RA, Naci H, Goettsch WG, et al. Decision Making Under Uncertainty: Comparing Regulatory and Health Technology Assessment Reviews of Medicines in the United States and Europe. *Clin Pharmacol Ther*. 2020;0(0). doi:10.1002/cpt.1835

10. Towse A, Fenwick E. Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment? *Value Heal*. 2019;22(6):677-683. doi:10.1016/j.jval.2019.03.013

11. Angelis A, Naci H, Hackshaw A. Recalibrating Health Technology Assessment Methods for Cell and Gene Therapies. *Pharmacoeconomics*. 2020;(0123456789). doi:10.1007/s40273-020-00956-w

12. ten Ham RMT, Klungel OH, Leufkens HGM, Frederix GWJ. A Review of Methodological Considerations for Economic Evaluations of Gene Therapies and Their Application in Literature. *Value Heal*. 2020;23(9):1268-1280. doi:10.1016/j.jval.2020.04.1833

13. Petrou P. Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy. *Expert Rev Pharmacoecon Outcomes Res*. 2019;00(00):1-8. doi:10.1080/14737167.2019.1651646

14. Rozier P, Maria A, Goulabchand R, Jorgensen C, Guilpain P, Noël D. Mesenchymal Stem Cells in Systemic Sclerosis: Allogenic or Autologous Approaches for Therapeutic Use? *Front Immunol*. 2018;9(December):2938. doi:10.3389/fimmu.2018.02938

15. Gonçalves E. Advanced therapy medicinal products: value judgement and ethical evaluation in health technology assessment. *Eur J Heal Econ*. 2020;21(3):311-320. doi:10.1007/s10198-019-01147-x

16. Carr DR, Bradshaw SE. Gene therapies: The challenge of super-high-cost treatments and how to pay for them. *Regen Med*. 2016;11(4):381-393. doi:10.2217/rme-2016-0010

17. Jørgensen J, Kefalas P. Annuity payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. *J Mark Access Heal Policy*. 2017;5(1):1355203. doi:10.1080/20016689.2017.1355203

18. Barlow J, Bens C, Brent T, et al. AMCP Partnership Forum: Designing benefits and payment models for innovative high-investment medications. *J Manag Care Spec Pharm*. 2019;25(2):156-162. doi:10.18553/jmcp.2019.25.2.156

19. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. *J Mark Access Heal Policy*. 2015;3(1):29321. doi:10.3402/jmahp.v3.29321

20. Hanna E, Rémuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. *J Mark Access Heal Policy*. 2016;4(1):31036. doi:10.3402/jmahp.v4.31036

21. Facey K, Scalzo A Lo. EUnetHTA HTA Core Model: Patient and Social Aspects EUnetHTA JA2 HTA Core Model. In: Welfare NI for H and, ed. *EUnetHTA HTA Core Model v3.0*. 1st ed. Diemen, the Netherlands; 2016:411.

22. Bloem LT, Vreman RA, van Oirschot S, et al. The Role of Regulator-Imposed Post-Approval Studies in Health Technology Assessments for Conditionally Approved Drugs. *Int J Heal Policy Manag*. 2020;(x):1-9. doi:10.34172/ijhpm.2020.198

23. Lipska I, Hoekman J, McAuslane N, Leufkens HGM, Hövels AM. Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions? *Clin Pharmacol Ther*. 2015;98(5):489-491. doi:10.1002/cpt.198

24. Kleijnen S, Lipska I, Leonardo Alves T, et al. Relative effectiveness assessments of oncology medicines for pricing and reimbursement decisions in European countries. *Ann Oncol*. 2016;27(9):1768-1775. doi:10.1093/annonc/mdw233

25. EUnetHTA Joint Action. HTA Core Model Handbook. *EUnetHTA JA*. 2011;2:1-14. https://www.eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf%0Ahttp://www.corehta.info.

26. Allen N, Liberti L, Walker SR, Salek S. A comparison of reimbursement recommendations by European HTA agencies: Is there opportunity for further alignment? *Front Pharmacol*. 2017;8(JUN). doi:10.3389/fphar.2017.00384

27. Allen N, Walker SR, Liberti L, Salek S. Health Technology Assessment (HTA) Case Studies: Factors Influencing Divergent HTA Reimbursement Recommendations in Australia, Canada, England, and Scotland. *Value Heal*. 2017;20(3):320-328. doi:10.1016/j.jval.2016.10.014

28. EUnetHTA JA2. *The HTA Core Model® Guiding Principles on Use*. Diemen, the Netherlands; 2011. https://eunethta.eu/wp-content/uploads/2018/01/The-HTA-Core-Model_Guiding-principles-on-use_20151218.pdf.

29. Phan YH Le, De Abreu Lourenco R, Haas M, van der Linden N. Key considerations in reimbursement decision-making for multiple sclerosis drugs in Australia. *Mult Scler Relat Disord*. 2018;25(May):144-149. doi:10.1016/j.msard.2018.07.020

30. Ajay Bailey, Hutter I. *Qualitative Research Methods*. 1st ed. (Hutter I, ed.). SAGE Publications, Inc.; 2010.

31. Healthcare improvement sctoland. *Patient and Clinician Engagement (PACE) Process.*; 2014. https://www.scottishmedicines.org.uk/how-we-decide/pace/.

32. CDF England Team. Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund) A new deal for patients, taxpayers and industry. *Off Doc Publ by NHS Engl (available https//www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf)*. 2016;(7):1-65. https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf.

33. Buckland KF, Bobby Gaspar H. Gene and cell therapy for children - New medicines, new challenges? *Adv Drug Deliv Rev*. 2014;73(February):162-169. doi:10.1016/j.addr.2014.02.010

34. Coppens DGM. Regulating gene and cell-based therapies as medicinal products. 2020. https://dspace.library.uu.nl/handle/1874/390654.

35. Kanters TA. Health technology assessment of orphan drugs. The example of Pompe disease. 2016. https://repub.eur.nl/pub/94383.

36. Griffiths EA, Macaulay R, Vadlamudi NK, Uddin J, Samuels ER. The Role of Noncomparative Evidence in Health Technology Assessment Decisions. *Value Heal*. 2017;20(10):1245-1251. doi:10.1016/j.jval.2017.06.015

37. Phillippo DM, Dias S, Elsada A, Ades AE, Welton NJ. Population Adjustment Methods for Indirect Comparisons: A Review of National Institute for Health and Care Excellence Technology Appraisals. *Int J Technol Assess Health Care*. 2019;35(3):221-228. doi:10.1017/S0266462319000333

38. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: An exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess (Rockv)*. 2017;21(7):1-204. doi:10.3310/hta21070

39. Vreman RA, de Ruijter AS, Zawada A, et al. Assessment of significant benefit for orphan medicinal products by European regulators may support subsequent relative effectiveness assessments by health technology assessment organizations. *Drug Discov Today*. 2020;25(7):1223-1231. doi:10.1016/j.drudis.2020.04.012

40. Vettoretto N, Foglia E, Ferrario L, et al. Could fluorescence-guided surgery be an efficient and sustainable option? A SICE (Italian Society of Endoscopic Surgery) health technology assessment summary. *Surg Endosc*. 2020;34(7):3270-3284. doi:10.1007/s00464-020-07542-3

41. Radaelli G, Lettieri E, Masella C, Merlino L, Strada A, Tringali M. Implementation of eunethta core model® in lombardia: The VTS framework. *Int J Technol Assess Health Care*. 2014;30(1):105-112. doi:10.1017/S0266462313000639

42. Brenna E, Polistena B, Spandonaro F. The implementation of health technology assessment principles in public decisions concerning orphan drugs. *Eur J Clin Pharmacol*. 2020;76(6):755-764. doi:10.1007/s00228-020-02855-7

43. Drummond M, Towse A. Is rate of return pricing a useful approach when value-based pricing is not appropriate? *Eur J Heal Econ*. 2019;0(0):0. doi:10.1007/s10198-019-01032-7

44. Hanna E, Toumi M, Dussart C, et al. Funding breakthrough therapies : A systematic review and recommendation. *Health Policy (New York)*. 2018;122(3):217-229. doi:10.1016/j.healthpol.2017.11.012

45. Drummond MF, Neumann PJ, Sullivan SD, et al. Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy. *Value Heal*. 2019;22(6):661-668. doi:10.1016/j.jval.2019.03.012

46. Jönsson B. Economic Evaluation of Health Care Technologies. *Encycl Public Heal*. 2008;128 Suppl(PG-50-4):316-316. doi:10.1007/978-1-4020-5614-7_917

47. Leung L. Validity, reliability, and generalizability in qualitative research. *J Fam Med Prim Care*. 2015;4(3):324-327. doi:10.4103/2249-4863.161306

48. Allen N, Pichler F, Wang T, Patel S, Salek S. Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. *Health Policy (New York)*. 2013;113(3):305-312. doi:10.1016/j.healthpol.2013.09.007

49. Uzkurt C, Kumar R, Ensari N. Assessing organizational readiness for innovation: An exploratory study on organizational charachteristics of innovativeness. *Int J Innov Technol Manag.* 2013;10(4). doi:https://doi.org/10.1142/S0219877013500181

50. Rashman L, Withers E, Hartley J. Organizational learning and knowledge in public service organizations: A systematic review of the literature. *Int J Manag Rev.* 2009;11(4):463-494. doi:10.1111/j.1468-2370.2009.00257.x

Supplemental Materials

Table S1. Identified health technology assessment reports per jurisdiction.

Product	Indication	Scotland (SMC)	England (NICE)	The Netherlands (ZIN)
ChondroCelect®	Cartilage defect in the knee	N/A	N/A	ZA/2011043883
Glybera®	Hyperlipo-proteinemia	N/A	N/A	N/A
MACI®	Cartilage defect in the knee	N/A	N/A	N/A
Provenge®	Prostate cancer	N/A	N/A	N/A
Holoclar®	Limbal stem cell deficiency	N/A	TA-467	N/A
Imlyglic®	Metastatic melanoma	N/A	TA-410	N/A
Strimvelis®	ADA-SCID	N/A	HST-7	N/A
Zalmoxis®	Adjuvant to HSCT in hematologic malignancies	N/A	N/A	N/A
Spherox®	Cartilage defects in knee	N/A	TA-508	N/A
Alofisel®	Crohn's disease	SMC2115	TA-556	N/A
Yescarta®	DLBCL	SMC2189	TA-559	2019005725
Kymriah®	ALL	SMC2129	TA-554	2018062717
	DLBCL	SMC2141	TA-567	2019006480
Luxturna®	Inherited retinal dystrophy	SMC2228	Under assessment	2020001290
Zynteglo®	b-thalassaemia	N/A	Under assessment	N/A
Zolgensma®	SMA type 1	N/A	N/A	Under assessment

ADA-SCID - Adenosine deaminase-severe combined immunodeficiency. HSCT – Hematopoietic Stem Cell Transplant. DLBCL – Diffuse Large B-cell Lymphoma. ALL – Acute Lymphoblastic Leukaemia. SMA – Spinal muscular Atrophy. SMC - Scottish Medicines Consortium. ZIN - Dutch National Healthcare institute. NICE - National Institute for Health and Care Excellence.

Scotland (SMC)			
Domain	**Contra**	**Pro**	**Key considerations**
CUR		5	Unmet medical need
		3	No treatment available
		2	Clinical advancement due to new mode of action
		2	High treatment burden of standard of care
		2	Intervention is considered therapeutic advancement
		2	Severely debilitating indication
TEC	4		Intervention manufactured in specialist laboratory
EFF		4	Product demonstrated significant benefit
		3	Patient may resume work, self-care and social activities
		3	Long-term efficacy data awaited
		2	Ongoing remission may reduce emotional and financial burden of patients, family and caregivers
		2	Long term effect biologically plausible
	5		Uncertainty about long term efficacy
	3		Only single-arm studies available
	3		Longer term benefit of treatment is unclear
	3		Only open-label studies available
	2		Pooling of studies possibly inappropriate due to study differences
	2		High overall study dropout, which may affect long term results
	2		Uncertainty of retreatment effect
	2		Uncertainty what patients may respond
SAF		3	Longer term safety data awaited
		2	Intervention generally well tolerated
		2	Patients and family willing to accept inconvenience of prolonged inpatient stay
		2	Patients and family willing to accept inconvenience of prolonged monitoring
	3		Significant toxicities associated with intervention
	2		Uncertainty about long-term safety
ECO		3	Survival extrapolation approaches included in sensitivity analysis
		2	Comprehensive sensitivity analysis
	3		Uncertainty in measurement of utilities
	3		Bridging therapy may have had impact on product efficacy
	3		High ICER
	3		High upfront costs expected to have service implications
	3		High upfront cost associated with financial risk in combination with uncertain long-term benefits
	3		Uncertainty in plausibility of extrapolated effectiveness
	3		Indirect comparison
	3		Efficacy data informing analysis may be enriched by delay in production of product
	2		Uncertainty about cure assumptions
	2		Insufficient robust economic analysis
	2		Primary outcome in CEA differs from trial
	2		Proxy data used to model effect of comparator
	2		Utility data based on small sample of clinician responses
ETH		5	Orphan indication
ORG	4		Appropriate facilities and experienced personnel needed for admission, manufacturing and monitoring
	3		Implications for the service in preparing patients for administering
	3		Introduction of product requires additional consultant and medical support
	2		Emergency equipment needed on-site to manage adverse events
SOC		4	Possibility of long-term disease control is likely to outweigh risk
		3	Product offer prospect to increase QoL and reduce disease burden (patient and caregivers)
		3	SOC has high treatment burden
		3	SOC requires successive courses
		3	SOC requires frequent follow-up and hospital attendances
		3	Intervention is one-off treatment which may be advantage to patient and their family
		3	Responders may become self-caring
		3	Responders may be able to return to work or education
		3	Responders may regain independence
		3	Responders may have overall improved QoL
		3	Responders may recover quicker
		3	Product may reduce caring responsibilities and psychological distress for patient's family
		3	Symptoms have negative impact on mental health patients, family and carers.
		2	Product appears to be well tolerated
		2	Population is often younger resulting in lifetime disease burden
		2	Product offers prospect of long-term healing
	2		Long-term effects are unknown
	2		Patients requires significant initial monitoring after treatment
LEG		5	Product has EMA orphan designation
		5	Product meets SMC orphan criteria
		5	SMC can accept greater uncertainty in the economic case for this product by assessment in orphan framework
		3	Product meets SMC end of life criteria
OTH	2		Another (similar) technology is currently undergoing SMC assessment for the treatment of DLBCL

Table S1. Identified key consideration in Scotland in health technology assessment reports from the Scottish Medicines Consortium (SMC)

Netherlands (ZIN)			
Domain	**Contra**	**Pro**	**Key considerations**
CUR		5	High disease burden
		5	Limited treatment options
		2	Unmet medical need
TEC	3		3-4 week delay to treatment start due to manufacturing. Comparator can be started immediately.
EFF		4	A significant and relevant improvement was found in effectiveness
		3	Discontinuation of treatment is not applicable in a one-off treatment
		3	Applicability intervention is acceptable
		3	Long term effectiveness data awaited
		2	Improvement occurs quickly (within a month after injection)
		2	Effectiveness data suggests persistence
		2	Percentage drop-out not relevant endpoint due to one-time treatment
		2	Significant increase in estimated overall survival (>3 months, which is minimal clinically relevant)
		2	It is not expected the true incremental OS is less than 3 months
	4		Treatment effects based on indirect comparison which introduces uncertainty
	4		Treatment effect is uncertain due to low quality of evidence
	4		No data on maintaining effectiveness is available
	3		Discontinuation of pre-treatment can occur
	3		Uncertainty around generalisability to Dutch patient population
	3		Lack of retreatment data
	3		Cure assumption based on very little number of patients introducing uncertainty
	2		Blinding of treatment not possible due to additional surgery required in treatment
	2		Effect of intervention cannot be separated from pre-treatment.
	2		Even when follow-up is continued the quality of evidence will remain low
	2		Effect size estimate uncertain due to bias of residual confounding
	2		Relative effect insufficiently substantiated: Too much uncertainty to draw conclusion
SAF		3	Long-term safety data awaited
		3	EMA compelled developer to develop safety materials to decrease is of Aes
		2	Adverse events may be severe but are well treatable
		2	Measures can be put in place to limit risk of adverse events
		2	Considering the severity of the condition, the adverse effects are considered acceptable
	3		Treatment associated with high risk of severe adverse events
	2		Long term safety is uncertain
	2		Lack of long-term safety data
	2		No comparison was made between adverse events of intervention and comparator
ECO		2	Expected BI below Dutch threshold to conduct mandatory economic evaluation: No CEA is conducted
		2	Product may replace several therapies
		2	No indication expansions expected, (short term)
		2	No off label expected as product is only applicable for specific mutation
	2		Cost-effectiveness analysis was found to be of insufficient methodological quality
	2		Model is sensitivity to changes in overall survival estimates
	2		Cure assumptions inadequately addressed in sensitivity analyses
	2		Model is highly sensitive to changes in the cure assumption
	2		Product is investigated for multiple indication which expected to increase budget impact
ETH		4	Orphan indication
ORG	5		Experience with product is limited
	4		Product will only be supplied to qualified treatment centres
	3		Treatment centres are required to have emergency equipment available
	2		Treatment centres are required to stock AE management treatment
SOC		4	Ease of use is found acceptable given disease severity
		3	One-time treatment
		3	Ease of use is found irrelevant in life threatening diseases
		2	Halting of disease progression is important for patients
		2	Pre- and post-treatment should be considered in ease of use assessment
	2		After admission patient are required to stay 10 days in vicinity of hospital, this is found burdensome
	2		Less ease of use compared to comparator due to additional surgery
LEG		4	Product has orphan designation
		2	Orphan drug agreement should include appropriate use (e.g. indication committee and evaluation via i
OTH	-	-	-

Table S2. Identified key consideration in the Netherlands in health technology assessment reports from the Dutch National Health Care Institute (ZIN)

England (NICE)			
Domain	**Contra**	**Pro**	**Key considerations**
CUR		5	Unmet medical need
		4	Limited treatment options available
		3	Most appropriate SOC was used in submission
		3	SOC is associated with severe side effects
		2	SOC is usually not curative and remission rates are low
	2		Experts explained that evidence on the natural history of indication is limited
TEC		8	Product found to be innovative
	2		Because of its short shelf life, planning and scheduling is necessary to avoid cancelation and waste
EFF		6	Product is found clinically effective
		6	Intervention demonstrated incremental relative effectiveness compared to comparator
		6	Clinical evidence is awaited
		5	Study results considered generalisable to UK clinical practice
		4	Despite long-term data limitations, no alternative data available for SOC. Therefore was data accepted
		2	The approach to compare product with SOC was appropriate for decision making
	6		Evidence consists of single arm studies only, no direct comparison possible
	5		Lack of comparative data makes comparative assessment challenging
	5		Long-term evidence is uncertain and it is known if treatment is curative
	4		Relative effectiveness subject to uncertainty due to differences in trial populations
	3		It is unclear how long the treatment benefit will last
	3		Number of patient needing an aSCT is found highly uncertain
	2		Small patient numbers made OS results uncertain
	2		Survival data was found to be immature
	2		Uncertainty in generalisability of comparator arm to UK clinical practice
	2		Newly submitted long term benefit evidence did not clarify uncertainties
	2		Rate of subsequent aSCTs has substantial impact on CE estimates
	2		HRQOL trial data not collected according to NICE technology appraisal guidance
	2		Choice of curves has a large impact in the ICER
	2		Utility values in some health state were found low
	2		CE estimates highly uncertain, therefore not possible to decide on most plausible CE estimate
SAF		2	Clinical experts find improved toxicity profile compared to SOCs major benefit
	2		Unknown how many patients may need AE treatment
	2		Intervention is associated with frequent and severe adverse events
ECO		6	Model structure was found appropriate for decision making
		6	No additional benefit that had not been captured in CEA
		3	Discounting was applied according to the guidance
		2	Newly submitted data after consultation was found informative
		2	More uncertainty was accepted given the small sample size
		2	In response to consultation, company provided updated analysis to better reflect UK clinical practice
		2	The company's approach may have underestimated OS for SOC
		2	Applied model structure was found reasonable for decision making
		2	The company's revised base case included most of the committee's preferred assumptions
	5		Most plausible CE-estimates are higher than what is considered acceptable
	5		Extrapolation of OS is important source of uncertainty in model
	2		Not enough treatment cost evidence
	2		Cost of AE management is uncertain but expected to have impact
	2		Lack of long-term data reflected in large cure variance
	2		Specific utility values were found highly uncertain
	2		Applied differential discounting rates do not adhere with NICE TA guidance
ETH		2	Ultra-orphan condition
ORG	4		Great need of staff training required to treat and handle adverse events
	4		It is suggested product is only administered in specialist centres
	3		Introduction of intervention needs provision of a new service
	2		Interevention logistics (Transport, storage, administration accreditation, staff training and IC access to manage AEs) need to be included
SOC		4	Patient welcome new treatments options that with improved effectiveness
		3	Condition is highly debilitating
		2	Condition has big effect of everyday life
		2	Condition greatly reduces patient's quality of life
		2	Condition is associated with high levels of pain
		2	Condition limits patients in their everyday activities
LEG		3	Intervention met both of NICE's criteria to be considered a life-extending treatment at the end of life
		2	Ultra-orphan designation
		2	PPRS payment mechanism was not relevant in considering the CEA of technology in this appraisal
OTH	-	-	-

Table S3. Identified key consideration in England in health technology assessment reports from the National Institute of Health and Care Excellence (NICE)

4

Cost-effectiveness, value and affordability of gene and cell-based therapies

4.1

A Review of methodological considerations for economic evaluations of gene therapies and their application in literature

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Abstract

To identify methodological considerations discussed in literature addressing economic evaluations (EEs) of gene therapies (GTs). Additionally, we assessed if these considerations are applied in published GT EEs to increase understanding and explore impact.

First a peer-reviewed literature review was performed to identify research addressing methodological considerations of GT EEs until August 2019. Identified considerations were grouped in themes using thematic content analysis. A second literature search was conducted in which we identified published evaluations. The EE quality of reporting was assessed using Consolidated Health Economic Evaluation Reporting Standards.

The first literature search yielded 13 articles discussing methodological considerations. The second search provided 12 EEs. Considerations identified were payment models, definition of perspectives, addressing uncertainty, data extrapolation, discount rates, novel value elements, and use of indirect and surrogate endpoints. All EEs scored satisfactory to good according to Consolidated Health Economic Evaluation Reporting Standards. Regarding methodological application, we found 1 methodological element (payment models) was applied in 2 base cases. Scenarios explored alternative perspectives, survival assumptions, and extrapolation methods in 10 EEs.

Although EE quality of reporting was considered good, their informativeness for health technology assessment and decision makers seemed limited owing to many uncertainties. We suggest accepted EE methods can broadly be applied to GTs, but few elements may need adjustment. Further research and multi-stakeholder consensus is needed to determine appropriateness and application of individual methodological considerations. For now, we recommend including scenario analyses to explore impact of methodological choices and (clinical) uncertainties. This study contributes to better understanding of perceived appropriate evaluation of GTs and informs best modelling practices.

Introduction

Recent advances in biomedical research resulted in the introduction of gene therapies (GTs) to clinical practice.[1] GTs have the potential to provide significant long-term benefits for conditions that currently have no or few treatment options. Pharmaceutical development forecasts show over a dozen GTs are expected to apply for market authorization in the next few years.[2] Despite a steady increase in market authorizations, widespread reimbursement and patient access is not yet observed.[3] Up-front high prices combined with long-term value claims supported by little clinical evidence raise concerns for reimbursement and affordability by health technology assessment (HTA) authorities and payers.[4,5]

GTs are said to have specific characteristics, suggesting traditional HTA should be adapted, in particular the economic evaluations (EEs).[6] In anticipation of the first ex-vivo chimeric antigen receptor T-cell (CAR-T) receiving central marketing authorization (MA), the National Institute for Health and Care Excellence (NICE) proactively issued a mock appraisal of an exemplar CAR-T therapy.[7] This mock appraisal concluded that overall, NICE's existing technical appraisal methods and decision framework is applicable to GTs. But specific elements need adjustment to integrally appraise the uncertainty of their long-term cost and benefit.[7] These elements were introduction of risk sharing via innovative payment schemes, quantification of decision uncertainty, and choice of discount rate[7] . Since publication of the NICE mock appraisal, more methodological elements for incorporation in the economical evaluations of GTs were discussed in literature.[6,8–13]

The importance of EEs in healthcare decision making is well recognized.[14] Although individual jurisdictions might weigh the results of the evaluations differently, the requirement by authorities to include EEs in assessments is increasing. Nevertheless, with the introduction of GTs, the question is raised whether accepted good modeling practices are suited to assess and value these novel therapies.[6,8] With the expected influx of GTs, early identification and adjustment of appropriate methodology is essential.

An increasing number of perspective and commentary-style articles explore and discuss specific elements of EEs that warrant adjustment when modeling GTs.[6,11,15,16] Work by Jørgenson et al. is the first to explore the impact of a specific methodological element by modeling the budget impact of an annuity payment model compared to a traditional one-off payment in a hypothetical high-value treatment.[17] This first impact quantification of a novel payment model proves to be insightful and may inform authorities to design payment schemes, yet it remains a hypothetical scenario. Additionally, 1 systematic review was identified of CAR-T EEs indicated for acute lymphoblastic leukemia.[18] Although informative, this article included a specific type of GT EEs for 1 single indication and adheres to traditional EE practices. So far, no timely overview has been made of methodological elements discussed in literature specifically relating to EEs for curative GTs. Nor has their application and impact been explored in EEs of GTs published in literature.

Therefore, the primary objective of this research is to identify methodological considerations discussed in literature specifically addressing EEs for GTs. Next, we will assess if these methodological elements are applied in published GT EE studies to increase understanding of these methods and their impact.

This study will contribute to a better understanding of discussions regarding appropriate evaluation of costs and benefits of GTs and inform best modelling practices.

Methods

Study design

We conducted a literature review with the primary aim to identify peer-reviewed papers addressing methodological considerations, specifically addressing EEs of GTs, published between January 2007 and August 2019. January 2007 was chosen because this is the year in which the European Advanced Therapy Medicinal Product regulation was invoked.[19] This regulation was the first to formally define GTs as a medicinal product.[19] The secondary aim was to identify EEs of GTs in the same time frame. GTs in this research are defined as products that are one-off administered or have a short-term treatment course, with the intention to achieve substantial sustained or curative effect.[20] This definition includes both in-vivo and ex-vivo GTs.[19] GT EEs were included if the products were intended to or authorized by a private authorization holder. This excludes GTs developed in hospitals or primarily in an academic setting, as well as products applied under managed access programs (e.g., named patient use, compassionate use, hospital exemption schemes) that do not intend to formally apply for market authorization.

Search strategy and study selection

To identify studies addressing methodological considerations as well as EEs for GTs, we conducted a systematic search of MEDLINE, Embase, PubMed, Cochrane, Database of Abstracts and reviews of Effects, National Healthcare Service Economic Evaluation Database, and Tufts Cost-Effectiveness Analysis Registry We used the following (shortened) search query in all databases: ("economic evaluation"[MeSH] AND "gene therapy" [all items]).

An additional manual snowball search was done, in which references of included studies were reviewed. We conducted another manual search of each database using "economic evaluation"[MESH] combined with brand and generic names of GT products that applied for initial European Medicines Agency and US Food and Drug Administration market authorization to date (August 2019).[2] Broad search terms were deliberately used to identify all scientific literature addressing GTs, methodological considerations, and EEs.

Research discussing methodological considerations included commentaries, perspectives, editorials, or invited contributions (hereafter called commentaries) and were required to identify 1 or more challenges as well as propose solutions. Commentaries only discussing affordability challenges or cost without proposing solutions were excluded.

Eligible EEs had to report both effectiveness and cost outcomes such as cost-utility analyses, cost-effectiveness analyses, and early economic analyses. Studies reporting only effectiveness data—such as clinical trials, patient-reported outcomes, or quality-of-life data—or only cost findings—such as cost-minimization analyses, cost-benefit analyses, burden of disease, or cost of illness—were excluded. EEs were required to be primary research excluding National Institute of Health Research technology appraisals or systematic reviews.

Both commentaries and EEs had to be written in English with access to full articles. Conference abstracts were excluded as well as EEs of fictive treatments. Articles addressing genetic tests, genotyping, and whole genome sequencing interventions were also excluded. Both the literature search and eligibility assessment of identified literature was performed independently by 2 researchers (R.t.H. and G.F.). Results were compared and discrepancies were discussed until consensus was reached.

Data extraction and quality assessment

Methodological considerations were extracted from included commentaries using a predefined data extraction form. Data extraction was done independently by 2 researchers (R.t.H. and G.F.). Discrepancies were discussed until consensus was reached. Considerations were grouped into themes using thematic content analysis methods.[21]

Study characteristics of included EEs were collected using a predefined data extraction form. The quality of EE reporting was assessed using Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[22] The CHEERS checklist was again scored independently by 2 researchers (R.t.H. and G.F.). Scoring discrepancies were discussed until consensus was reached. Last, a descriptive analysis was performed comparing methodological elements identified in commentaries and their application in published EEs.

Results

In total, 2613 records were identified, 2605 via the database search and 8 through manual and snowball search. Results of the search are presented in Figure 1 in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.[23] After identification, 229 duplicate records were removed. Screening of titles and abstracts led to exclusion of 2335 studies for not being in English (n = 66), irrelevant outcomes (n = 1602) meaning not including both cost and effect, or irrelevant interventions (n = 667) meaning not a GT. Detailed screening of full articles led to exclusion of 24 more records for reasons further specified in Figure 1.

The first literature search yielded 13 commentaries. Data extraction provided 61 considerations, which were grouped into 7 themes.21 Themes and associated considerations are presented in Table 1. Themes were defined to be mutually exclusive. Grouping of the 61 extracted methodological elements led to 41 unique considerations.

The second literature search yielded 12 EEs. Study characteristics are presented in Table 2. These EEs reported 8 different GTs intended for 8 distinct indications. Of these indications, 5 were oncologic: prostate cancer, acute lymphoblastic leukaemia (2x), diffuse lymphoma, and metastatic melanoma. [24–30] Other indications were haemophilia A, b-thalassemia, spinal muscular atrophy, and inherited retinal disease. [31–35] The MA of the GT-indicated product for prostate cancer (sipuleucel-T) was withdrawn from the EU market by the MA holder at time of our search. The haemophilia A (AAV5-hFVIII-SQ) and b-thalassemia (no generic or brand name reported) products did not yet file for MA in the United States or Europe, but a secondary search confirmed the developers intend to do so. Products reported in the remaining 9 EEs currently have active MAs in both the United States and/or Europe. [24–30,33–35].

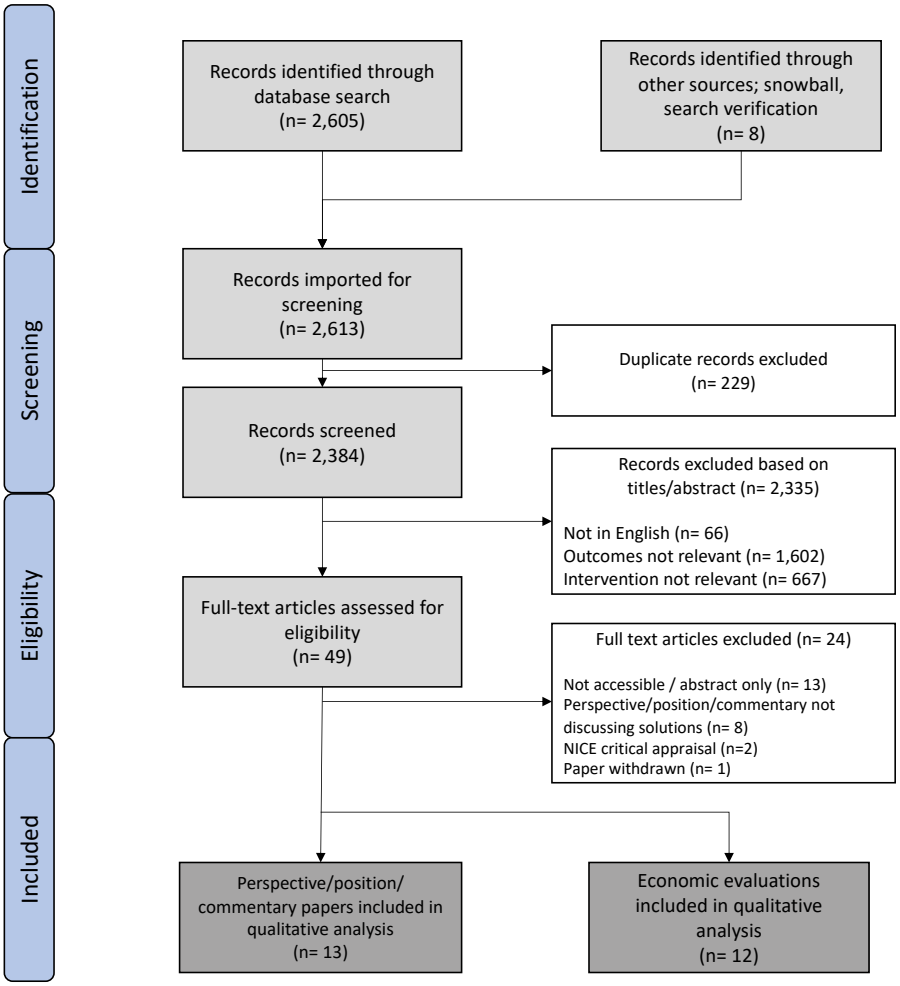

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. NICE - National Institute for Health and Care Excellence.

Three studies (25%) reported use of the CHEERS checklist. [24,29,30] Of these studies, 2 authored by the same group, also incorporated recommendations of the Second Panel on CostEffectiveness in Health and Medicines.[24,30,36] One study (8%) reported validation via the panel's recommendations alone.26 Eight studies (67%) did not report use of a quality or validation tool.[25,28,31–35] We assessed the quality of reporting of all included EEs with the CHEERS checklist. The populated CHEERS table is included as a supplemental table (see Appendix Table 1 in Supplemental Materials). Based on Appendix Table 1, we find that the quality of reporting of the included EEs ranges from enough to good. Below, a descriptive analysis is given of the identified methodological considerations per theme and how they may be incorporated in EEs.

Table 1. Methodological considerations discussed in literature to properly value both benefits and cost of curative gene therapies in economic evaluations.

Theme	Considerations	Source
Payment models	Performance based contracts (*including mile-stone based contract, value-based contract, pay-for performance scheme, performance-based risk-sharing arrangements, outcome-based agreements, outcome-based contracts, performance-based risk-sharing arrangements, performance-linked, value based agreement reimbursement)*	6, 8, 9, 11, 15, 16, 37
	Annuity payment *(including instalment payments)*	8, 9, 11, 16
	Value Based Pricing	6, 37
	Leased Payments	15, 16
	Amortization	15, 16
	Reinsurance Market	8
	Managed Entry Agreement	37
	Intellectual property-based payment	37
	Fund Based Payment	37
	Rate of return pricing	10
	Total Cost of Care	13
	Capitation	13
	Shared Savings	13
(Re)definition of perspectives	Besides the impact on patient quality of life, aspects with a greater economic impact on the society should be included.	6, 13
	Inclusion of wider personal, social, and economic benefits besides treatment cost only.	37
	Structural inclusion of 2 reference cases: one with a societal perspective and the other with a healthcare sector perspective.	6
	Inclusion of an impact inventory to address that GTs can have important non-health consequences such as effects on family caregivers, education costs, and economic productivity	6
	Inclusion of infrastructure and capital cost to administer these drugs to reflect not all patients have access to specialized treatment centres.	14
Addressing uncertainty	Consideration of (routine) use of Expected Value of information.	6, 15
	Inclusion of other complementary non-randomized data for example natural history data, registries, utility data, and the use of pooled data.	15, 37
	Inclusion of (probabilistic) sensitivity analyses to characterize and quantify decision uncertainty.	14
	Inclusion of Net Health Effects as outcome to provide information on the size of the uncertainty.	16
	There is a need for more sophisticated methods that reduce decision uncertainty in economic evaluations.	14
Data extrapolation	Structural incorporation of the potential for patients to discontinue treatment due to any reason including failure of manufacturing process.	14, 16

Table 1. (continued)

Theme	Considerations	Source
	Inclusion of analyses using different time-horizons relating different levels of certainty about treatment effect or scenarios to address the current available short-term evidence which extrapolated to simulate long-term benefits.	6
	Inclusion of adverse health effects which may be irreversible in the case of a one-off cure.	16
	Parametric methods may underestimate survival, primarily when a plateau of long-term survival is observed. A mixed cure model allows incorporation of cured and non-cured patients.	15
	Partitioned survival models are often used for the economic evaluation oncology treatments, this modelling approach often seems to fail to properly incorporate the complexity of the disease and novel technologies.	14
Discount rates	Sensitivity analysis should routinely include use of discount rates of 0% to 5%	6, 15
	The practice to use of same discount rate for both costs and benefits is questioned for curative therapies.	6
	Use of a lower discount rate would increase the relative size of the irreversibility, because long-term effects will have a higher present value.	16
	Exploration of differential discounting whereby health benefits are discounted at a typically lower rate than costs, and variable discounting whereby the rate is altered over time.	15
	Discount rates on health effects should be 1–3.5% lower than the discount rate applied to costs.	15
Novel value elements	Broadening the definition of "value" to capture elements of value not captured in the QALY, considering the value of ATMPs and the value forgone in other disease areas.	15
	Severity of disease should be considered.	11
	To comprehensively capture the value of (high investment) medications novel value assessment methodologies, such as multiple criteria decision analysis, may need to be applied.	8
	The following aspects are currently not adequately captured in calculations of QALYs: Valuation of 'cure' as opposed to wider incremental benefits, social value beyond health gain, patient preferences for treatments beyond health gain, process utilities, option value and value of spill overs linked to innovation	15
	"Novel" elements of value can be relevant for GTs and are worthy of consideration: Scientific spill over, equity, real option value, value of hope, severity of disease, insurance value, fear of contagion, reduction in uncertainty.	6
	There is a need for new methods that more accurately capture the value of new innovative drugs that might include treatment to cure for some fraction of the treated patients	15
Use of indirect comparisons and surrogate endpoints	The primary endpoint is of GT EEs are often surrogate endpoints. This raises questions about their validity and predictability, especially in rare, poorly studied conditions. Ideally, the value of the standard of care has been identified and quantified for use in new treatment comparisons.	6, 8

Table 1. (continued)

Theme	Considerations	Source
	Use of a surrogate endpoint is sometimes unavoidable. Therefore, it is important to know whether any attempts have been made to evaluate and validate them.	6
	GTs often fulfil a previously unmet need and therefore there is no existing therapy to be replaced. This may generate cost-offsets.	10
	Historical cohorts may be acceptable when the population is relatively homogeneous, when confounding factors are well known, when patient management is established and standardized, when the primary endpoint is objective and robust, and when the effect size of the new therapy is substantial versus the historical cohort.	6

Payment models

Payment and billing in healthcare systems is generally organized to occur at the same time treatment is provided.[11,13] For chronic treatments this results in a longitudinal and predictable spending pattern, which allows payers to plan budgets and spending.[31] Additionally, if a treatment is deemed ineffective, a treatment can be stopped, and payment is discontinued. In the case of curative GTs, the treatment is administered in the present time, as is payment, while the effect is to be benefitted from in the future. These so-called up-front payments are found to be substantial for the products currently on the market, while the long-term effectiveness is uncertain and often not clinically confirmed.[2] Also, if a GT proves to be less effective than claimed, the treatment cannot be stopped, nor can the cost be recouped. Alternative payment models are often mentioned in the context of GTs and affordability as a measure to decrease budget impact and spread payment over more multiple financial years.

Main arguments in favour of these alternative payment models given in the commentaries are risk-sharing between the payer and manufacturer and spreading cost by allowing payers to make instalment payments over an extended period.[8] This was said to be driven by the way health systems are organized as well as addressing affordability concerns.10 Current reimbursement models rely on up-front payments.[37] Therefore, implementation of alternative payment models would require structural changes and significant administrative preparations.[11] The commentaries propose 13 different payment models for curative GTs (Table 1). Of these payment models, performance-based contracts (albeit using different names, e.g., pay-for-performance schemes, milestone based contract) and annuity payments were mentioned most. Performance-based contracts are said to be preferred over annuity payments in situations with high budget impact and considerable uncertainty in the evidence base.[15] The key to success with these contracts is described to be collection of relevant and unbiased data.[15] Other models mentioned are value-based pricing (VBP), leased payments, amortization, reinsurance market, intellectual property–based payment, fund-based payment, rate of return pricing, total cost of care, capitation, and shared saving managed entry agreements (Table 1).

In the included EEs, 2 outcome-based payment models were modelled (17%).[26,33] The remaining 10 studies (83%) mention no specific payment scheme, in which we assumed a classic one-off payment model is applied (Table 1). An outcome-based payment model is evaluated by Whittington et al

and entails payment after treatment response 1 month post-treatment.[26] After initial introduction of the payment model, the authors do not discuss the implications of this choice. Malone et al describes a similar scheme, defined as payment after a 3-month response.[33] Like Whittington, the authors do not further discuss the impact of their choice.

(Re)definition of perspectives

With the translation of GTs to the clinic, new treatment options might become available for indications previously deemed uncurable.[38] With these new opportunities, new cost elements are introduced, expanded, or diminished.[11] More common elements such as introduction of (cured) individuals to the workforce could become impactful, while informal care may decrease. Also, new cost elements are introduced, which are associated with the unique GT supply chain and specialized care.[39]

Redefinition of value elements recently has been discussed more broadly in the health economics field.[40] Considerations discussed in the commentaries included in this theme include structural inclusion of wider cost items such as social care, effects on family and caregivers, (healthcare worker) education costs, and economic productivity.[6] Authors reason that GTs address high burden disease, which also affects relatives and caregivers.[6,13,37] Treatment with GTs may result in (re)introduction of these patients and their caregivers to the workforce, which could generate tax income and (informal) care savings. Drummond et al and Ettinger et al propose structural inclusion of these costs to reflect this greater economic impact.[6,13] Carr et al advocates to, besides cost of treatment, also include personal, social, and economic benefits but does not specify what exactly this entails.[37] Raymakers et al takes it a step further and proposes inclusion of infrastructure and capital cost in evaluations.[14] He reasons not all patients have direct access to the specialized treatment centres that are often required to administer these therapies.[14] Last, Drummond et al proposes structural inclusion of 2 reference cases into evaluations: 1 base case using a societal perspective and 1 from a healthcare sector perspective.[6] This same commentary proposes an impact inventory that incorporates non-health consequences such as education cost, effect on family caregivers, and productivity. [6] The suggestion to implement 2 reference cases and an impact inventory is adopted from recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine.[36]

The primary perspective applied in EEs was the payer perspective (n = 7, 58%)[26,27,29–31,33], of which 3 studies further specified their perspective as a public payer,[29] commercial insurer,[33] and healthcare payer perspective[30]. Three studies (25%) used a healthcare perspective.[31,32,34] Gong et al was the only research to take a societal perspective in a US setting (8%), which is uncommon.[25] A rationale for this choice was not given. One (8%) study did not report which perspective was applied but observing direct medical and indirect nonmedical were included, we assume a modified societal perspective was used.[35] Two studies explored an alternative perspective in a scenario[26,29]: Whittington et al explored a commercial payer and public payer perspective, the difference being inclusion of hospital mark-up cost for treatment acquisition in the private scenario. This resulted in an estimated incremental cost-effectiveness ratio (ICER) of $896 600 per QALY for public payers and $1 615 000 per QALY for commercial payers, showing considerable impact. In line with the considerations of the Second Panel and Drummond et al is the additional societal scenario to the base-case healthcare perspective evaluated in Coquerelle et al.[32] The societal scenario here only takes productivity losses into account.[32] This EE shows the impact of productivity loss inclusion on 2-year

treatment cost, which was higher in the hematopoietic stem cell transplantation comparator group (€ 13 971/patient) than in the GT intervention group (€ 7545/patient). Nevertheless, the societal perspective applied in this study does not comply with the formal societal perspective definition in literature[41] and authority guidelines.[42]

Addressing uncertainty

Occurrence of uncertainty in EEs is a given and to a certain extent accepted.[43,44] Yet, in the context of GTs it seems more uncertainty is perceived.[14] This may partially be attributed to novelty of indications and technologies, but also to the combination of (high) up-front payment for uncertain long-term clinically confirmed effectiveness. In this theme, Raymakers et al state that to quantify and characterize decision uncertainty inclusion of sensitivity analyses, especially probabilistic sensitivity analyses (PSAs), are vital and stipulated by EE best practices.[45] Additionally, both Drummond et al and Jönssen et al suggest use of expected value of information (EVI) analyses.[6,15]

Although EVI may help quantify and prioritize uncertainty, it does not directly inform reimbursement decisions and is often used to guide future investments in data collection.[6,15] Similarly, to generate more insight in initial investment on a patient and population level, calculation of a break-even point, return of investment, and size of uncertainty are proposed by Brennan et al.[9] Towse et al proposes use of net health effect[16]. But whether net health effect adds anything over ICER, cost-effectiveness acceptability curve (CEAC), and EVI remains undecised.16 A practical suggestion by Raymakers et al is to include scenarios to inform decision makers about changes in specific model parameters, for example, drug prices. In addition, Raymakers et al concludes his discussion with the request for more sophisticated modeling methodology to appropriately incorporate uncertainty and complexities of these new therapies.[14] Last, Towse et al suggests more routine use of nonrandomized data in EEs as well as part of the reimbursement conditions in Coverage with Evidence Development schemes to manage decision uncertainty.[16]

Although conducting sensitivity analyses to test impact of assumptions and model robustness on outcomes is considered good practice, not all EEs incorporated such analyses.[44] Nine studies (75%) conducted a deterministic sensitivity analysis (DSA), and 9 EEs (75%) conducted a PSA. These were not necessarily the same EEs, because Machin et al conducted only a DSA[31] and Whittington only conducted a PSA.[26] Six EEs (50%) report a cost-effectiveness acceptability curve[25,27,28,30,34,35] and 1 EE (8%) reported the net monetary benefit (NMB) measure.[25] Coquerelle et al reported use of a bootstrap simulation to explore uncertainty, but only reported the result of varying 2 parameters (patient weight and number of patients treated).[32] Although PSAs were performed in most of the studies (75%), the interpretation and discussion of their results was found minimal. For example, none of the EEs included a PSA scatterplot in the primary article. Results of DSAs were reported in tornado diagrams. Lin and Lerman et al and Lin and Muffly et al also reported a 2-way sensitivity diagram displaying cost effectiveness at varying GT price and 5-year survival.[24,31] EVIs were not conducted in the included EEs.

Data extrapolation

It is common in EEs that the chosen time horizon exceeds the time frame of the (clinical) data available, especially when a lifetime horizon is applied. Data with a shorter follow-up than the evaluated time horizon require extrapolation.[46] GT trials often include single-arm studies in small patient populations with surrogate endpoints. Owing to the often deemed high unmet medical need, trails show shorter follow-up compared to more conventional products when offered to regulatory bodies.[47] Additionally, because of novel indications and treatment effects, it is uncertain if conventional extrapolation methods and distributions are appropriate for these products and if the applied surrogate endpoints are predictors for (long-term) survival.

Drummond et al proposes structural inclusion of different time horizon scenarios in evaluations to simulate different curative time frames or variance in treatment waning.[6] Besides extrapolation of effects, Towse et al. finds assumptions should be made around the permanence of side effects.[16] This comment is informed by the curative or prolonged value claim, yet he states this is not known for adverse effects. Regarding extrapolation methodology, commonly used parametric survival models (PSMs) are said to fail in properly capturing complexity of disease and underestimate survival.[15] A solution mentioned is use of mixed cure models by Jönssen et al, which allows for survival to be measured for cured and non-cured patients. [15] The last element mentioned is structural incorporation of treatment discontinuation, either owing to manufacturing fails or deterioration of patient health.[14,16].

Additional survival extrapolation scenarios are observed in 6 (50%) of the studies and simulate multiple time horizons and treatment waning ranging from 0% to 100% over 3 to 5 years.[24,26,27,30,34,35] The outcome of these scenarios shows large variance. Nevertheless, which scenario best represents clinical practice is found difficult to assess and can only be informed by continued clinical follow-up or expert opinion. Gong et al, dating from 2013 and the oldest study included, used the Declining Exponential Approximation of Life Expectancy method to extrapolate data.[25,48] The Declining Exponential Approximation of Life Expectancy method was popular in the 1980s to 1990s but lost traction owing to introduction of more sophisticated methods. Nowadays other methods such as PSMs or hazard models are more common. PSMs were applied in 7 EEs (58%).[26–29,33–35] Almutairi et al and Zimmerman et al both applied 1 PSM model, respectively, the Weibull and exponential.[28,34] The reasoning behind their choices lacks. The other 5 EEs using PSMs explore between 4 and 7 different monotonic and non-monotonic hazard models for best fit[26,27,29,33,35] via visual inspection, Akaike Information Criterion and Bayesian Information Criterion metrics, or expert opinion. Whittington et al modelled 6 PSMs. Instead of determining best fit, the authors used the extreme outcomes as a range for both effect and cost outcomes.[29] This results in a an ICER estimate between $82 400 and $230 900. Less common extrapolation methods applied are pricewise exponential function and model calibration.[24,31] Coquerelle et al did not extrapolate data, because the chosen 2-year time horizon for the analysis was directly informed by 2 years of clinical data.[32] Machin et al did not report how data were extrapolated.[31]

Discount rates

In EEs, the timing of incurred cost and effects is relevant, because people generally value future costs and effects less with value diminishing over time.[50] Therefore, the value of costs and effects are adjusted with an annual rate for the time at which they occur. This adjustment is known as

discounting.[50] In the case of GTs, payment is often requested up front while the benefits are claimed to last for multiple years. Therefore, the discrepancy between time of cost and effect is much larger than in more conventional and chronic treatments.

Discount rates are specifically addressed by 3 commentaries.[6,15,16] Methodological adjustments are proposed by Jönsson et al, who advocate to apply 1.5% to 3.0% lower discount rates for effect than cost.[15] Drummond et al agrees to apply lower discount rates for effect compared to cost, because this would value the current relative size of the irreversible effect at present time higher, but they do not provide a quantification.[6] Jönssen et al proposes application of differential discounting. To evaluate the impact, Drummond and Towse et al propose to include discount rates as a parameter in deterministic sensitivity analyses (DSA) varying between 0% and 5%.[10]

Variation in discount rate is applied by Whittington et al in a separate scenario and showed to have a considerable impact on the ICER value.[26] Base case (3% discount rate) yielded an ICER of $46 000 per QALY and scenario analysis (1.5% discount rate effect) estimated an ICER of $37 000 per QALY. With the exception of Whittington et al,[26] no specific attention is given to discount rates in the included EEs. All evaluations that addressed discounting applied a rate of 3% to effects and costs, which is based on recommendations of the first panel on cost-effectiveness.[51] In the 9 DSAs reported by the 12 EEs (75%), discount rates appear in 4 analyses in the top 10 (ranked between 2 and 9) most sensitive parameters.[24,25,27,30] In the study by Roth et al, the only study in which the DSA figure included exact numbers of parameter variation impact, varying the discount rate between 1% and 5% resulted in an ICER estimate between $3980 and $74 918.[27] Whether the discount rates were not included in the remaining 5 studies or were not found to be sensitive enough to be reported in the DSA is unclear.

Novel value elements

The considerations included in this theme include discussions of whether benefit of GTs may include more than increased length and quality of life.[6] Similar to the discussions around (re)definition of applied perspectives, new treatment opportunities may introduce novel value elements and benefits across domains. Examples of such benefits according to Drummond et al and Jönssen et al are the value forgone in other disease areas, valuation of cure as opposed to wider incremental benefits, social value beyond health gain, patient preferences for treatments beyond health gain, process utilities, option value, and value of spill overs linked to innovation.[6,15] Some of these proposed elements are difficult to quantify, such as scientific spill over, option value, or value foregone for other disease areas. Yet others can be quantified with existing methods, such as reiterated by Barlow et al, who advocate structural use of multicriteria decision modeling.[8] Incorporation of disease severity, as mentioned by Garrison et al,[11] is more of a policy consideration also heard outside of the GT space.[52,53] Consequently, keeping in mind most GTs in development claim to address high unmet medical need populations, the last consideration can potentially have considerable impact.

Most reported outcomes in included EEs are life-years (LYs), quality-adjusted life-years (QALYs), cost, and ICER. Gong et al additionally reports an average cost-effectiveness ratio[25] and Almutairi progression-free (PF) LYs, PF QALYs, PF ICER, and PF incremental cost-utility ratio, as well as a disease-specific measure, objective response rate.[28] The study by Zimmerman also reports disease

Table 2. Characteristics of gene therapy economic evaluations published in peer-reviewed literature until August 2019. Studies listed in order of publication year.

	Gong et al[49]	Machin et al[31]	Lin et al[24]
General			
Base case population	Pre-docetaxel asymptomatic mCRPC with no prior chemotherapy	30- to 40-year-old male patients with uncomplicated severe haemophilia A	Patients <25 years with B-cell acute lymphoblastic leukaemia that is refractory or in second or later relapse
Geography	USA	USA	USA
Study Design	Cost utility analysis	Cost utility analysis	Cost utility analysis
Intervention (gene therapy)	Provenge (sipuleulcel-T)	AAV5-hFVIII-SQ	Kymriah (tisagenlecleucel)
Comparator(s)	Abiraterone (ABI), prednisone (Pred)	Prophylactic factor VIII	Blinatumomab
Model			
Model structure	Markov Model	Markov model	Markov model
Time horizon	Lifetime	10 years	Lifetime
Perspective	Societal perspective	third party healthcare perspective	Payer perspective
Cycle length	Monthly	Monthly	Monthly
Effect measure and unit	LYs, QALYs, cost, ACER, ICER	QALYs, cost, ICER	LYs, QALYs, cost, ICER
Input parameters			
Clinical data	3 year trial data	2 year trial data and 10 year animal data	13 month trial data
Utility data	Secondary literature	Literature and clinician estimates	Secondary literature
Data extrapolation	DEALE method	NR	Model calibration
Scenarios	NR	NR	1: 5-year PFS 20% 2: 5-year PFS 0% 3: bridge to transplantation 4: Clofarabine combination* 5: Clofarabine monotherapy
Payment model	NR	one-off payment	outcome-based payment scheme
Currency (year)	USD (2013)	USD (NR)	USD (2017)
Discounting (effect / cost)	3% / 3%	3% / 3%	3% / 3%
Outcomes			
Comparator effect	ABI: 2.70LYs/1.87 QALY Pred:2.28LYs/1.44 QALY	6.62 QALYs	8.55 LYs 3.57 QALYs

Whittington et al [26] (Kymriah)	Roth et al[27]	Almutairu et al[28]
Patients <25 years with B-cell acute lymphoblastic leukaemia that is refractory or in second or later relapse	Adults with relapsed/ refractory large DLBCL	Histologically confirmed stage IIIB- IVM1c malignant unresectable melanoma
USA	USA	USA
Cost utility analysis	Cost utility analysis	Cost utility analysis
Kymriah (tisagenlecleucel)	Yescarta (axicabtagene ciloleucel)	Imlygic (talimogene Laherparepvec) and ipilimumab
Clofarabine	Salvage chemotherapy (R-DHAP)	Ipilimumab
Decision tree followed by Markov model	Decision tree followed by Markov model	Markov
Lifetime	Lifetime	Lifetime
Payer perspective	Payer perspective	Payer perspective
NR	Monthly	NR
LYs, QALY's, cost, ICER	LYs, QALYs, costs, ICER	PF-LY, PF-QALYs, ORR, PF-ICER, PF-ICUR
18.6 month trial data	1 year trial data	3 year trial data
NR	EQ-5D-5L with US tariffs alongside clinical trial	Secondary literature
Weibull, exponential, log-normal, log-logistic, Gompertz	Weibull, LogLog, LogLogistic, Gompertz	Weibull
1: discount rates 1.5% 2: standard parametric modeling as lower bound 3: Intention to treat 4: Exclusion future healthcare costs	1: Worst case scenario (patients on remission have 10-20% higher mortality rates) 2: Intention to treat	1: BRAFV600E wild 2: BRAFV600E mutant 3: stage IIIB/IIIC/IVM1a 4: stageIVM1b/IVM1c
outcome-based payment scheme	one-off payment	NR
USD (2017) 3% / 3%	USD (2017) 3% / 3%	USD (2017) 3% / 3%
2.43 LYs 2.10 QALYs	2.60 LYs 1.13 QALYs	0.98 PF-LYs 0.79 PF-QALYs

Table 2. (continued)

	Gong et al[49]	Machin et al[31]	Lin et al[24]
Intervention effect (base case)	2.44LYs/1.60 QALYs	8.33 QALYs	20.6 LYs 8.74 QALYs
Comparator cost (base case)	ABI: $214,584 Pred: $44,583	$ 1,693,630	$ 282,000
Intervention cost (base case)	$ 135,994	$ 1,022,249	$ 599,000
ICER (base case)	ABI: $547,298 Pred:$388,846	Dominated	$ 61,000
BIA	NR	NR	NR
WTP threshold(s)	$ 150,000	$ 100,000 USD	$50,000, $100,000, $150,000
Validation			
Sensitivity analysis	DSA, PSA, CEAC, NMB	DSA	DSA, two-way SA, PSA
Checklist or validation tools	NR	NR	CHEERS checklist and Second Panel on Cost-Effectiveness in Health and Medicine recommendations

specific measures visual acuity and visual function.[34] None of the novel value elements discussed in the perspective article are incorporated in the published EEs.

Use of Indirect Comparisons and Surrogate Endpoints

Evidence generation in new and orphan indications is associated with challenges around small sample sizes, little historical data, disease knowledge, and limited associations between surrogate and hard endpoints.[54]

The evidence base currently supporting decisions around GTs consists of mostly short-term studies with surrogate (novel) endpoints.[54] Drummond et al justifies use of such data partially by transparency around validation attempts to properly combine data sources.[6] Barlow et al and Drummond et al justify use of historical data under certain conditions; homogeneous population, when confounding factors are well known, when patient management is established and standardized, when the primary endpoint is objective and robust, and when the effect size of the new therapy is substantial versus the historical cohort.[6]

The included EEs have seemingly given little attention to the validity and generalizability of applied endpoints. Although few surrogate endpoints are included in the EEs, most outcomes are expressed as an ICER. Only 3 studies (25%) had the availability of direct clinical comparison.[28,32,35] The remaining

Whittington et al [26] (Kymriah)	Roth et al[27]	Almutairu et al[28]
10.34 LYs 9.28 QALYs	9.49 LYs 7.67 QALYs	1.15 PF-LYs 0.95 PF-QALYs
$ 337,256	$ 172,737	$ 132,950
$ 666,754	$ 552,921	$ 494,983
$ 45,871	$ 58,146	$ 2,262,706
NR $50,000, $100,000, $150,000	NR $50,000, $100,000, $150,000	NR $ 1,683,191
PSA	DSA, PSA, CEAC	PSA, DSA, CEAC
Second Panel on Cost-Effectiveness in Health and Medicine recommendations	NR	NR

9 EEs (75%) dedicated little words to any comparability or adjustment analyses performed when combining clinical data sources.

Discussion

With several new GTs expected to apply for market authorization in the next few years, the high prices combined with uncertain value claims of these products cause concern.[2] This is reflected in recent commentaries addressing valuation, affordability, and payment of GTs. Here, we created an overview of methodological considerations described in these commentaries and assessed their application in published peer-reviewed EEs. The identified considerations were grouped in 7 themes: payment models, (re)definition or perspectives, addressing uncertainty, data extrapolations, discount rates, novel value elements, and use of indirect comparisons and surrogate endpoints. We searched for EEs of GTs in the literature and assessed their quality of reporting using CHEERS. Additionally, we explored whether the identified methodological elements were applied in these evaluations. We found that the reporting quality of these EEs in general was acceptable to good. The proposed methodological elements were incorporated in a minority of these published EEs. Yet, the few EEs that did include these considerations in their evaluation showed substantial impact. To our knowledge, this is the first review that has taken this approach.

Table 2. (continued)

	Zimmermann et al[34]	Whittington et al [29] (Yescarta)	Malone et al[33]
General			
Base case population	Biallelic RPE-mediated inherited retinal disease	Adults with relapsed/ refractory large DLBCL	Infants with genetically confirmed SMA1, two copies of SMN2, diagnosed <6 months
Geography	USA	USA	USA
Study Design	Cost utility analysis	Cost utility analysis	Cost utility analysis
Intervention (gene therapy)	Luxturna (voretigene neparvovec)	Yescarta (Axicabtagene Ciloleucel)	Zolgensma (onasemnogene abeparvovec-xioi)
Comparator	Regular physician visits and supportive care	Salvage chemotherapy R-DHAP	nusinersen with non-disease best supportive care
Model			
Model structure	Markov structure	Decision tree followed by Markov model	Markov model
Time horizon	Lifetime	Lifetime	Lifetime horizon
Perspective	Healthcare perspective	Public payer perspective	Commercial insurer perspective
Cycle length	1 year	Monthly	Six months (first three years), then yearly
Effect measure and unit	Visual acuity (VA). Visual field (VF), QALYs, Cost, ICER	LYs, QALYs, Cost, ICER	LYs, QALYs, Cost, ICER
Input parameters			
Clinical data available	2 years trial data and 7-year anecdotal follow-up	2 year trial data	2 year clinical trial
Utility data included	Mapping study	Literature	CHERISH-trial
Data extrapolation	Exponential	Standard parametric, flexible parametric, 2 mixture cure models, flexible parametric mixture model	Exponential, log-normal, log-logistic, Weibull, generalized gamma, Gompertz
Scenarios	1: Modified societal perspective 2: 3 year effect + 3 year waning period 3: Lifetime treatment effect	1: Commercial payer perspective 2: Short term survival (trial based)	1: alternative utility data 2: comparator group treated outpatient
Payment model	one-off payment	one-off payment	one-off payment
Currency (year)	USD (2017)	USD (NR)	USD (NR)
Discounting (effect / cost)	3% / 3%	3% / 3%	3% / 3%
Outcomes			
Comparator effect (base case)	16.0 QALY	0.94 – 3.37 LYs 0.55-2.72 QALYs	7.11 LYs 5.29 QALYs

Lin & Muffly et al[30]	Coquerelle et al[32]	Johnson et al[35]
Adults with relapsed/ refractory large DLBCL	major β-thalassemia	Biallelic RPE-mediated inherited retinal disease
USA	France	USA
Cost utility analysis	monocentric retrospective comparative micro-costing and CEA	Cost utility analysis
Yescarta (Axicabtagene Ciloleucel [A]) Kymriah (tisagenlecleucel[T])	NR	Luxturna (Voretigene neparvovec-rzyl)
Salavage chemotherapy	HSCT	Psychological support and visual rehabilitation
Markov model	NA	Markov model
Lifetime	2 years	Lifetime
healthcare payer perspective	healthcare perspective	NR
Monthly	NR	NR
LYs, QALYs, Cost, ICER	2-year survival without major complications	QALY, cost, ICER
A: 27 months T: 14months	2 year follow-up	1,5 year trial
lymphoma literature	NA	literature and expert opinion
Piecewise exponential function	NA	Exponential, Weibul, Gompertz, loglogistic, lognormal, generalized gamma
1: A; 5-year 30%, and 20% PFS. 2: T; 5-year at 25%, and 15%. 3: alternative payment agreement	1: Societal perspective	1: 5% reduction in long-term treatment effect > 3 years 2: Idem, 10% reduction 3: Idem, 50% reduction 4: Idem, 100% reduction
one-off payment	NR	one-off payment
USD (2018)	Euro (NR)	USD (2018)
3% / 3%	NR / NR	3% / 3%
3.65LYs 1.78 QALYs	100% survival with no major complications	8.6 QALY

Table 2. (continued)

	Zimmermann et al[34]	Whittington et al [29] (Yescarta)	Malone et al[33]
Intervention effect (base case)	17.3 QALY	2.83-9.19 LYs 2.07-7.62 QALYs	19.81 LYs 15.65 QALYs
Comparator cost (base case)	$213,399	$108,600-151,200	$ 6,316,711
Intervention cost (base case)	$1,039,019	$459,700-554,700	$ 6,641,564
ICER (base case)	$643,813	$ 82,400-230,900	$ 31,379
BIA	NR	NR	NR
WTP threshold	$250,000	NR	$ 150,000 and $ 500,000
Validation			
Sensitivity analysis	DSA, PSA, CEAC	NR	DSA,PSA
Checklist or validation tools	NR	CHEERS-checklist	NR

NA – not applicable, NR – not reported, DLBCL – diffuse large B-cell lymphoma, HSCT – hematopoietic stem cell transplantation, USA - United States of America, LY – Life Years, QALY – Quality Adjusted Life Year, ICER – Incremental Cost-Effectiveness Ratio, ACER – Average Cost-Effectiveness Ratio, ICUR – Incremental Cost-Utility Analysis, PF – Progression Free, ORR - Objective Response Rate, DSA –Deterministic Sensitivity Analysis, PSA – Probabilistic Sensitivity Analysis, CEAC – Cost-Effectiveness Acceptability Curve, NMB – Net Monetary Benefit, SA – sensitivity analysis, CHEERS - Consolidated Health Economic Evaluation Reporting Standards, RPE - retinal pigment epithelium, SMA – Spinal Muscular Atrophy. * clorafabine, etoposide, cyclophosphamide.

Taking a closer look at the identified methodological considerations and placing them into a broader context, it stands out that VBP is only mentioned twice as a suitable alterative payment model. VBP has taken a flight in the recent years and is often mentioned in discussions around affordability of personalized medicines.[55] Perhaps this observation is linked to the identified theme: novel value elements and (re)definition of perspectives. Unclear definition and calculation of (added) value of these curative therapies makes pricing based on their value difficult. In the 2 studies that did include an alternative payment model with performance assessment, the assessment of treatment response occurred within 1 to 3 months after admission.[26,31] One can argue whether assessment after such short time is appropriate for a product with a multiyear curative claim, and whether maximum treatment potential is reached at point of assessment. In literature when referring to annuity-based or pay-for-performance payment models, a multiyear payment plan is meant.[6,11,15,16,37]

Regarding perspectives, we noticed the included cost and benefits do not always comply with the definitions in guidelines and literature.[32,35,45] This phenomenon is previously described in the literature.[56] When exploring novel value elements and considering (re)definition of perspectives for novel therapies, it is important to be transparent in applied methodologies and adhere to claimed definitions. Another difficulty when discussing perspectives is country preference. For example, in

Lin & Muffly et al[30]	Coquerelle et al[32]	Johnson et al[35]
A 11.8 LYs/ 5.50 QALYs T 8.25 LYs / 3.92 QALYs	100% survival with one major complication	18.1 QALY
$ 169,000	$ 215,571	$ 2,780,106
A $ 651,000 T $ 529,000	$ 608,086	$ 2,220,069
A 129,000 T 168,000	NA	Dominated
A $12 billion over 5 years T $9 billion over 5 years	NR	treating 2000 patients expected 1-time cost of $1,7 billion
$50,000, $100,000 and $150,000	NR	$150,000
DSA, PSA, CEAC	Bootstrap simulation	DSA, PSA, CEAC
CHEERS-checklist and Second Panel of Cost effectiveness.	NR	NR

the United States mostly the healthcare payer perspective is applied. In the United Kingdom, NICE asks for a National Healthcare Service perspective, and French guidelines specifically ask for an all-payers perspective.[42,57] More elements, in which country-specific preferences play a role, are utility measures and discount rates. To illustrate, the Dutch National Healthcare Institute requests application of differential discounting with higher effect (1.5%) than cost (4.5%) percentages in their evaluations,[58] and UK NICE requests 3.5% for both cost and effects.[42] The commentaries seem to agree that current discount rate preferences are worth revisiting, but no uniform recommendation could be formulated. Admittedly, the US Second Panel on Cost-Effectiveness in Health and Medicine adheres to the recommendation given by the first panel, but the authors also mention the commonly applied 3% might be too high, especially from a healthcare perspective.[50] Therefore, when changes are proposed to specific elements such as perspectives, novel value elements, or discount rates, it is not only important to align with the decision makers, but also to realize specific methodological considerations can differ per country.

DSAs and PSAs are often requested in HTA authority guidelines, and their application and interpretation are considered good practice health economics.[42,44,58,59] Nevertheless, we find only 75% of EEs included a DSA or a PSA. Moreover, in the EEs in which modelers did conduct a sensitivity

analysis, the interpretation and discussion of results and impact was found minimal. This is especially surprising, because discussions around GT EEs are dominated by perceived uncertainties.[6,14–16,37] More advanced analyses to explore and quantify uncertainty were proposed in the perspectives such as EVI.[6,15] Currently no EVI analyses for GTs were found in the literature. Given limited resources and high burden disease, conducting such an analysis can help guide investment and prioritization setting in additional research, although this is perhaps more of interest to developers and investors than EEs for HTA. Further, a need is expressed by Raymakers et al to use and develop methods that can contribute to reducing uncertainty in EEs.[14] More sophisticated methods can be insightful in the identification and quantification uncertainty. Additionally, it is proposed elsewhere that authorities should also learn how to become more comfortable making decisions under uncertainty.[43] The latter could help increase organizational readiness of HTA organizations to cope with the emerging GT pipeline as well as prepare for inevitable introduction of innovative products in the future.[60]

When assessing the methodological elements, a distinction can be made between considerations specific for GTs and more generic considerations. One of the characteristics that makes the EE of GTs different in the current policy environment is their curative claim in combination with high up-front payment and uncertain longitudinal effectiveness data. This is reflected in the most often mentioned element: payment models. These alternative payment models aim to share risk between developer and payer and spread payment over time. Another predominantly GT specific element is discounting rates. This theme was also discussed in NICE's mock appraisal and the Valuing a Cure technical brief by the Institute for Clinical and Economic Review.[7,20] Similar arguments as we found are put forth in these reports, stating effects should be discounted at a lower rate than costs reflecting higher present value for future effects. Next, the promise of cure for novel and previously debilitating disease may influence the definition of perspectives and novel value elements. Both considerations address the underlying assumption that GTs may be accompanied by benefits other than prolonged life and increased quality of life. The redefinition of perspectives theme presents this by stating that benefits are achieved in the personal, social, and economic domains with a greater impact for society.[37] Novel value elements have previously been discussed in a broader context outside of the GT field, as well as the use of multi-criteria decision analyses to support the complex decision making.[61] Other elements mentioned—addressing uncertainty, data extrapolation, and use of indirect comparisons and surrogate endpoints—can also be attributed to the intended indications, which currently are mostly orphan disease and new indications. Orphan indications are associated with little and single-arm data, making use of indirect comparisons or historical comparisons necessary.[62] The GT field can therefore acquire information from learning elsewhere and vice versa.

Limitations

Despite our best efforts, this study had some limitations. One limitation of our study was that only perspectives and EEs published in peer-reviewed literature were included. As a result, methodological considerations and evaluations reported elsewhere (e.g., conferences, white papers, HTA dossiers) were excluded from this research. The second limitation was that that 11 of 12 identified EEs were conducted from a US perspective, which may limit generalizability. Nevertheless, when comparing our results to recent non–peer-reviewed reports such as the NICE mock appraisal in the United Kingdom and a value assessment conducted by the US-based Institute for Clinical and Economic Review, we find similar findings and recommendations.[7,20] Compared to the EEs, the authors of

the included commentaries have a more global spread, giving the methodological considerations a more global character. A third limitation could be that most commentaries were published before or around the same time as the included EEs. This allows for little spill over of the discussed considerations in the identified EEs. Nevertheless, it is not our intent to score the included EEs to which extent they include the proposed methodological elements. We intended to create a timely overview of current practices around EEs specific for GTs and explore their impact and implementation. Similarly, we observe that all but 1 of the included EEs were published in 2018 and 2019. This emphasizes the relevance and timeliness of this topic. Therefore, periodic reassessment of this analysis could be of interest to track both the methodological discussions as well as the implementation and impact. To continue, we only included articles published between 2007 and August 2019, which may have omitted earlier or future GT EEs. We chose 2007 as a starting point because this is the year in which GTs were first formally defined as medicinal products.[19] Last, we used the CHEERS checklist to assess the quality of reporting of included EEs.[22] We did not systematically assess the risk of bias within or across studies. Although several tools are developed to assess different types of bias, we found systematic assessment was out of scope for this research.[63] Additional to the quality-of-reporting assessment using CHEERS, we aimed to critically reflect on sources, methods, and assumptions applied in included studies.

Implications and recommendations for future practices and research

Given the unique and novel characteristics of curative GTs, a lively discussion is seen in the literature addressing affordability and methods for proper value estimation.[64,65] Following the commentaries included in this review, more are to be expected.[64,65] So far, this is the first research to systematically summarize current considerations and explored their applications. Yet, no work is done to assess the appropriateness of these novel considerations. The fundamental question underlying this work is whether EEs of curative GTs are essentially different from other interventions. Our research suggests at least the EEs of GTs are not radically different from evaluations of more conventional medicinal products, but only few elements may need adjustment. We therefore recommend future research to explore, per element, which approach is best suitable and appropriate for economic models of curative GTs. This review aims to provide an overview and prioritization of methodological elements to investigate. Furthermore, when combining these elements, this may lead to development of a curative GT-specific model. Similarly to disease specific models, a standard curative GT model can improve comparability of future health EEs and increase uniformity in modelling choices.[66] According to this study, this model should at least address discounting rate, different perspectives and scenarios that explore the impact of payment models, and treatment waning. When input parameters are highly uncertain, scenario analyses should be included to explore the impact of different assumptions. In addition to the methodological uniformity, we strongly recommend both DSA and PSA to be routinely included and reported.

To conclude, we created a timely overview of methodological considerations discussed in the literature specifically addressing EEs of GTs. We found that these elements, to date, are hardly applied and explored in peer-reviewed published evaluations. The few EEs that do explore these elements show they have considerable impact. This shows that although an EE may be considered of sufficient reporting quality according to accepted CHEERS standards, it may lack informativeness.[67] Future research should explore, per element, if and how the element is appropriate for routine

application in economic models of GTs. Development and implementation of methodological recommendations for EEs should occur in collaboration with payers and authorities whose decisions these evaluations aim to inform.

References

1. Al-Zaidy SA, Mendell JR. From Clinical Trials to Clinical Practice: Practical Considerations for Gene Replacement Therapy in SMA Type 1. *Pediatr Neurol.* 2019;[Epub ahea:1-9. doi:10.1016/j.pediatrneurol.2019.06.007

2. Eder C, Wild C. Technology forecast : advanced therapies in late clinical research , EMA approval or clinical application via hospital exemption. *J Mark Access Heal Policy.* 2019;7(1). doi:10.1080/20016689.2019.1600939

3. Hollier-Hann G, Cork D, Ralston S, Curry A. Health Technology Assessment of Gene Therapies for Inherited Genetic Disorders in the US and Europe. *Value Heal.* 2018;21(2012):S210. doi:10.1016/j.jval.2018.04.1421

4. Hanna E, Tavella F, Rémuzat C, Auquier P, Toumi M. Market Access of Atmps: Overview and Expected Challenges. *Value Heal.* 2015;18(7):A518-A519. doi:10.1016/j.jval.2015.09.1580

5. Salzman R, Cook F, Hunt T, et al. Addressing the Value of Gene Therapy and Enhancing Patient Access to Transformative Treatments. *Mol Ther.* 2018;26(12):2717-2726. doi:10.1016/j.ymthe.2018.10.017

6. Drummond MF, Neumann PJ, Sullivan SD, et al. Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy. *Value Heal.* 2019;22(6):661-668. doi:10.1016/j.jval.2019.03.012

7. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: An exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess (Rockv).* 2017;21(7):1-204. doi:10.3310/hta21070

8. Barlow J, Bens C, Brent T, et al. AMCP Partnership Forum: Designing benefits and payment models for innovative high-investment medications. *J Manag Care Spec Pharm.* 2019;25(2):156-162. doi:10.18553/jmcp.2019.25.2.156

9. Brennan TA, Wilson JM. The special case of gene therapy pricing. *Nat Biotechnol.* 2014;32(9):874-876. doi:10.1038/nbt.3003

10. Drummond M, Towse A. Is rate of return pricing a useful approach when value-based pricing is not appropriate? *Eur J Heal Econ.* 2019;0(0):0. doi:10.1007/s10198-019-01032-7

11. Garrison LP, Jackson T, Paul D, Kenston M. Value-based pricing for emerging gene therapies: The economic case for a higher cost-effectiveness threshold. *J Manag Care Spec Pharm.* 2019;25(7):793-799. doi:10.18553/jmcp.2019.18378

12. Ramsey S. Drug pricing should depend on shared values. *Nature.* 2017;552(7685):S78-S78. doi:10.1038/d41586-017-08314-1

13. Ettinger WH, Flotte TR. The role of gene and cell therapy in the era of health care reform. *Hum Gene Ther.* 2011;22(11):1307-1309. doi:10.1089/hum.2011.2526

14. Raymakers AJN, Regier DA, Peacock SJ. Modelling uncertainty in survival and cost-effectiveness is vital in the era of gene therapies: the case of axicabtagene ciloleucel. *Heal Policy Technol.* 2019;8(2):103-104. doi:10.1016/j.hlpt.2019.05.009

15. Jönsson B, Hampson G, Michaels J, Towse A, von der Schulenburg JMG, Wong O. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *Eur J Heal Econ.* 2019;20(3):427-438. doi: 10.1007/s10198-018-1007-x

16. Towse A, Fenwick E. Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment? *Value Heal.* 2019;22(6):677-683. doi: 10.1016/j.jval.2019.03.013

17. Jørgensen J, Kefalas P. Annuity payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. *J Mark Access Heal Policy.* 2017;5(1):1355203. doi: 10.1080/20016689.2017.1355203

18. Petrou P. Is it a Chimera? A systematic review of the economic evaluations of CAR-T cell therapy. *Expert Rev Pharmacoecon Outcomes Res.* 2019;00(00):1-8. doi: 10.1080/14737167.2019.1651646

19. The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council. *Off J Eur Union.* 2007;324((EC)1394/2007):121-138. http://data.europa.eu/eli/reg/2007/1397/oj.

20. Chapman R, Kumar V, Samur S, Zaim R, Segel C, Pearson S. *Value Assessment Methods and Pricing Recommendations for Potential Cures: A Technical Brief.* Boston, MA; 2019. https://icer-review.org/wp-content/uploads/2019/08/Valuing-a-Cure-Technical-Brief.pdf.

21. Ajay Bailey, Hutter I. *Qualitative Research Methods.* 1st ed. (Hutter I, ed.). SAGE Publications, Inc.; 2010.

22. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)-explanation and elaboration: A report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Heal.* 2013;16(2):231-250. doi: 10.1016/j.jval.2013.02.002

23. Moher D, Liberat A, Tetzlaff J, Altman DG, The PRISMA Group, Group, The Prisma: Moher D, Liberati A, Tetzlaff J AD. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PloS Med.* 2009;6(7):1-5. doi: 10.1371/journal.pmed.1000097

24. Lin JK, Lerman BJ, Barnes JI, et al. Cost effectiveness of chimeric antigen receptor T-cell therapy in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia. *J Clin Oncol.* 2018;36(32):3192-3202. doi: 10.1200/JCO.2018.79.0642

25. Gong CL, Hay JW. Cost-effectiveness analysis of abiraterone and sipuleucel-T in asymptomatic metastatic castration-resistant prostate cancer. *J Natl Compr Cancer Netw.* 2014;12(10):1417-1425. doi: 10.6004/jnccn.2014.0139

26. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients With Relapsed or Refractory Leukemia. *JAMA Pediatr.* 2018;172(12):1161. doi: 10.1001/jamapediatrics.2018.2530

27. Roth JA, Sullivan SD, Lin VW, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. *J Med Econ.* 2018;21(12):1238-1245. doi: 10.1080/13696998.2018.1529674

28. Almutairi AR, Alkhatib NS, Oh M, et al. Economic Evaluation of Talimogene Laherparepvec Plus Ipilimumab Combination Therapy vs Ipilimumab Monotherapy in Patients with Advanced Unresectable Melanoma. *JAMA Dermatology.* 2019;155(1):22-28. doi: 10.1001/jamadermatol.2018.3958

29. Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucel vs Chemotherapy for Treatment of B-Cell Lymphoma. *JAMA Netw Open.* 2019;2(2):e190035. doi: 10.1001/jamanetworkopen.2019.0035

30. Lin JK, Muffly LS, Spinner MA, Barnes JI, Owens DK, Goldhaber-Fiebert JD. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Multiply Relapsed or Refractory Adult Large B-Cell Lymphoma. *J Clin Oncol*. 2019:JCO.18.02079. doi:10.1200/jco.18.02079

31. Machin N, Ragni M V., Smith KJ. Gene therapy in hemophilia A: a cost-effectiveness analysis. *Blood Adv*. 2018;2(14):1792-1798. doi:10.1182/bloodadvances.2018021345

32. Coquerelle S, Ghardallou M, Rais S, et al. Innovative Curative Treatment of Beta Thalassemia: Cost-Efficacy Analysis of Gene Therapy Versus Allogenic Hematopoietic Stem-Cell Transplantation. *Hum Gene Ther*. 2019;30(6):753-761. doi:10.1089/hum.2018.178

33. Malone DC, Dean R, Arjunji R, et al. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. *J Mark Access Heal Policy*. 2019;7(1):1601484. doi:10.1080/20016689.2019.1601484

34. Zimmermann M, Lubinga SJ, Banken R, et al. Cost Utility of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease. *Value Heal*. 2019;22(2):161-167. doi:10.1016/j.jval.2018.09.2841

35. Johnson S, Buessing M, O'Connell T, Pitluck S, Ciulla TA. Cost-effectiveness of Voretigene Neparvovec-rzyl vs Standard Care for RPE65 -Mediated Inherited Retinal Disease . *JAMA Ophthalmol*. 2019;02186. doi:10.1001/jamaophthalmol.2019.2512

36. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA - J Am Med Assoc Am Med Assoc*. 2016;316(10):1093-1103. doi:10.1001/jama.2016.12195

37. Carr DR, Bradshaw SE. Gene therapies: The challenge of super-high-cost treatments and how to pay for them. *Regen Med*. 2016;11(4):381-393. doi:10.2217/rme-2016-0010

38. Al-Zaidy SA, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol*. 2019;54(2):179-185. doi:10.1002/ppul.24203

39. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. *Cell Stem Cell*. 2016;19(3):293-297. doi:10.1016/j.stem.2016.08.012

40. Neumann PJ, Willke RJ, Garrison LP. A Health Economics Approach to US Value Assessment Frameworks—Introduction: An ISPOR Special Task Force Report. *Value Heal*. 2018;21(2):119-123. doi:10.1016/j.jval.2017.12.012

41. Garrison LP, Mansley EC, Abbott TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: A societal perspective: The ISPOR drug cost task force report - Part II. *Value Heal*. 2010;13(1):8-13. doi:10.1111/j.1524-4733.2009.00660.x

42. National Institute for Health and care Excellece. *Guide to the Methods of Technology Appraisal*. London, UK; 2013. nice.org.uk/process/pmg9.

43. Barnsley P, Cubi-Molla P, Fischer A, Towse A. *Uncertainty and Risk in HTA Decision Making*. London, UK; 2016. https://www.ohe.org/publications/uncertainty-and-risk-hta-decision-making.

44. Briggs A, Claxton K, Sculpher M, et al. *Decision Modelling for Health Economic Evaluation*. 2nd Editio. (Gray A, Briggs AH, eds.). Oxford, UK: Oxford University Press; 2006.

45. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Vol 2. 2nd ed. (Cartwright WS, ed.). Oxford University Press; 1999.

46. Bojke L, Manca A, Asaria M, Mahon R, Ren S, Palmer S. How to Appropriately Extrapolate Costs and Utilities in Cost-Effectiveness Analysis. *Pharmacoeconomics*. 2017;35(8):767-776. doi:10.1007/s40273-017-0512-6

47. Wilde S De, Coppens DGM, Hoekman J, et al. EU decision-making for marketing authorization of advanced therapy medicinal products: a case study. *Drug Discov Today*. 2018;23(7):1328-1333. doi:10.1016/j.drudis.2018.03.008

48. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the "DEALE"). I. validation of the method. *Am J Med*. 1982;73(6):883-888. doi:10.1016/0002-9343(82)90786-0

49. Machin N, Ragni M V., Smith KJ, et al. Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Large B-Cell Lymphoma. *JAMA Pediatr*. 2019;2(12):1-44. doi:10.1001/jamapediatrics.2018.2530

50. Attema AE, Brouwer WBF, Claxton K. Discounting in Economic Evaluations. *Pharmacoeconomics*. 2018;36(7):745-758. doi:10.1007/s40273-018-0672-z

51. Paulden M, O'Mahony JF, McCabe C. Discounting the Recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine. *Pharmacoeconomics*. 2017;35(1):5-13. doi:10.1007/s40273-016-0482-0

52. Lawerman-van de Wetering EJ. Valuing and refining outcome measures for economic evaluations in health care. 2016. http://hdl.handle.net/1765/94502.

53. Geale K, Henriksson M, Schmitt-Egenolf M. How is disease severity associated with quality of life in psoriasis patients? Evidence from a longitudinal population-based study in Sweden. *Health Qual Life Outcomes*. 2017;15(1):1-9. doi:10.1186/s12955-017-0721-x

54. ten Ham RMT, Hoekman J, Hövels AM, Broekmans AW, Leufkens HGM, Klungel OH. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Mol Ther - Methods Clin Dev*. 2018;11(December):121-130. doi:10.1016/j.omtm.2018.10.003

55. Levaggi R, Pertile P. Value - Based Pricing Alternatives for Personalised Drugs : Implications of Asymmetric Information and Competition. *Appl Health Econ Health Policy*. 2019:6. doi:10.1007/s40258-019-00541-z

56. Drost RMWA, Van Der Putten IM, Ruwaard D, Evers SMAA, Paulus ATG. Conceptualizations of the societal perspective within economic evaluations: A systematic review. *Int J Technol Assess Health Care*. 2017;33(2):251-260. doi:10.1017/S0266462317000526

57. Massetti M, Aballéa S, Videau Y, Rémuzat C, Roïz J, Toumi M. A comparison of HAS & NICE guidelines for the economic evaluation of health technologies in the context of their respective national health care systems and cultural environments. *J Mark Access Heal Policy*. 2015;3(1):24966. doi:10.3402/jmahp.v3.24966

58. Tan SS, Bouwmans CAM, Rutten FFH, Hakkaart-van Roijen L. Update of the Dutch Manual for Costing in Economic Evaluations. *Int J Technol Assess Health Care*. 2012;28(2):152-158. doi:10.1017/S0266462312000062

59. Claxton K, Sculpher M, McCabe C, et al. Probabilistic sensitivity analysis for NICE technology assessment: Not an optional extra. *Health Econ*. 2005;14(4):339-347. doi:10.1002/hec.985

60. Uzkurt C, Kumar R, Ensari N. Assessing organizational readiness for innovation: An exploratory study on organizational charachteristics of innovativeness. *Int J Innov Technol Manag*. 2013;10(4). doi:https://doi.org/10.1142/S0219877013500181

61. Guarini MR, Battisti F, Chiovitti A. A methodology for the selection of multi-criteria decision analysis methods in real estate and land management processes. *Sustain*. 2018;10(2). doi:10.3390/su10020507

62. Fonseca DA, Amaral I, Pinto AC, Cotrim MD. Orphan drugs: major development challenges at the clinical stage. *Drug Discov Today*. 2019;24(3):867-872. doi:10.1016/j.drudis.2019.01.005

63. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:10.7326/M18-0850

64. Priedane E, Gomes-Faria R. PRO32: De novo conomic model to assess the impact of size and durability of effect of effect of curative cell and gene therapies in treatment of patients with congenital dyserythropoietic anemia (CDA). *Value Heal*. 2019;22 (supple:1. doi:10.1016/j.jval.2019.09.2362

65. Agirrezabal I, Beswick L, Fielden DJ HA. PBI35: Heath economic modelling for Advanced Therapy Medicinal Products - A targeted literature review. *Value Heal*. 2019;22 (supple. https://www.ispor.org/heor-resources/presentations-database/presentation/euro2019-3120/94533.

66. Haji Ali Afzali H, Karnon J. Exploring structural uncertainty in model-based economic evaluations. *Pharmacoeconomics*. 2015;33(5):435-443. doi:10.1007/s40273-015-0256-0

67. Frederix GWJ. Check Your Checklist: The Danger of Over- and Underestimating the Quality of Economic Evaluations. *PharmacoEconomics - Open*. 2019;3(4):433-435. doi:10.1007/s41669-019-0118-3

Supplemental Material

Table S1. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist

Item No	Item label	Gong [49]	Machin [31]	Lin & Lerman[24]	Whittington [26] [Kymriah]	Roth [27]	Almutairu [28]	Zimmerman [34]	Whittington [29] [Yescarta]	Malone[33]	Lin & Muffly[30]	Coquerelle [32]	Johnson [35]
1	Title	R	PR	R	R	R	R	R	R	R	R	R	R
2	Abstract	R	PR	R	PR	R	R	R	PR	PR	R	PR	PR
3	Background & Objectives	R	R	R	R	R	R	R	R	R	R	R	R
4	Population & Subgroups	PR	PR	PR	PR	PR	R	PR	PR	PR	R	PR	PR
5	Setting & Location	PR	PR	PR	R	PR	R	PR	PR	R	R	PR	PR
6	Study Perspectives	R	R	R	R	R	R	R	R	R	PR	R	NR
7	Comparator(s)	R	R	R	R	R	R	R	R	R	R	R	R
8	Time horizon	R	R	PR	PR	PR	PR	PR	R	R	PR	PR	R
9	Discount rate	PR	PR	R	R	PR	PR	PR	PR	R	PR	NR	R
10	Choice of health outcomes	PR	R	R	R	R	PR	R	R	R	R	R	R
11a	Measurement of effectiveness: single study based estimates	NA	NA	NA	NA	NA	R	NA	PR	NA	NA	R	R
11b	Measurement of effectiveness: synthesis-based estimates	R	R	R	R	R	NA	R	NA	R	R	NA	NA
12	Measurement and valuation of preference-based outcomes	R	R	R	R	R	R	R	PR	R	R	NA	R
13a	Estimating resources and costs: single study based economic evaluation	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	R	NA

Table S1. (continued)

Item No	Item label	Gong [49]	Machin [31]	Lin & Lerman[24]	Whittington [26] [Kymriah]	Roth [27]	Almutairu [28]	Zimmerman [34]	Whittington [29] [Yescarta]	Malone[33]	Lin & Muffly[30]	Coquerelle [32]	Johnson [35]
13b	Estimating resources and costs: model-based economic evaluation	R	R	R	R	R	R	PR	PR	R	R	NA	R
14	Currency, price, date, and conversion	PR	PR	R	R	R	R	PR	PR	R	R	PR	R
15	Choice of model	R	R	R	R	R	R	R	R	R	R	NR	R
16	Assumptions	PR	R	R	R	PR	R	PR	R	R	R	PR	R
17	Analytical Methods	R	PR	R	R	R	R	R	R	R	R	PR	R
18	Study parameters	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR
19	Incr costs & outcomes	R	R	R	R	R	R	R	R	R	R	PR	R
20	Characterizing uncertainty	R	PR	PR	PR	PR	R	PR	NR	R	R	PR	R
21	Characterizing heterogeneity	PR	PR	PR	PR	PR	R	PR	PR	R	R	PR	R
22	Study findings, limitations, generalizability, current knowledge	PR	R	R	R	R	R	PR	PR	R	R	PR	R
23	Source of funding	R	R	R	R	R	NR	R	R	R	R	R	R
24	Conflicts of interest	R	R	R	R	R	R	NR	R	R	R	R	R

4.2

Modelling cost-effectiveness, value, and uncertainty of gene therapies in hemophilia A

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Submitted for publication

Abstract

The objective of this study is to assess cost-effectiveness of valoctocogene roxaparvovec (valrox; Roctavian®) compared to prophylactic factor (F) VIII and prophylactic emicizumab (Hemlibra®) in patients with severe Hemophilia A without detectable antibodies in the Netherlands. Additionally, alternative payment models, value-based pricing and break-even point are explored.

A Markov model was adapted to include a gene therapy arm simulating bleed rates based on FVIII level. Additionally, treatment durability parameters (initial treatment effect and treatment waning) were included. Evidence was taken from clinical trials substituted and validated by expert elicitation. Robustness of results to changes in model assumptions were tested through deterministic and probabilistic sensitivity analyses.

Treatment with valrox compared to prophylactic FVIII as well as to prophylactic emicizumab showed more QALYs and less costs resulting in a dominated incremental cost- effectiveness ratio (ICER). Payment models showed to impact annual treatment cost, time of payment as well as uncertainty. Mean maximum value based price (MVBP) of valrox in the base case was estimated at €2,579,396, varying from 1,013,837 to €4,492,856 in scenario analyses including discounted FVIII prices. Mean break-even time for future benefits to offset upfront payment of valrox was 8.09 years compared to FVIII prophylaxis and 5.76 years compared to emicizumab prophylaxis. Results were sensitive to tests of uncertainty and variation in key model parameters.

Treatment of patients with severe hemophilia A without antibodies in the Netherlands with a one-time gene therapy valrox yielded incremental QALYs and cost savings when compared to chronic FVIII prophylaxis as well as chronic emicizumab emicizumab. More research is needed to characterise uncertainty and their impact in decision making. Also, availability of more clinical evidence may help characterize variance and uncertainties in order to facilitate early and sustained patient access of these novel therapies.

Introduction

Haemophilia A (HA) is a rare hereditary X-linked bleeding disorder caused by a mutation in the gene *FVIII* coding for coagulation factor (F) VIII.[1] This mutation results in activity impaired hemostasis causing a bleeding tendency.[2] The risk of is strongly associated with the proportion of circulating FVIII activity compared to normal individuals, classified as mild (>5-40% FVIII), moderate-severe (1-5% FVIII) or severe (<1% FVIII).[3,4] In patients with severe and moderate severe hemophilia, bleeds can even occur spontaneously and are predominantly seen in joints and muscles. Repeated joint bleeds lead to arthropathy and causes pain, immobility and disability eventually leading to a decreased quality of life.[5–7] Treatment of severe HA focuses predominantly on bleed prevention, especially prevention of joint bleeds.[8]

Treatment guidelines recommend prophylactic treatment with exogenous intravenous substitution with (recombinant) FVIII every 1-3 days in order to prevent bleeds.[9] Recently, FVIII products with extended half-life have been added to the treatment formularies, as well as the first monoclonal antibody emicizumab (Hemlibra®). Emicizumab®), which mimics the function of FVIII and is administered subcutaneously every 1 to 4 weeks and is expected to have rapid global uptake. The longer acting FVIII substitutes and non-factor replacement therapies (NRTs) allow less frequent (intravenous) administrations increasing patient mobility and quality of life.[10]

The latest innovation in HA-treatment is the emergence of gene therapies.[11] The promise of a one-time treatment inducing prolonged or sustained near-normal FVIII level is considered a gamechanger for patient management and creates high hopes and expectations amongst patients and their physicians.[12] These hopes are not unfounded as the first gene therapy indicated for severe HA is in an advanced clinical stage. A recent Phase I/II trial of valoctocogene roxaparvovec (valrox, Roctavian® developed by BioMarin®) showed promising results with FVIII levels up to 84IU/dL (or 84%) after 3 years in a small population (n=13).[13,14] Although the data shows interpatient variability and treatment waning, BioMarin's request for accelerated assessment for market authorisation was granted by the European medicines Agency (EMA).[15] The developer applied for centralised marketing authorization in late 2019.[16] However, in November of 2020, the market authorization application of valrox was withdrawn after the EMA – following the FDA - requested at least one additional year of data from the ongoing Phase III trial. Additional to the uncertainty in its clinical evidence, the costs associated with valrox are expected to have a large impact on the Dutch healthcare budget. Although no formal price has been announced for the European market, a reported price in the US is US$2,500,000 (corresponding to approximately

€2,100,000.-). Additionally, the irrecoverability of the upfront payment and uncertainty around speed and extent of future health benefit and savings raises both practical and affordability concerns amongst health technology assessment (HTA) bodies and payers (e.g., will the intervention break even and when?).[17–19]

To inform HTA, cost-effectiveness analyses (CEA's) are used to quantify benefits, costs and uncertainties. So far, few CEAs have been published assessing cost-effectiveness of gene therapies for severe HA. Machin et al was the first to assess cost-effectiveness in a US setting and found

the gene therapy appeared to dominate (meaning cost saving and more effective) compared with FVIII prophylaxis.[20] The results appeared robust to most clinical uncertainties and the main uncertainty appeared to be the cost of the therapy itself. The base case price was set at $1 million/ treatment. More recent Cook et al took a different approach to assess cost-effectiveness of valrox compared to FVIII prophylaxis in severe HA.[21] The authors constructed a micro-simulation model and incorporated individual patient FVIII levels and Pettersson Scores (PS).[21] By incorporating FVIII levels, the authors enabled inclusion of initial treatment effect (max %FVIII level) and treatment waning over time. These two parameters are used more widely to determine treatment durability of gene therapies.[22,23] Additionally, PS is an accepted arthropathy classification associated with patient quality of life.[24] A microsimulation model takes an individual patient approach, which requires access to individual patient data.[25] This limits use of Cook et al.'s model for population level policy decisions.[26] Lastly, the US-based Institute for Clinical and Economic Review (US ICER institute) conducted an assessment of emicizumab (Hemlibra®) compared to prophylactic FVIIII and more recently of valrox vs emicizumab.[27,28] The latter analysis also reports cost savings with more effect. Although conducted in a US setting, methodological considerations and elements may be transferable to the Dutch setting.[29] So far, no economic evaluations have been performed for a gene therapy intended to treat severe HA in the Netherlands.

Therefore, the objective of this study is to assess cost-effectiveness of valoctocogene roxaparvovec (Roctavian®) compared to prophylactic FVIII and prophylactic emicizumab (Hemlibra®) in patients with severe Hemophilia A without detectable antibodies in the Netherlands. Additionally, alternative payment models, value-based pricing and break-even point are explored.

Methods

To model cost and effects of valrox in patients with severe uncomplicated HA in the Netherlands, a Markov state transition model was constructed in Excel (Microsoft, Redmond, WA). We compared a hypothetical group of patients who received valrox, or prophylactic FVIII or prophylactic emicizumab (which are both standards of care in the Netherlands). Payment models included in the assessment were (i) one-off payment model, (ii) annuity payment and (iii) an outcome-based payment model.[30,31]

FVIII and emicizumab are typically purchased at a discount.[32] A maximum value-based price (MVBP) of valrox in the Dutch setting was explored using mean FVIII/IE cost (€0.56/IE) as base case.[32] Via scenario's impact of smaller and larger discounts are explored (0-80%). Unique in the assessment of one-off treatments is their upfront irreversible cost (e.g., cost of the therapy). At time of administration this irreversible cost exceeds the immediate health benefit (expressed as negative net benefit). Cost savings (net monetary benefits) and health gains (net health benefits) experiences over time will slowly compensate the 'investment'. The break-even point was estimated, e.g., when accumulated benefits have offset the irreversible treatment cost.

All input parameters including ranges for sensitivity analyses are specified in **Table 1**. This method section is constructed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting standards.[33]

Model overview

The structure of the Markov model was based on a previously published model in which prophylactic emicizumab was compared to prophylactic and on demand FVIII.[28] This model was adapted to include a gene therapy arm, incorporating patient FVIII levels and treatment waning (**see Figure 1**). This was done by simulating population level FVIII levels overtime following treatment and corresponding annual bleed rates (ABR).[34–36] Bleed occurence was linked to a cost and a quality-of-life decrement. The model had 5 health states and distinguishes different types of bleeds with more severe bleeds acquiring higher cost and utility decrement: No bleed, untreated bleed, treated bleed not into target joint, treated target joint bleed and death (any cause). A target joint is defined as a single joint with three or more spontaneous bleeds into it within a consecutive six-month period.[37] Cycle length was 1 month with patients returning to the no bleed-health state at the end of each cycle. The model time horizon was 10 years, based on sustained curative value of this gene therapy in hemophilia A for approximately 7-10 years and absence of retreatment data.[15]

Within the model three sub models are distinguished: i) No target joint, ii) 1 target joint and iii) 2+ target joints (**Figure 1**).[28] Transition between sub models was driven by number of joint bleeds which were translated into an increasing PS.[38] A PS≥28 was assumed to indicate a target joint where after a patient transitioned to subsequent sub model after acquiring cost and utility decrement for a total joint replacement therapy (assumed 50% knee/50% hip).[39] The model takes a societal perspective and adheres to the Dutch guidelines on economic evaluations in healthcare.[40]

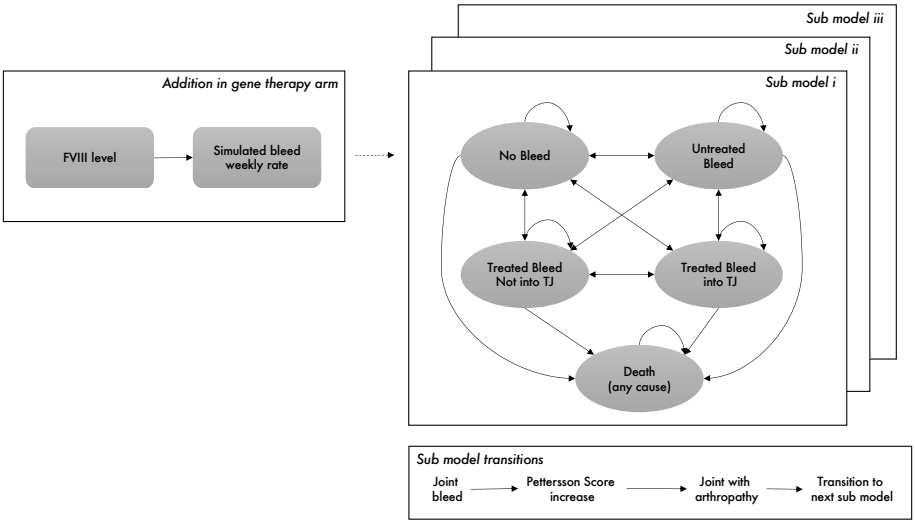

Figure 1. Structure of Markov model. Sub models have same structure. FVIII-Factor VIII clotting factor. TJ-target joint. Joint with arthropathy was defined as Pettersson Score ≥28. Sub model i: No target joints. Sub model ii: 1 target joint. Sub model iii: 2+ target joints.

Population

The model simulated a hypothetical cohort of patients with severe HA (defined as adults with congenital factor VIII deficiency without an inhibitor to FVIII with FVIII<1%) without detectable antibodies to adeno-associated virus serotype 5. The cohort matched the characteristics of cohort 3 of the Phase I/II study by Pasi et al.[13] It was assumed the cohort had same life expectancy as the Dutch population. Consequently, Dutch life tables for background mortality were applied.[41] Mean age of the cohort was 31 (23-42)years and mean weight 85kg (68-102)[13], see **Table 1**. Weight was varied by age and adjusted for sex using 2019 Dutch population statistics.[13,41] Prevalence of existing target joint was 70% in this cohort, of which 70% had more than one target joint. Baseline PS in sub model ii and iii was 24.1.[38]

Interventions

The intervention is valrox (dosed 6×10^{13} vg/kg in one intravenous admission).[13] Mean factor levels and adverse events were derived from the Phase I/II study and extrapolated beyond study duration of four years.[13,42] In the first 2 months after treatment with valrox, patients received additional FVIII prophylaxis (including costs and adverse events) which reflects trial protocol.[13] Patient also received prophylactic glucocorticosteroids (40mg/day) which was tapered from week 3 onwards.[14] In addition, the Phase I/II study showed 1 of 7 patients (15%) in cohort 3 demonstrated very limited response (FVIII% <4 after 2 years).[13] As a result 15% of patient in the base case were characterized a limited-responder and assumed to switch back to prophylactic FVIII, as emicizumab is not reimbursed for mild-moderate HA in the Netherlands.

Standard of care for patients with severe uncomplicated HA in the Netherlands is prophylactic factor FVIII (dosed 30IE/kg three times a week intravenous).[43,44] The valrox-intervention was also compared to emicizumab (Hemlibra®) which was approved for reimbursement in the Netherlands in July 2020 and is expected to show rapid clinical uptake.[36] Dosing regimen was 3 mg/kg week subcutaneous in the first month followed by maintenance dose of 3 mg/kg biweekly.[43] ABRs and adverse events of were obtained from the HAVEN-3 study and the technology assessment by ZIN.[35,44]

Despite treatment, spontaneous or traumatic breakthrough bleeds could occur. These were treated the same across treatment arms with on demand (OD) FVIII dosed according to Dutch treatment formulary (kg * desired FVIII activity (50%) * 0.5 twice daily for 3,5 days).[9,36,43]

Efficacy

Differences in treatment effect were driven by treatment specific ABRs. In the valrox-arm ABRs were simulated based on FVIII%. It was assumed after week 26, maximum FVIII levels were achieved (the initial treatment effect). From the initial treatment effect number of joint bleeds was derived using the study by den Uijl et al.[34] This study describes an S-curved association between FVIII% and annual joint bleeds. A sigmoid curve was fitted to allow simulation of joint bleeds in our model, which were translated to all bleeds assuming 70% of all bleeds were joint bleeds.[21,27] Treatment waning was incorporated by assuming mean linear decline of -5.7% FVIII per year.[13,15]

To best reflect in bleed rates in HA disease stages, different bleeding- and treatment-assumptions were applied. When patient FVIII levels remained >15% all bleeds were assumed untreated bleeds with a base case ABR of 1.0.[21] With FVIII levels were >5% but ≤ 15%, 60% of bleeds were assumed joint bleeds of which 40% target joint bleeds and FVIII.[21] When FVIII continued to decrease and reached FVIII >1% but ≤5% (corresponding to moderate-severe HA), 25% returned to prophylactic FVIII therapy and with FVIII ≤1%, it was assumed all returned to chronic prophylactic FVIII therapy.

ABRs and adverse events of prophylactic FVIII and emicizumab were derived from the HAVEN-3 trial and the Dutch technology assessment of emicizumab conducted by the National Healthcare Institute (Zorginstituut Nederland; ZIN).[44] ABRs were transformed to weekly rates before used in the model.

Expect elicitation was conducted to assess validity of disease progression, treatment assumptions, treatment algorithms and agreement with Dutch population. Expert opinion was obtained via semi-structured interviews with three clinical experts.[45]

Outcomes

Health outcomes assessed were life years (LYs), Quality Adjusted Life Years (QALYs), Pettersson Score (PS) and (joint) bleeds. A QALY is a generic outcome which captures survival and health related quality of life.[46] It is an accepted and generic measure which allows for comparison across indications.[46] Baseline utility (e.g. health related quality of life score between 0 and 1) was 0.82 for patients in the no bleed-health state in sub model i (no target joints).[47,48] In the 1 and 2+ target joint sub models, utilities were based on a study in which PS was associated with quality of life using the SF-6D questionnaire (Short-Form with 6 dimensions) with higher PS linked to lower quality of life.[24] Patient experiencing a bleed were assigned an utility of 0.66 for 2 days in all sub models.[48] A target joint bleed was assigned an additional disutility of -0.12.[47] A disutility of -0.39 was assigned for 1 month to patients undergoing orthopaedic surgery.[49]

Resource use and costs

Drug costs were expressed in 2019 euro's (€). No Dutch price of valrox has been disclosed by the developer, therefore our base case scenario used the US price converted to 2019 Euro's.[27] The discounted prophylactic FVIII cost applied was € 0.56/IE.[32] Emicizumab drug costs was derived from the Dutch list price.[50] Frequency of non-pharmaceutical health care utilization, both bleed and non-bleed related, were derived from literature and includes outpatient visits, hospitalization and emergency room visits. Per bleed resource use was obtained from a real-world study and assumed similar across treatment arms.[51] Non-bleed related healthcare utilization was divided into 19-45 year of age and >45 years old and also assumed same across treatment arms.[52] The healthcare utilization was matched with Dutch Treatment and Diagnosis Combination (DBCs) and tariffs from the Dutch Healthcare Authority (Nederlandse Zorgautoriteit; NZa) to calculate costs.[40,51–53] DBCs represent a lumpsum payment received by a hospital. Untreated bleeds were assumed to accrue no cost only disutility.[28]

Costs were grouped into health care costs and non-healthcare costs. Health care costs were subdivided into pharmaceutical costs (prophylactic and on demand treatment) and non-

pharmaceutical costs. Non-health care cost included costs for patient and family (rehabilitation after surgery and travel expenses) and costs spilling over in other sectors (loss of productivity).[40,54]

Analyses

The incremental analysis assessed benefits and costs between treatment arms and expressed as Incremental Cost-Effectiveness Ratio (ICER)[46], which captures the incremental cost per unit of outcome of one intervention compared to another. This ratio is calculated as: ($Cost_{intervention}$ – $Cost_{control}$) / ($QALY_{intervention}$ - $QALY_{control}$).[46,55] Costs and (QA)LYs were discounted at 4.0% and 1.5% per annum respectively.[40]

Uncertainty around parameters and assumptions were quantified via sensitivity analyses.[46,56] Deterministic sensitivity analyses (DSA) show the impacts of varying each individual parameter to minimum and maximum value as specified in ***Table 1***. Minimum and maximum values were derived from literature (e.g. via reported confidence intervals, standard deviation (sd) or standard error (se)) or indirectly (by deriving 95% CI, sd or se from patient characteristics using epidemiological methods.[46] When no variability measures were available, parameters were varied +/-20%. The probabilistic sensitivity analysis (PSA) provides a comprehensive estimate of the uncertainty around the model outcomes by sampling uncertainty in all input parameters simultaneously. This was done by sampling 1,000 iterations of random values for all model input parameters according to their individual distributions (***Table 1***).[57] PSA results are typically presented as a scatterplot in a cost-effectiveness

Table 1. Input parameters and ranges used in deterministic and probabilistic sensitivity analyses.

Input parameter	Base case	Low	High	Distribution	Source
Characteristics and disease progression					
Age	31	23	42	Normal	13
Weight	85	68	102	Normal	41
Sex (%male)	100%	-	-	fixed	13
Prevalence existing target joint (%)	70%	56%	84%	Beta	58
Prevalence existing >1 target joint (%)	70%	56%	84%	Beta	58
Pettersson score (baseline sub model ii/iii)	24.1	20.0	30.0	LogNormal	38
# joint bleeds per Pettersson Score increase	12.6	11.1	14.7	Lognormal	38
Valrox intervention					
Initial FVIII level (week 26)	67.00	20	84	Lognormal	[13]
FVIII waning (annual)	-5.72%	-1.56%	-10%	Lognormal	15
Limited responders (%)	15%	0.4%	45.9%	Lognormal	13,14
FVIII% >15: All bleeds (ABR)	1.0	0	2.0	Lognormal	Expert elicitation
FVIII% >5 & <15: joint bleeds (%)	60%	48%	72%	Lognormal	21

Table 1. (continued)

Input parameter	Base case	Low	High	Distribution	Source
FVIII% >5 & <15: joint bleeds into target joint (%)	40%	32%	48%	Lognormal	21
FVIII% >1 & <5: Patients receiving FVIII prophylaxis	25%	5%	40%	Lognormal	Expert elicitation
FVIII prophylaxis					
All bleeds (ABR)	4.80	3.20	7.10	Lognormal	35,44
Treated bleeds (ABR)	4.33	3.46	5.20	Lognormal	35,44
Treated joint bleeds (ABR)	2.90	2.32	3.48	Lognormal	35,44
Treated target joint bleeds (ABR)	2.50	2.00	3.00	Lognormal	35,44
Adherence	100%	-	-	fixed	Expert elicitation
Emicizumab prophylaxis					
All bleeds (ABR)	2.60	1.60	1.92	Lognormal	35,44
Treated bleeds (ABR)	1.30	0.80	1.70	Lognormal	35,44
Treated joint bleeds (ABR)	0.90	0.40	0.96	Lognormal	35,44
Treated target joint bleeds (ABR)	0.70	0.30	0.84	Lognormal	35,44
Adherence during trial (0-24 weeks)	100%	80%	100%	Beta	59
Adherence post trial (>24 weeks)	86%	69%	100%	Beta	59
Quality of life					
Utility, No bleed sub model i	0.88	0.66	0.98	Beta	48
Utility, Bleed sub model i	0.66	0.53	0.79	Beta	48
Disutility target joint bleed sub model i	-0.12	-0.10	-0.14	Beta	48
Duration disutility bleed	2 days	-	-	Fixed	27
Utility PS 4-12, sub model ii/iii	0.82	0.78	0.86	Beta	24
Utility PS 13-21, sub model ii/iii	0.79	0.75	0.83	Beta	24
Utility PS 22-39, sub model ii/iii	0.73	0.69	0.77	Beta	24
Utility PS 40-78, sub model ii/iii	0.72	0.68	0.76	Beta	24
Disutility orthopaedic surgery	-0.39	-0.31	-0.46	Beta	49
Duration disutility orthopaedic surgery	1 month	-	-	Fixed	27
Cost (2019 Euro)					
Health care cost: Pharmaceutical					
Cost/unit valrox	2.125.000	1.700.000	2.550.000	Gamma	27
Cost/unit FVIII prophylaxis (IE)	0.56	0.20	1.20	Gamma	32
Cost/unit emicizumab prophylaxis (30mg/mL vial)	2.476	1.980	2.971	Gamma	43,50
Cost/bleed FVIII on demand (IE)	73.50/kg	58.80	88.20	Gamma	43,50
Health care cost: Non-pharmaceutical					
Bleed related, 19-44 years	904.55	723.64	1.085.46	Gamma	51,53
Bleed related, >44 years	3.735.80	2.988.64	4.482.95	Gamma	51,53
Not bleed related, no TJ (weekly)	112.38			Gamma	52,53
Not bleed related, >1 TJ (weekly)	176.21			Gamma	52,53

Table 1. (continued)

Input parameter	Base case	Low	High	Distribution	Source
Arthropathy surgery cost (50%TKR/50%THR)	11.850,50	9.480,40	14.220,60	Gamma	53,60
Surgical follow-up	20 years	-	-	Fixed	27
Adverse events valrox (week 1)	401.29	321.03	481.55	Gamma	13,14,53
Adverse events, FVIII prophylaxis (weekly)	2.01	1.61	2.41	Gamma	35,44,53
Adverse events, emicizumab prophylaxis (weekly)	2.06	1.65	2.47	Gamma	35,44,53
Non-health care cost					
Lost productivity after bleed	1 day			Fixed	27
Lost days of productivity after hospitalization	Duration of stay + 2 days			Fixed	27
Hourly wage 2019 (adjusted for sex)	40.46	32.27	48.55	Gamma	40

plane. A key output of the PSA is the proportion of cost-effective iterations in relation to the willingness-to-pay (WTP) threshold, which can be presented in a cost-effectiveness acceptability curve (CEAC). The Dutch informal WTP-threshold of €80,000/incremental QALY was applied here.[40]

Impact of three payment models was explored on total treatment cost over time one a population level. Using the Dutch hemophilia registry (HemoNed), it was estimated that ±100 patients reside with severe HA are between 30 and 44 years old.[61] The first payment model - one-off payment - is current practice in the Netherlands and was included in the base case. The annuity payment model (model ii) was applied by dividing valrox base case price into 5 instalments. Once a every 12 months a discounted payment was made, starting on day of treatment. The last model was the out-comes based payment (model iii). Many different outcome-based payment models exist, in this research a population based scheme is applied as proposed by the US ICER institute.[27] This model describes that for patients who do not respond to valrox no payment for the drug is made. More specific, treatment of the patients meeting following conditions after 2 years will not be reimbursed: FVIII activity level is < 5% as measured by one stage assay; >2 spontaneous bleeds and/or one life-threatening spontaneous bleed or return to continuous prophylactic FVIII products. Here these conditions are interpreted as no payment is made for the limited responder group. For responders a payment is made after 2 years, at the start of year 3. For all payment models an annual uptake of 25% was applied, assuming all patient are treated with valrox after 4 years.

The maximum value-based price (MVBP) was calculated by calculating the net monetary benefit of valrox when its price was set to zero.[62] Given that both the price of valrox and granted discounts on FVIII clotting factors are unknown, scenario's explored the MVBP under scenario's ranging from 0% to 80% discount.[32] Here 0% discount corresponds with the Dutch list price (€ 1.00/IE) and 44% with the base case (€ 0.56/IE).

Last, the break-even point was estimated by deriving a linear function from a plot of cumulative NHBs and NMBs over time. The interception with the x-axis (when y=0) was interpreted as the time point where the initial losses at time of treatment (negative NHB and NMB) where compensated by the future benefits (NHBs) and cost savings (NMBs), or break-even point.

Results

Base case

Base case results in Table 2 show cost and outcomes of treatment arms over 10 years. Drug costs are major cost drivers, with mean prophylactic drug costs accounting for 91%, 84% and 93% of total cost for the valrox, FVIII prophylaxis and emicizumab arm respectively. Valrox patients experienced 6.7 bleeds overall compared to 42.1 in the FVIII-group and 11.5 with emicizumab. This result is reflected proportionally lower Pettersson Score, higher total QALYs and less on demand drug cost in the valrox arm, compared to the prophylaxis-arm.

Similar results are seen in **Table 3**. Here valrox was found to dominate both prophylactic treatments as it shows marginal incremental benefits at lower costs. The valrox intervention has a 55.6% probability of being cost-effectives when compared to FVIII prophylaxis. This means 55.6% of ICER estimates in the PSA were lower than €80,000/QALY. When valrox is compared to emicizumab prophylaxis this probability is 39.5%. Cumulative bleeds (all bleeds and joint bleeds) and costs per treatment over time as simulated by the model are shown in **Figure S1 and S2**.

Outcome of the deterministic sensitivity analysis is provided in **Figure S3**: valrox compared to FVIII prophylaxis and **Figure S4**: valrox compared to emicizumab prophylaxis. In both comparisons similar parameters demonstrate large impact on outcomes; cost/unit of drug (valrox, emicizumab a FVIII), initial treatment effect, distribution of limited responders and treatment waning. The results of the PSA are shown in **Figure 4**. The figure shows a scatter plot of ICER-values of valrox compared to FVIII prophylaxis (4A) and valrox compared to emicizumab prophylaxis (4B) in a cost-effectiveness plane. Included in **Figure 4** is the Dutch Willingness to Pay threshold of 80,000,-/QALY (red dotted line). This figure shows the spread of uncertainty of our estimates with (dominated) base case mean values marked with a red and purple cross.

From the PSA a cost-effectiveness acceptability curves (CEAC) were derived. (**Figure 5A & Figure 5B)**. Figure 5A shows the CEAC for choice of strategy showing probability of a being cost effective vs WTP for each individual treatment. The treatment with the highest probability is the most cost-effective option give the WTP. The figure shows this may vary as WTP increases. Given that the three lines lay close together indicates high uncertainty an no clear choice. Additionally, being the most-cost-effective treatment option, does not necessarily mean it is cost-effective. Figure 5B shows the CEAC for pairwise comparison showing valrox compared to FVIII prophylaxis has a higher chance of being cost-effective than when compared to emicizumab, as was indicated in **Table 2.**

Table 2. Base case benefits and costs per treatment.

	Valrox		FVIII prophylaxis		Emicizumab prophylaxis	
	Deterministic analysis	95% credible range PSA	Deterministic analysis	95% credible range PSA	Deterministic analysis	95% credible range PSA
Costs						
Prophylactic drug cost	€ 2,560,911	(€213,850 - €8,743,630)	€ 2,688,162	(€58,073 - €9,059,742)	€ 3,930,144	(€119,050 - €14,031,724)
On demand drug cost	€ 35,007	(€438 – €490,558)	€ 218,059	(€4,705 - €770,041)	€ 66,451	(€1,392 - €228,655)
Non-pharmaceutical cost	€ 89,035	(€82,534 - €211,467)	€ 120,181	(€90,667 - €265,708)	€ 94,766	(€84,829 - €171,392)
Societal cost	€ 122,268	(€5,072 - €704,084)	€ 183,032	(€6,458 - €1,014,811)	€ 119,015	(€4,898 - €661,952)
Total cost	€ 2,807,221	(€431,528 - €9,287,507)	€ 3,209,433	(€292,789 - € 10,093,949)	€ 4,210,377	(€394,884 - € 14,354,286)
Benefits						
Maximum Pettersson Score	24.2	(12.15 - 40.55)	25.1	(12.86 - 41.46)	24.4	(11.82 – 40.82)
Treated non target joint bleeds	2.8	(.52 - 21.78)	17.9	(8.66 - 27.21)	4.6	(1.29 - 7.15)
Treated target joint bleeds	3.8	(.76 - 25.12)	24.3	(20.09 - 29.58)	6.9	(4.01 - 10.9)
Total QALYs	7.03	(5.86 - 8.2)	6.38	(5.62 - 7.35)	6.90	(5.99 - 7.92)
Total Life years	9.28	(8.04 - 10.52)	9.28	(8.17 - 9.95)	9.28	(8.17 - 9.95)

FVIII – factor VIII, QALY – quality adjusted life year. Valrox - valoctocogene roxaparvovec (Roctavian®). *Time horizon: 10 years.*

Table 3. Incremental results per treatment in base case analysis. ***FVIII and emicizumab prophylaxis are both compared to valrox treatment.

Treatment	Benefits (QALYs)	Costs €	incr Benefit	incr Cost	ICER	Probability of being cost-effective*
Valrox	7.03	€ 2,807,221	-	-	-	-
FVIII prophylaxis*	6.38	€ 3,209,433	0.65	-€ 402,212	DOMINATED	55.6%
Emicizumab prophylaxis*	6.90	€ 4,210,377	0.13	-€ 1,403,156	DOMINATED	39.5%

FVIII – factor VIII, incr – incremental, QALY – quality adjusted life year, ICER – incremental cost-effectiveness ratio. Valrox - valoctocogene roxaparvovec (Roctavian®). Probability of being cost-effective using a willingness-to-pay threshold of €80,000/incremental QALY.

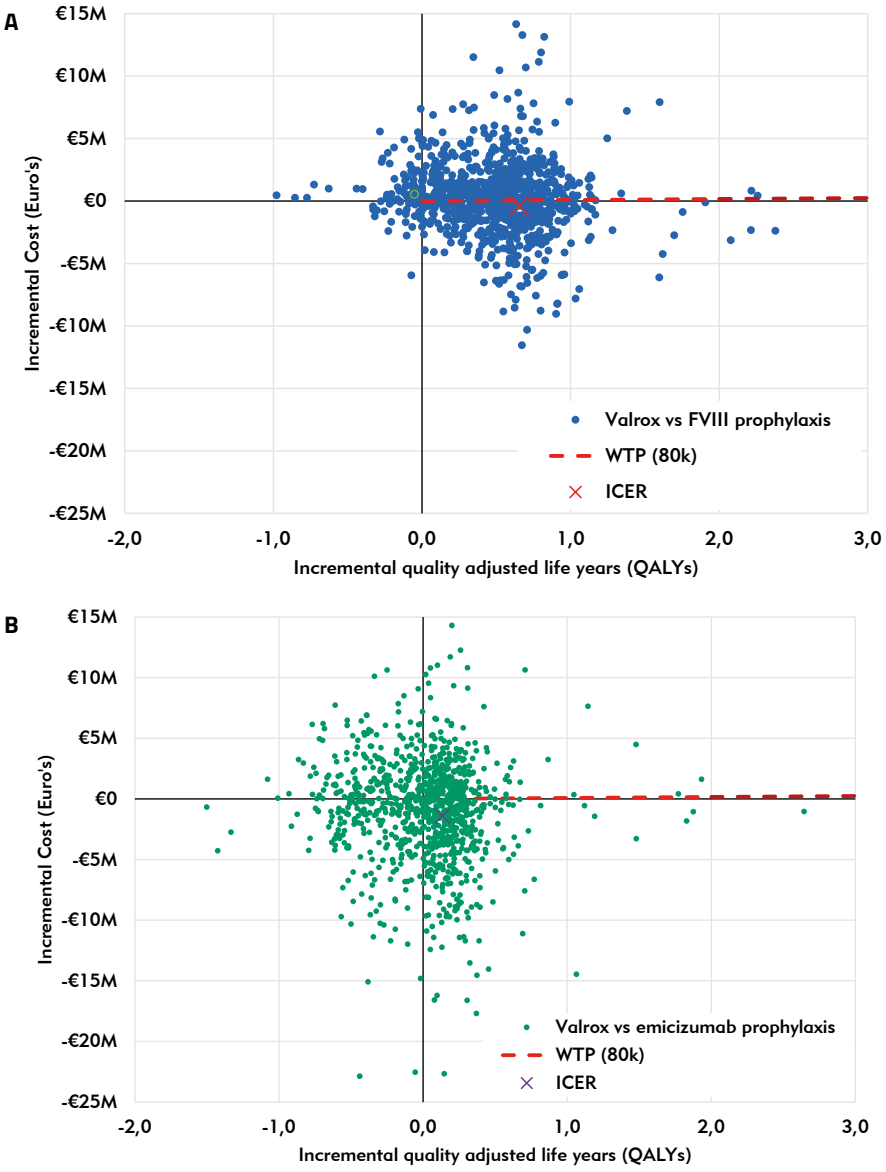

Figure 4. Results of the probabilistic sensitivity analysis in a cost-effectiveness plane. [A] valrox compared to FVIII prophylaxis and [B] valrox compared to emicizumab prophylaxis. ICER - Incremental cost-effectiveness ration. Valrox - valoctocogene roxaparvovec (Roctavian®). WTP – Willingness to pay threshold.

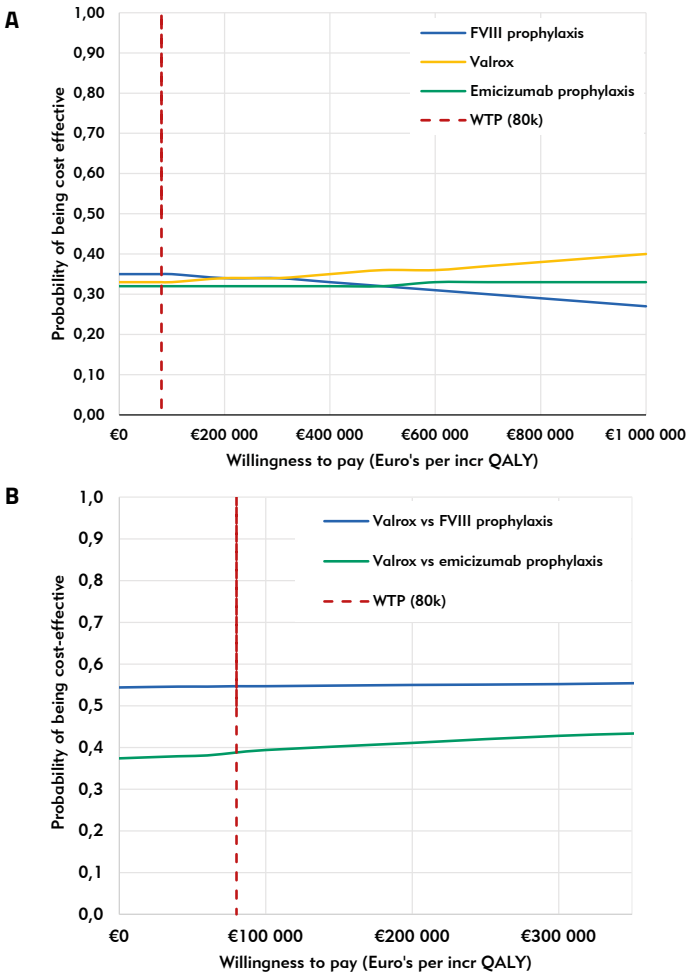

Figure 5. Cost-effectiveness acceptability curve for choice of strategy[A], and cost-effectiveness acceptability curve for pairwise comparison[B]. Valrox - valoctocogene roxaparvovec (Roctavian®). WTP – Willingness to pay threshold. QALY – Quality adjusted life year.

Total cost of the Dutch HA population over time per payment model is shown in **Figure 6**. The analysis shows that the annuity payment dampens annual cost and spreads it over time when compared to one-off payment (model i). The outcome-based payment (model iii) shows to decrease uncertainty and delay in payment. Model iii has little to no effect on total budget impact on a Dutch population level when compared to the one-off payment (model i).

The maximum value based price (MVBP) under discounted scenario's is shown in figure 7. In the base case (44% discount from list price) the MVBP was estimated at €2,579,396 (€2,515,059 – €2,618,649), varying from €4,492,856 (€4,428,519 – €4,532,109) in the most conservative

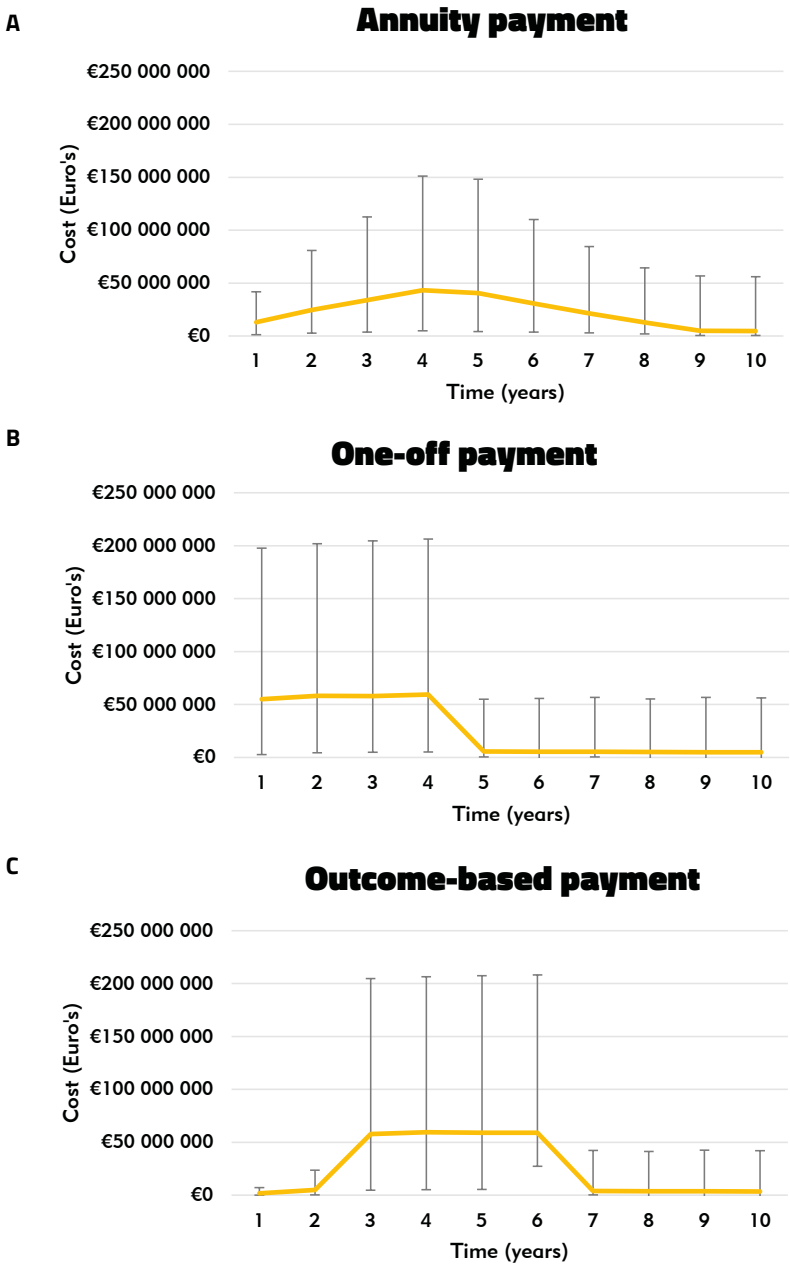

Figure 6. Annual cost of valrox treatment on a Dutch population level. [A] one-off payment, [B] annuity payment and [B] outcome-based payment. Valrox - valoctocogene roxaparvovec (Roctavian®).

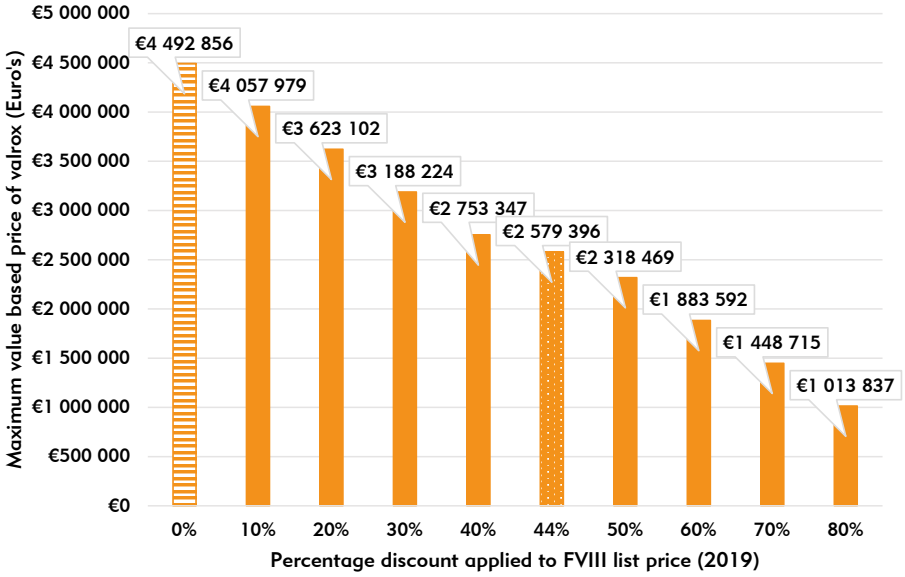

Figure 7. Maximum value based price of valrox under FVIII discount scenario's. 0% discount represents Dutch list price (striped bar at €1.0/IE), and 44% discount aligns with the base case analysis (dotted bar at €0.56/IE). FVIII – factor VIII. Valrox - valoctocogene roxaparvovec (Roctavian®).

scenario (0% discount) to 1,013,837 (€949,500 – €1,053,090) under the most optimistic scenario (80%). The most conservative scenario (Figure *7*: *striped bar at* €1.0/IE) corresponds to the list price.[50]

The break-even-point was estimated at 8.09 (-1.21 – 114.02) years for valrox compared to FVIII prophylaxis and 5.76 (-92.75 – 152.74) years when compared to emicizumab (see Figure 1). Both estimates are associated with considerable uncertainty expressed in wide 95% confidence intervals. The cumulative NMB and NHB over time calculated to estimate the break-even point are visualized in **Figure S5**.

Discussion

The results of this economic evaluation show that the intervention of the novel gene therapy valoctocogene roxaparvovec (valrox; Roctavian®) compared to prophylactic FVIII as well as to prophylactic emicizumab yielded more QALYs against less costs resulting in a dominated incremental cost- effectiveness ratio (ICER). Additionally, we observed that payment models can impact annual treatment cost, time of payment as well as uncertainty associated with cost over time. The cost-effectiveness and value based price of valrox were found to be linked to price discount of the FVIII prophylaxis. To break-even on the initial irrecoverable upfront investment of valrox, in the base case the benefit should on average be at least 8.09 years compared to FVIII prophylaxis and 5.76 years

compared to emicizumab prophylaxis. Although these estimates are associated with considerable uncertainty, they are in line with previous analysis of gene therapies in severe haemophilia A.[20,21]

To elaborate, the economic evaluation conducted by Machin et al. took a 10-year time horizon and also showed a dominated ICER.[20] However, considerably lower cumulative costs and higher benefits were reported by the authors. This can be caused by several differences in our methodologies and between jurisdictions. The lower costs can be explained as Machin and colleagues included only direct medical costs, applied lower FVIII dosage and assumed a lower valrox price (i.e., $850.000/ treatment). Additionally, the study applied a utility value of 1.00 to patients after successful gene therapy treatment which is higher than our 0.82-0.88. The analysis by Cook et al was the first evaluation to include durability of valrox reflected as treatment waning and initial response.[21] Average durability of the therapy was estimated to be 11.0 years (ranging 3-50 years), which is in line with our findings which showed mean FVIII level of 15.8 FVIII% after 10 years. Again, the ICER shows to be dominated as incremental QALYs were achieved for less cost. Contrary to Machin et al.'s analysis, the cumulative costs in this study are considerably higher.[20,21] Cook estimated around $8.5 million costs for FVIII prophylaxis and almost $3.5million for the valrox arm after 10 years. This large difference could partially be explained by the applied FVIII costs, which were ±3 times higher than our base case value. This large cost saving can also explain the break-even difference, which was estimated at 2.4 years.[21]

Recently the US ICER institute published a report assessing haemophilia A treatments including valrox.[27] The biggest change compared to their previous report, assessing emicizumab and FVIII which we used to inform our study design, is its model structure.[28] The new model no longer included a three sub model approach, but used a Markov model preceded by a decision tree. The Markov model had a more simplified three health state structure (arthropathy, no arthropathy and death) and put more emphasis on joint damage. Translating this to the Dutch situation, arthropathy is likely to be more relevant in an elder hemophilia A population due to early onset of FVIII prophylaxis in more recent guidelines and therefore less in the here presented study cohort. Additionally, the arthropathy state included tunnel states based on incremental Pettersson Score. Other changes were inclusion of higher utility values and gene therapy specific measures such as treatment waning, derived from literature updates. Although the US ICER institute reports are placed in a US setting and takes a life-time horizon, again we see less cost are associated with valrox treatment compared to FVIII and emicizumab prophylaxis with little incremental QALY's. Additionally, the fair number of changes in two reports assessing therapies in the same indication area may reflect rapid technological and clinical advancement in the HA space.

Although achieving incremental health benefits against less costs sounds attractive, a couple considerations should be explored in more detail. First to reiterate, gene therapies with a sustained or curative claim are administered in the present time, as is the irreversible payment. This irreversible upfront treatment cost is only offset by future health benefits and cost saving. To add, the long-term benefits are seldom clinically confirmed and highly uncertain. If a gene therapy proves to be less effective than claimed, the treatment cannot be discontinued, nor can the cost be recouped.[63] To continue, a treatment may appear cost-effective over time or appear cost-saving as was conclude here. However, budget impact and timing of payment may still cause affordability challenges

amongst payers as was briefly explored in our budget impact analyses.[64] Next, our results reflect benefits and cost on a population level. From the clinical evidence supporting this analysis, as well as previously conducted microsimulation (i.e. patient level analyses), it is known that intra-patient variability in this population is considerable.[13,21,42] This means that some patients may achieve more benefit with even less costs and vice-versa. In addition, the potential side effects of gene therapy on the long term have not been taken into account. Short term side effects are immunological responses, that may lead to liver function abnormalities and even decrease of FVIII levels and failure of therapy. We aimed to address the latter by including non-response in our estimates.

Literature assessing economic evaluations and affordability in the context of gene therapies has identified several market access and pricing challenges.[17,18,65] As briefly mentioned before, the combination of both evidentiary uncertainties as well as high (upfront) costs are most prone.[31,66–68] One of the solutions often proposed to address both these challenges is use of payment models.[31,66–68] In our analysis we aimed to assess impact on cost and uncertainty in the theoretical application of the three most mentioned payment models.[63] Our analysis showed that annuity payment may decrease and spread annual treatment cost. The outcome-based payment model applying conditions described elsewhere showed to decrease some uncertainty and postponed payments.[27] However, the specific design and conditions of an alternative payment can vary by great extent. To accommodate their implications in practice, more research is needed to explore impact of different models, conditions and combinations as well as evidence needs.[69,70] So far it seems the benefits and effects of payment models in general remain theoretical, as little evidence is available of impact or implementation in practice.[31,70] This observation is in line with findings outside the gene therapy space. A case study studying a conditional financing scheme from the Netherlands described that - although promising to warrant quick access to new therapies - numerous procedural, methodological and decision making short comings were encountered leading to halting of the scheme.[71] Since, more learnings of several payment models have been reported.[30,71–73] In the design and implementation of payment models in practice for gene therapies, these learnings should be applied.

Limitations

This study has some limitations. First, our analyses is based on clinical data from a small Phase I/II gene therapy trial.[13,42] Key parameters describing treatment durability (e.g., initial response, response rate and treatment waning) are uncertain and also showed considerable impact on outcomes. In line, the single arm design of the Phase I/II trial incited indirect comparisons between treatment arms. Together with different approaches takes in the valrox arm (simulation of bleed rates using FVIII levels) and prophylactic arms (bleeds rates derived from literature), this may cause additional bias which has not been quantified in our sensitivity analyses. We aimed to somewhat address these limitations by matching inputs based on patient characteristics and using effectiveness parameters from a meta-analysis reported in the technology assessment conducted by ZIN where possible.[27,36] Also, expert elicitation was conducted to increase validity of disease and treatment assumptions. One of these assumptions in the adherence rate of prophylactic FVIII, which assumed to be 100%. Although this percentage is based on the work by the US ICER institute, as stated earlier this may be an over estimation.[28] To continue, the dosing regimen used for prophylactic emicizumab is in line with

the ZIN-assessment.[44] However, national treatment guidelines dictate lower dosage. This may cause our pharmaceutical costs in the emicizumab arm to be an overestimation.

Furthermore, utility values used in our analysis reflected quality of life (QoL) of HA patients with inhibitors as these were the only available at that time.[28] Patient without inhibitors are expected to have higher QoL, therefore our QoL values may be underestimated.[10] Consequently, less bleeds and less infusions may result in higher productivity and lower societal costs. In line, no costs were included associated with medical aids needed due to reduced mobility. This, due to lack of evidence to support estimations. However, impact may be limited as literature shows that HA-patients currently aged ±30 may lead near to normal lives due to early onset of prophylactic treatment leading less joint damage.[2] To continue, our approach to use a biomarker (FVIII%) to simulate bleeding rates was chosen to incorporate treatment durability and as well overcome the limitation that valrox and prophylactic FVIII are FVIII level driven, and emicizumab is not.[74] Meaning, emicizumab treated patients no FVIII levels can be measured as the therapy renders FVIII assays useless. Treatment effects in the emicizumab arm are therefore based on literature derived ABRs. This issue seems specific for the haemophilia indication and is likely to be encountered in future assessments with several non-replacement in late clinical development.[75] Last, expert elicitation and incidental patient reporting put forward contradicting information regarding adverse events of patients treated with gene therapy, especially in the first year after treatment. However, little evidence allowed us to quantify these observations. This analysis includes adverse events reported in the clinical trials, however we acknowledge this may be an underestimation reflecting less cost and higher QALYs.[13,42]

The sensitivity analyses conducted in this research have quantified provided the direction of uncertainty, however the informativeness for decision making is limited. Future research could extend on our work with additional analyses to better inform a broader set of policy decisions. For example, expected value of information analyses (EVI) are an extension to probabilistic CEAs and provide information on the strategy when a 'wrong' strategy is adopted, which is not captured in DSAs, PSA's or CEACs.[76] EVIs inform the decision maker about the expected cost of uncertainty and parameters for which additional research is most useful (expected value of perfect information or EVPI) or which may contribute most to uncertainty (partial EVPI).[76,77] This may be useful to design coverage with evidence development payment models but can also be applied earlier on in decision making. For example, the EMAs decision to request additional data lead to withdrawal market authorization by the developer. An EVI and forgone health assessment could quantify monetary and health won or lost by delaying market authorization and requesting the developer to submit additional data from an ongoing Phase III trial. Providing insight in the implications of decision strategies and usefulness to obtain additional evidence.

Conclusion

The results of this economic evaluation of valoctocogene roxaparvovec (valrox; Roctavian®) and FVIII prophylaxis and valrox and emicizumab in severe haemophilia A patients in the Netherlands on a population level shows in both comparisons that incremental QALYs were achieved for less costs. Additionally, different payment models showed to impact annual treatment costs, time of payment and uncertainty. However, because of little availability of clinical evidence and experience with

gene therapies for hemophilia A , estimated benefits and costs show high variance. More studies are needed to characterise uncertainty and their impact in decision making. Also, availability of more clinical evidence of phase 3 studies with larger patient numbers and longer follow-up may help characterize variance and uncertainties in order to facilitate early and sustained patient access of these novel therapies.

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References

1. Fijnvandraat K, Cnossen MH, Leebeek FWG, Peters M. Diagnosis and management of haemophilia. *BMJ*. 2012;344. doi:10.1136/bmj.e2707

2. Mannucci PM, Tuddenham EGD. The hemophilias — From royal genes to gene therapy. *NEJM*. 2001;344(23):1773-1779. doi:10.1056/NEJM200106073442307

3. Biggs R, Macfarlane RG. Haemophilia and Related Conditions: A Survey of 187 Cases. *Br J Haematol*. 1958;4:1-27. doi:https://doi.org/10.1111/j.1365-2141.1958.tb03830.x

4. Tantawy AAG. Molecular genetics of hemophilia A: Clinical perspectives. *Egypt J Med Hum Genet*. 2010;11(2):105-114. doi:10.1016/j.ejmhg.2010.10.005

5. Boehlen F, Graf L, Berntorp E. Outcome measures in haemophilia: A systematic review. *Eur J Haematol*. 2014;93(S76):2-15. doi:10.1111/ejh.12369

6. Limperg PF, Terwee CB, Young NL, et al. Health-related quality of life questionnaires in individuals with haemophilia: a systematic review of their measurement properties. *Haemophilia*. 2017;23(4):497-510. doi:10.1111/hae.13197

7. Gouw SC, Timmer MA, Srivastava A, et al. Measurement of joint health in persons with haemophilia: A systematic review of the measurement properties of haemophilia-specific instruments. *Haemophilia*. 2019;25(1):e1-e10. doi:10.1111/hae.13631

8. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1). doi:10.1111/j.1365-2516.2012.02909.x

9. Nederlandse Vereniging van Hemofiliebehandelaars, (NVHB). *Diagnostiek En Behandeling van Hemofilie En Aanverwante Hemostasestoornissen*. 1st ed. (Mauser-Bunschoten EP, ed.). Alphen aan den Rijn: Van Zuiden Communications B.V.; 2009.

10. Pedra G, Christoffersen P, Khair K, et al. The impact of factor infusion frequency on health-related quality of life in people with haemophilia. *J Haemoph Pract*. 2020;7(1):102-109. doi:10.17225/jhp00158

11. Detela G, Lodge A. EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation. *Mol Ther - Methods Clin Dev*. 2019;13(June):205-232. doi:10.1016/j.omtm.2019.01.010

12. van Balen EC, Wesselo ML, Baker BL, et al. Patient Perspectives on Novel Treatments in Haemophilia: A Qualitative Study. *Patient*. 2019;(0123456789). doi:10.1007/s40271-019-00395-6

13. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. *N Engl J Med*. 2020;382(1):29-40. doi:10.1056/NEJMoa1908490

14. Rangarajan S, Walsh L, Lester W, et al. AAV5-factor VIII gene transfer in severe hemophilia a. *N Engl J Med*. 2017;377(26):2519-2530. doi:10.1056/NEJMoa1708483

15. Fuchs H, Bienaime J. *Valoctocogene Roxaparvovec: Phase 2 and Phase 3 Update*. San Rafael, CA.; 2019. https://investors.biomarin.com/download/Valrox+Update_deck+__052919_Final_11am.pdf.

16. Eder C, Wild C. Technology forecast : advanced therapies in late clinical research , EMA approval or clinical application via hospital exemption. *J Mark Access Heal Policy*. 2019;7(1). doi:10.1080/20016689.2019.1600939

17. Morrow D, Ussi A, Migliaccio G. Addressing Pressing Needs in the Development of Advanced Therapies. *Front Bioeng Biotechnol*. 2017;5(9):1-6. doi:10.3389/fbioe.2017.00055

18. Hanna E, Tavella F, Rémuzat C, Auquier P, Toumi M. Market Access of Atmps: Overview and Expected Challenges. *Value Heal.* 2015;18(7):A518-A519. doi:10.1016/j.jval.2015.09.1580

19. Claxton K, Palmer S, Longworth L, et al. Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. *Health Technol Assess (Rockv).* 2012;16(46). doi:10.3310/hta16460

20. Machin N, Ragni M V., Smith KJ. Gene therapy in hemophilia A: a cost-effectiveness analysis. *Blood Adv.* 2018;2(14):1792-1798. doi:10.1182/bloodadvances.2018021345

21. Cook K, Forbes SP, Adamski K, Ma JJ, Chawla A, Garrison LP. Assessing the potential cost-effectiveness of a gene therapy for the treatment of hemophilia A. *J Med Econ.* 2020;23(5):501-512. doi:10.1080/13696998.2020.1721508

22. Azvolinsky A. Gene therapy "cure" for blindness wanes. *Nat Biotechnol.* 2015;33(7):678. doi:10.1038/nbt0715-678

23. Zimmermann M, Lubinga SJ, Banken R, et al. Cost Utility of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease. *Value Heal.* 2019;22(2):161-167. doi:10.1016/j.jval.2018.09.2841

24. Fischer K, de Kleijn P, Negrier C, et al. The association of haemophilic arthropathy with Health-Related Quality of Life: a post hoc analysis. *Haemophilia.* 2016;22(6):833-840. doi:10.1111/hae.13120

25. Kuehne F, Chancellor J, Mollon P, Weinstein M. Microsimulation or cohort modeling? A comparative case study in HIV infection. *Value Heal.* 2007;10(3):A170. doi:10.1016/S1098-3015(10)69056-0

26. National Research Council. Microsimulation Models: Then and Now. In: Citro C, Hanusek E, eds. *Improving Information for Social Policy Decisions - The Uses of Microsimulation Modeling.* Volume I. Washington, DC: National Academic Press; 1991:360.

27. David M. Rind, Agboola F, Herron-Smith S, et al. *Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value.* Boston, MA; 2020. https://icer-review.org/wp-content/uploads/2019/12/ICER_Hemophilia-A_Evidence-Report_101620.pdf.

28. Rind D, Agboola F, Kumar V, et al. *Emicizumab for Hemophilia A: Effectiveness and Value Final Evidence Report.* Boston, MA; 2018. http://icer-review.org/programs/new-england-cepac/.

29. Drummond M, Barbieri M, Cook J, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. *Value Heal J Int Soc Pharmacoeconomics Outcomes Res.* 2009;12(4):409-418. doi:10.1111/j.1524-4733.2008.00489.x

30. Jørgensen J, Servos S, Kefalas P. The potential price and access implications of the cost-utility and budget impact methodologies applied by NICE in England and ICER in the US for a novel gene therapy in Parkinson's disease. *J Mark Access Heal Policy.* 2018;6(1):1-15. doi:10.1080/20016689.2018.1500419

31. Jørgensen J, Kefalas P. Annuity payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. *J Mark Access Heal Policy.* 2017;5(1):1355203. doi:10.1080/20016689.2017.1355203

32. O'Mahony B, Noone D, Prihodova L. Survey of coagulation factor concentrates tender and procurement procedures in 38 European Countries. *Haemophilia.* 2015;21(4):436-443. doi:10.1111/hae.12720

33. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)-explanation and elaboration: A report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Heal.* 2013;16(2):231-250. doi:10.1016/j.jval.2013.02.002

34. den Uijl IEM, Mauser Bunschoten EP, Roosendaal G, et al. Clinical severity of haemophilia A: Does the classification of the 1950s still stand? *Haemophilia*. 2011;17(6):849-853. doi:10.1111/j.1365-2516.2011.02539.x

35. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. *N Engl J Med*. 2018;379(9):811-822. doi:10.1056/nejmoa1803550

36. Diemer F. *Farmacotherapeutisch Rapport Emicizumab (Hemlibra®) Als Routineprofylaxe van Bloedingen Bij Patiënten Met Ernstige Hemofilie A Zonder Remmers Tegen Factor VIII [DUTCH]*. Vol 3. Diemen, the Netherlands; 2019. https://www.zorginstituutnederland.nl/binaries/zinl/documenten/adviezen/2020/02/17/pakketadvies-emicizumab-hemlibra/Pakketadvies+emicizumab+%28Hemlibra®%29.pdf.

37. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939. doi:10.1111/jth.12672

38. Fischer K, van Hout BA, van der Bom JG, Grobbee DE, van den Berg HM. Association between joint bleeds and pettersson scores in severe haemophilia. *Acta radiol*. 2002;43(5):528-532. doi:10.1258/rsmacta.43.5.528

39. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop Relat Res*. 1980;NO 149:153-159. doi:10.1097/00003086-198006000-00018

40. Tan SS, Bouwmans CAM, Rutten FFH, Hakkaart-van Roijen L. Update of the Dutch Manual for Costing in Economic Evaluations. *Int J Technol Assess Health Care*. 2012;28(2):152-158. doi:10.1017/S0266462312000062

41. Centraal Bureau voor Statistiek (CBS). Statistics Netherlands. https://www.cbs.nl/. Published 2019. Accessed January 1, 2019.

42. Pasi KJ, Rangarajan S, Mitchell N, et al. First-in-human Evidence of Durable Therapeutic Efficacy and Safety of AAV Gene Therapy Over Three-years with Valoctocogene Roxaparvovec for Severe Haemophilia A (BMN 270-201 Study). *ISTH Acad*. 274198(Abstract LB 01.2):Presented at the International Society of Thrombos.

43. Zorginstituut Nederland. Farmacotherapeutisch Kompas. KNMP. https://farmacotherapeutischkompas.nl. Published 2020. Accessed November 25, 2020.

44. Zorginstituut Nederland (ZIN). *Package Advice Emicizumab (Hemlibra ®)*. Vol 3. Diemen, the Netherlands; 2020. https://english.zorginstituutnederland.nl/binaries/zinl-eng/documents/reports/2020/02/17/emicizumab-hemlibra/Emicizumab+%28Hemlibra®%29+package+advice.pdf.

45. Soares MO, Sharples L, Morton A, Claxton K, Bojke L. Experiences of Structured Elicitation for Model-Based Cost-Effectiveness Analyses. *Value Heal J Int Soc Pharmacoeconomics Outcomes Res*. 2018;21(6):715-723. doi:10.1016/j.jval.2018.01.019

46. Briggs A, Claxton K, Sculpher M, et al. *Decision Modelling for Health Economic Evaluation*. 2nd Editio. (Gray A, Briggs AH, eds.). Oxford, UK: Oxford University Press; 2006.

47. Mazza G, O'Hara J, Walsh S, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. *Health Qual Life Outcomes*. 2018;16(1):1-8. doi:10.1186/s12955-018-0908-9

48. Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: Observations from the dosing observational study in hemophilia. *Value Heal*. 2012;15(6):916-925. doi:10.1016/j.jval.2012.05.005

49. Ballal RD, Botteman MF, Foley I, Stephens JM, Wilke CT, Joshi A V. Economic evaluation of major knee surgery with recombinant activated factor VII in hemophilia patients with high titer inhibitors and advanced knee arthropathy: Exploratory results via literature-based modeling. *Curr Med Res Opin*. 2008;24(3):753-768. doi:10.1185/030079908X273048

50. Dutch National Health Institute (Zorginstituut Nederland). Drug costs in the Netherlands [Dutch]. https://www.medicijnkosten.nl/. Published 2019. Accessed July 1, 2019.

51. Shrestha A, Eldar-Lissai A, Hou N, Lakdawalla DN, Batt K. Real-world resource use and costs of haemophilia A-related bleeding. *Haemophilia*. 2017;23(4):e267-e275. doi:10.1111/hae.13220

52. O'Hara J, Walsh S, Camp C, et al. The relationship between target joints and direct resource use in severe haemophilia. *Health Econ Rev*. 2018;8(1):1-7. doi:10.1186/s13561-018-0185-7

53. Dutch Healthcare Authority (NZa). DBC product-finder for tariffs. 2019. http://www.nza.nl/organisatie/. Published 2019. Accessed July 1, 2019.

54. Netwerk Orthopedie. *Carepath Protocol Total Knee Replacement [DUTCH].*; 2015. https://netwerk-orthopedie.nl/wp-content/uploads/2015/05/Protocol-totale-knie-prothese-toelichting.pdf.

55. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Vol 2. 2nd ed. (Cartwright WS, ed.). Oxford University Press; 1999.

56. Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty analysis: A report of the ISPOR-SMDM modeling good research practices task force working group-6. *Med Decis Mak*. 2012;32(5):722-732. doi:10.1177/0272989X12458348

57. Hatswell AJ, Bullement A, Briggs A, Paulden M, Stevenson MD. Probabilistic Sensitivity Analysis in Cost-Effectiveness Models: Determining Model Convergence in Cohort Models. *Pharmacoeconomics*. 2018;36(12):1421-1426. doi:10.1007/s40273-018-0697-3

58. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *N Engl J Med*. 2017;377(9):809-818. doi:10.1056/nejmoa1703068

59. Burt RK, Balabanov R, Burman J, et al. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients with Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. *JAMA - J Am Med Assoc*. 2019;321(2):165-174. doi:10.1001/jama.2018.18743

60. Earnshaw SR, Graham CN, Mcdade CL, Spears JB, Kessler CM. Factor VIII alloantibody inhibitors: Cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. *Haemophilia*. 2015;21(3):310-319. doi:10.1111/hae.12621

61. HemoNED Dutch Hemophilia Registry. HemoNED Annual report 2019. HemoNed Foundation. https://hemoned.nl/publicaties/jaarrapportages/. Published 2019. Accessed December 23, 2020.

62. Mladsi D, Earnshaw S, Akashi-Ronquest N, Keith M. Threshold Pricing Model: Not Just Another Cost-effectiveness Model. *Value Heal*. 2010;13(7):A332. doi:10.1016/s1098-3015(11)72302-6

63. ten Ham RMT, Klungel OH, Leufkens HGM, Frederix GWJ. A Review of Methodological Considerations for Economic Evaluations of Gene Therapies and Their Application in Literature. *Value Heal*. 2020;23(9):1268-1280. doi:10.1016/j.jval.2020.04.1833

64. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. *J Mark Access Heal Policy*. 2015;3(1):29321. doi:10.3402/jmahp.v3.29321

65. ten Ham RMT, Hoekman J, Hövels AM, Broekmans AW, Leufkens HGM, Klungel OH. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Mol Ther - Methods Clin Dev*. 2018;11(December):121-130. doi:10.1016/j.omtm.2018.10.003

66. Coyle D, Durand-Zaleski I, Farrington J, et al. HTA methodology and value frameworks for evaluation and policy making for cell and gene therapies. *Eur J Heal Econ*. 2020;2:1421-1437. doi:10.1007/s10198-020-01212-w

67. Vogler S, Paris V, Ferrario A, et al. How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries. *Appl Health Econ Health Policy*. 2017;15(3):307-321. doi:10.1007/s40258-016-0300-z

68. Barlow J, Bens C, Brent T, et al. AMCP Partnership Forum: Designing benefits and payment models for innovative high-investment medications. *J Manag Care Spec Pharm*. 2019;25(2):156-162. doi:10.18553/jmcp.2019.25.2.156

69. Vreman RA, Broekhoff TF, Leufkens HGM, Mantel-Teeuwisse AK, Goettsch WG. Application of managed entry agreements for innovative therapies in different settings and combinations: A feasibility analysis. *Int J Environ Res Public Health*. 2020;17(22):1-20. doi:10.3390/ijerph17228309

70. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: An exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess (Rockv)*. 2017;21(7):1-204. doi:10.3310/hta21070

71. Makady A, van Veelen A, de Boer A, Hillege H, Klungel OH, Goettsch W. Implementing managed entry agreements in practice: The Dutch reality check. *Health Policy (New York)*. 2019;123(3):267-274. doi:10.1016/j.healthpol.2018.09.016

72. Buyukkaramikli NC, Wigfield P, Hoang MT. A MEA is a MEA is a MEA? Sequential decision making and the impact of different managed entry agreements at the manufacturer and payer level, using a case study for an oncology drug in England. *Eur J Heal Econ*. 2020;Online ahe. doi:10.1007/s10198-020-01228-2

73. Makady A, van Acker S, Nijmeijer H, et al. Conditional Financing of Drugs in the Netherlands: Past, Present, and Future—Results From Stakeholder Interviews. *Value Heal*. 2019;22(4):399-407. doi:10.1016/j.jval.2018.11.016

74. Bowyer A, Kitchen S, Maclean R. Effects of emicizumab on APTT, one-stage and chromogenic assays of factor VIII in artificially spiked plasma and in samples from haemophilia A patients with inhibitors. *Haemophilia*. 2020;26(3):536-542. doi:10.1111/hae.13990

75. Mannucci PM. Hemophilia therapy: the future has begun. *Haematologica*. 2020;105(3):545-553. doi:10.3324/haematol.2019.232132

76. Oostenbrink JB, Al MJ, Oppe M, Rutten-van Mölken MPMH. Expected Value of Perfect Information: An Empirical Example of Reducing Decision Uncertainty by Conducting Additional Research. *Value Heal*. 2008;11(7):1070-1080. doi:https://doi.org/10.1111/j.1524-4733.2008.00389.x

77. Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. *Health Technol Assess*. 2004;8(31):1-103, iii. doi:10.3310/hta8310

Supplemental materials

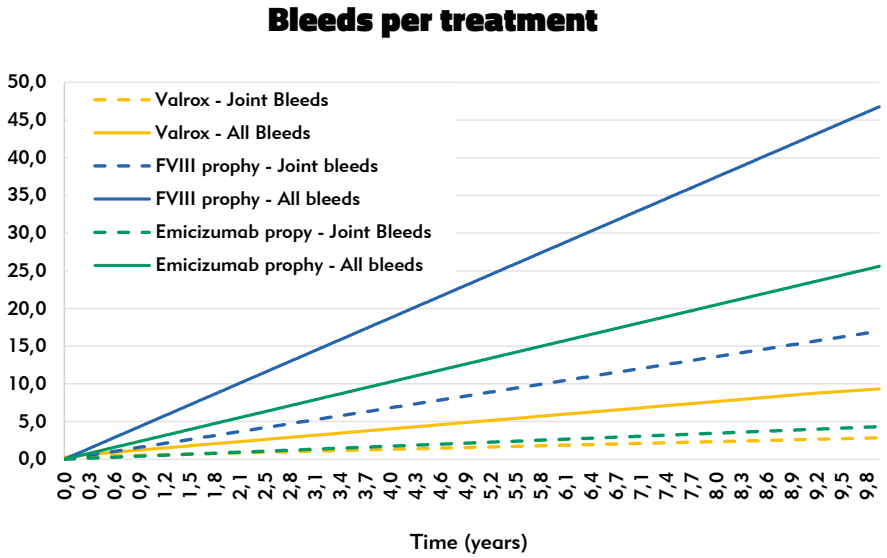


Figure S1. Simulated bleeds per treatment in the base case analysis (cumulative over time). FVIII – factor VIII. Prophy – prophylaxis. Valrox - valoctocogene roxaparvovec (Roctavian®).

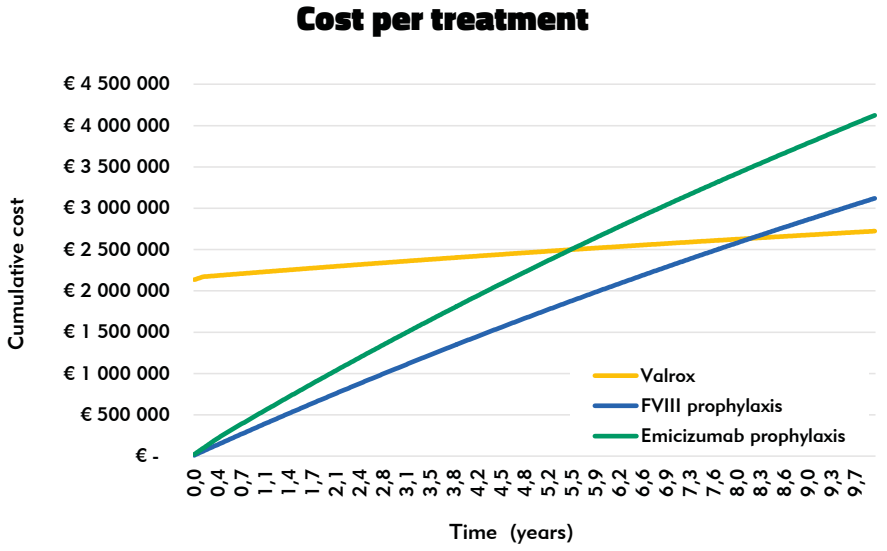
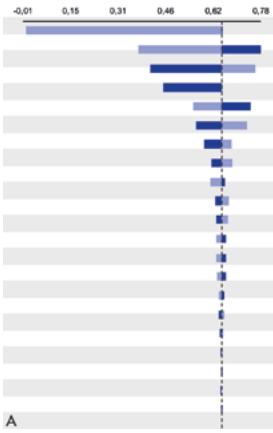
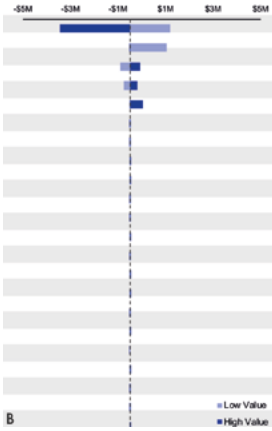


Figure S2. Simulated cost per treatment in the base case analysis (cumulative over time). FVIII – factor VIII. Valrox - valoctocogene roxaparvovec (Roctavian®).



	Parameter	Low Value	High Value	Low Result	High Result	Spread
A	Starting IU/dLlevel at 26 weeks (peak)	0,0	84,000	0,00	0,65	0,65
	Utility: hemophilia A, No Bleed	0,66	0,98	0,37	0,78	0,41
	Distribution 'Nonresponders'	0%	46%	0,76	0,41	0,35
	Annual IUlevel waning (IU/dL)	1,6	10,000	0,65	0,46	0,20
	FVIII Prophylaxis - Treated Joint Bleeds	2,32	3,48	0,56	0,75	0,19
	Adult % Existing Target Joint(s)	0,56	0,84	0,74	0,57	0,17
	valrox - All Bleeds	0,00	2,30	0,68	0,59	0,09
	IU level >5 & <15 joint bleeds	48%	72%	0,69	0,62	0,07
	Pettersson Score at Model Entry (TJ21)	20,00	30,00	0,61	0,66	0,05
	Utility: Pettersson Score 22-39	0,69	0,77	0,67	0,63	0,04
	valrox % Treated Bleeds	49%	73%	0,67	0,63	0,04
	FVIII Prophylaxis Arthropathy Transition Probability	0,00	0,00	0,63	0,67	0,04
	FVIII Prophylaxis - All Bleeds	3,20	7,10	0,63	0,67	0,04
	Proportion of Joint Bleeds	0,48	0,72	0,64	0,67	0,03
	IU level >5 & <15 target joint bleeds	32%	48%	0,64	0,66	0,02
	Joint Bleeds per Pettersson Increase	11,10	14,70	0,66	0,64	0,02
	valrox Arthropathy Transition Probability	0,00	0,00	0,66	0,65	0,01
	FVIII Prophylaxis - Treated Bleeds	3,46	5,20	0,65	0,65	0,01
	Adult % >1 Target Joint	0,56	0,84	0,65	0,65	0,00
	FVIII Prophylaxis - Treated Target Joint Bleeds	2,00	3,00	0,65	0,65	0,00
	Disutility: hemophilia A, Target Joint Bleed	0,10	0,14	0,65	0,65	0,00
	FVIII On demand - All Bleeds	28,5	56,7	0,65	0,65	0,00
	FVIII On demand - Treated Bleeds	28,5	79,5	0,65	0,65	0,00
	FVIII On demand - Treated Joint Bleeds	14,0	47,8	0,65	0,65	0,00
	FVIII On demand - Treated Target Joint Bleeds	5,2	32,2	0,65	0,65	0,00



	Parameter	Low Value	High Value	Low Result	High Result	Spread
B	Cost/unit: FVIII Prophy (per IE)	€0,20	€1,20	€1.188.474	-€3.466.480	€4.654.954
	Starting IU/dLlevel at 26 weeks (peak)	0,0	84,000	€1.046.979	-€488.876	€1.535.856
	Cost/unit: valrox	€1.700.000	€2.550.000	-€912.310	-€62.310	€850.000
	Distribution 'Nonresponders'	0%	46%	-€751.666	-€181.021	€570.645
	Annual IUlevel waning (IU/dL)	1,6	10,000	-€488.778	€48.840	€537.618
	FVIII Prophylaxis - Treated Joint Bleeds	2,32	3,48	-€445.626	-€528.427	€82.801
	2019 Wage (per day adjusted for sex)	€259	€388	-€475.258	-€499.361	€24.103
	Adult % Existing Target Joint(s)	0,56	0,84	-€496.567	-€478.052	€18.515
	Adult % >1 Target Joint	0,56	0,84	-€493.080	-€481.539	€11.540
	Non-Pharm Cost: valrox, emicuzumab, FVIII (19-44yrs)	€724	€1.085	-€482.050	-€492.569	€10.518
	FVIII Prophylaxis - Treated Bleeds	3,46	5,20	-€483.472	-€492.624	€9.152
	valrox - All Bleeds	0,00	2,30	-€489.128	-€483.926	€5.202
	IU level >5 & <15 joint bleeds	48%	72%	-€484.684	-€489.843	€5.158
	FVIII Prophylaxis Arthropathy Transition Probability	0,00	0,00	-€488.616	-€485.891	€2.725
	FVIII Prophylaxis - All Bleeds	3,20	7,10	-€488.614	-€485.895	€2.719
	Joint Bleeds per Pettersson Increase	11,10	14,70	-€486.129	-€488.510	€2.381
	Proportion of Joint Bleeds	0,48	0,72	-€488.512	-€486.148	€2.364
	Pettersson Score at Model Entry (TJ21)	20,00	30,00	-€487.310	-€489.391	€2.081
	IU level >5 & <15 target joint bleeds	32%	48%	-€488.038	-€486.574	€1.464
	valrox % Treated Bleeds	49%	73%	-€486.847	-€487.785	€939
	FVIII Prophy AE: Upper respiratory tract infection (%)	0,25	0,38	-€486.915	-€487.704	€790
	valrox Arthropathy Transition Probability	0,00	0,00	-€487.655	-€486.973	€683
	FVIII Prophylaxis - Treated Target Joint Bleeds	2,00	3,00	-€487.391	-€486.752	€639
	co-pay minimum (2019)	€385	€885	-€487.310	-€487.305	€5
	valrox AE: Pyrexia (grade 2) (%)	€ 0	€ 0	-€487.311	-€487.308	€3

Figure S3. Deterministic sensitivity analysis valrox compared to prophylactic FVIII. Listed are the parameters displaying largest spread of QALY- [A] and cost- outcomes [B].

Parameter	Low Value	High Value	Low Result	High Result	Spread
Starting IU/dL-level at 26 weeks (peak)	0,0	84,000	-0,52	0,13	0,65
Distribution 'Non-responders'	0%	46%	0,24	-0,11	0,35
Annual IU-level waning (IU/dL)	1,6	10,000	0,13	-0,06	0,20
emicizumab Prophylaxis - Treated Joint Bleeds	0,40	1,70	0,07	0,20	0,12
Utility: hemophilia A, No Bleed	0,66	0,98	0,06	0,16	0,10
valrox - All Bleeds	0,00	2,30	0,16	0,07	0,09
IU level >5 & <15 joint bleeds	48%	72%	0,17	0,10	0,07
Pettersson Score at Model Entry (TJ≥1)	20,00	30,00	0,12	0,06	0,06
valrox % Treated Bleeds	49%	73%	0,15	0,11	0,04
Adult % Existing Target Joint(s)	0,56	0,84	0,15	0,11	0,04
emicizumab Prophylaxis Arthropathy Transition Probab	0,00	0,00	0,11	0,15	0,04
FVIII Prophylaxis - Treated Joint Bleeds	2,32	3,48	0,15	0,11	0,04
Proportion of Joint Bleeds	0,48	0,72	0,12	0,15	0,03
emicizumab Prophylaxis - Treated Bleeds	0,80	0,96	0,06	0,09	0,02
IU level >5 & <15 target joint bleeds	32%	48%	0,12	0,14	0,02
Utility: Pettersson Score 22-39	0,69	0,77	0,14	0,12	0,01
valrox Arthropathy Transition Probability	0,00	0,00	0,14	0,13	0,01
Joint Bleeds per Pettersson Increase	11,10	14,70	0,14	0,13	0,01
FVIII Prophylaxis Arthropathy Transition Probability	0,00	0,00	0,14	0,13	0,01
FVIII Prophylaxis - All Bleeds	3,20	7,10	0,14	0,13	0,01
emicizumab Prophylaxis - Treated Target Joint Bleeds	0,30	0,84	0,13	0,13	0,00
Adult % >1 Target Joint	0,56	0,84	0,13	0,13	0,00
Disutility: hemophilia A, Target Joint Bleed	0,10	0,14	0,13	0,13	0,00
FVIII Prophylaxis - Treated Bleeds	3,46	5,20	0,13	0,13	0,00
FVIII Prophylaxis - Treated Target Joint Bleeds	2,00	3,00	0,13	0,13	0,00

Parameter	Low Value	High Value	Low Result	High Result	Spread
Cost/unit: Emi Prophy (1mL vial 30mg/mL)	€1.981	€2.971	-€788.734	-€2.360.792	€1.572.058
Starting IU/dL-level at 26 weeks (peak)	0,0	84,000	-€40.474	-€1.576.330	€1.535.856
Emi Prophy Post-Trial Adherence	69%	100%	-€836.733	-€2.175.485	€1.338.752
Cost/unit: valrox	€1.700.000	€2.550.000	-€1.999.763	-€1.149.763	€850.000
Distribution 'Non-responders'	0%	46%	-€1.839.119	-€1.268.474	€570.645
Annual IU-level waning (IU/dL)	1,6	10,000	-€1.576.231	-€1.038.613	€537.618
Cost/unit: FVIII Prophy (per IE)	€0,20	€1,20	-€1.724.546	-€1.308.482	€416.063
Emi Prophy 24-week Adherence	80%	100%	-€1.526.764	-€1.574.763	€47.999
FVIII Prophylaxis - Treated Joint Bleeds	2,32	3,48	-€1.582.695	-€1.566.939	€15.756
emicizumab Prophylaxis - Treated Bleeds	0,80	0,96	-€1.545.483	-€1.554.887	€9.403
emicizumab Prophylaxis - Treated Joint Bleeds	0,40	1,70	-€1.571.438	-€1.578.669	€7.230
valrox - All Bleeds	0,00	2,30	-€1.576.582	-€1.571.379	€5.202
IU level >5 & <15 joint bleeds	48%	72%	-€1.572.138	-€1.577.296	€5.158
Proportion of Joint Bleeds	0,48	0,72	-€1.575.965	-€1.573.601	€2.364
emicizumab Prophylaxis Arthropathy Transition Probab	0,00	0,00	-€1.573.659	-€1.575.775	€2.117
Adult % >1 Target Joint	0,56	0,84	-€1.573.822	-€1.575.704	€1.882
FVIII Prophylaxis - Treated Bleeds	3,46	5,20	-€1.575.505	-€1.573.735	€1.769
Non-Pharm Cost: valrox, emicizumab, FVIII (19-44yrs)	€724	€1.085	-€1.573.888	-€1.575.638	€1.750
IU level >5 & <15 target joint bleeds	32%	48%	-€1.575.491	-€1.574.027	€1.464
2019 Wage (per day adjusted for sex)	€259	€388	-€1.575.404	-€1.574.121	€1.283
emicizumab Prophylaxis - All Bleeds	1,60	1,92	-€1.571.364	-€1.572.459	€1.095
Joint Bleeds per Pettersson Increase	11,10	14,70	-€1.575.268	-€1.574.211	€1.057
Adult % Existing Target Joint(s)	0,56	0,84	-€1.575.275	-€1.574.251	€1.024
valrox % Treated Bleeds	49%	73%	-€1.574.300	-€1.575.238	€939
valrox Arthropathy Transition Probability	0,00	0,00	-€1.575.109	-€1.574.426	€683

Figure S4. Deterministic sensitivity analysis valrox compared to prophylactic emicizumab. Listed are the parameters displaying largest spread of QALY- [A] and cost- outcomes [B].

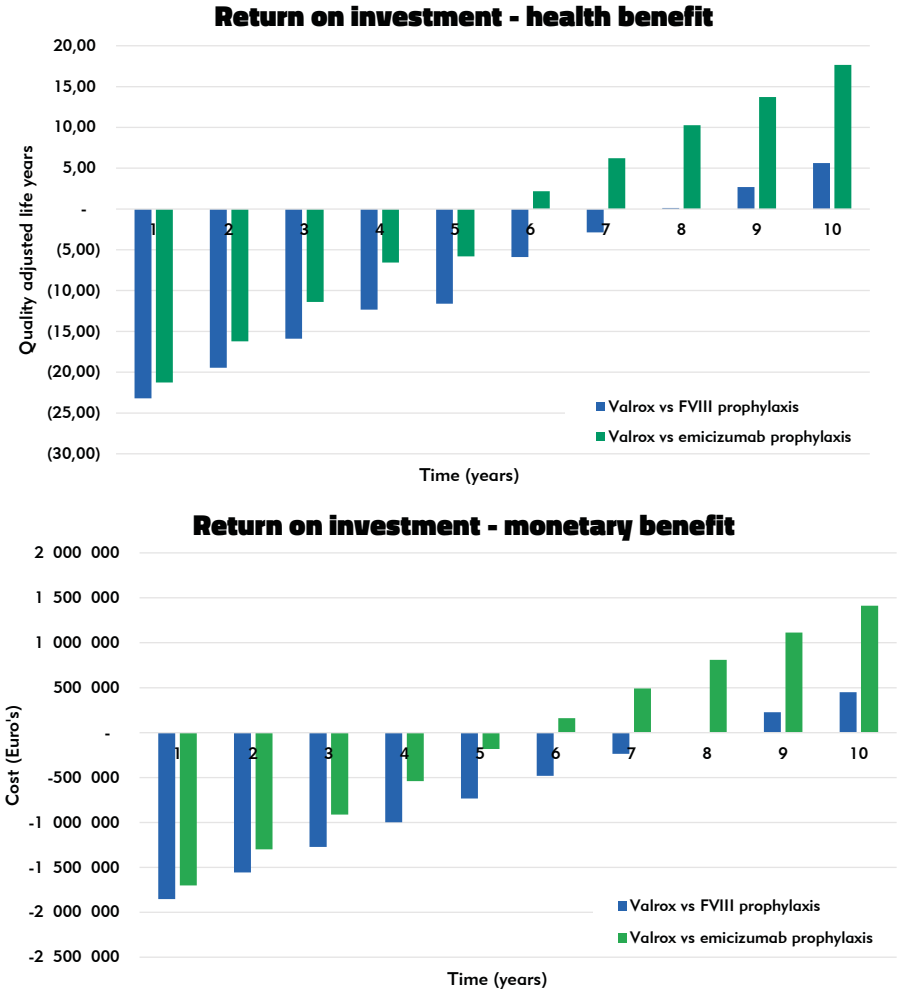


Figure S5. Return on investment expressed as breakeven point of net health benefit [A] and net monetary benefit [B]. FVIII – factor VIII. Valrox - valoctocogene roxaparvovec (Roctavian®).

5

General discussion

The aim of this thesis was to assess gene and cell-based therapy development challenges and how these challenges play a role in marketing authorization and market access, as well as develop tools and methods to mitigate market access challenges for developers. This chapter first describes the main findings of the research conducted in this thesis. These main findings are structured according to the three translational domains outlined in the introduction of this thesis: (i) development, (ii) regulation via centralized market authorization and (iii) market access of gene and cell-based therapies (GCTs Thereafter we will discuss these findings in line with the research aim followed by suggestions for future research and a general conclusion.

Main findings

In **Chapter 2** GCT development challenges were assessed from a commercial developer perspective. First, challenges experienced by companies in Europe were queried in **Chapter 2.1** using a survey.[1] The findings showed that the European GCT field is still in early stages of development (Phase I-II) with a high representation of small and medium-sized enterprises (SMEs). Most often mentioned were regulatory challenges, more specific related to country-specific requirements followed by manufacturing (technical challenge) and clinical trial design (clinical challenge). A distinction was made between challenges specific for GCTs and challenges with a more generic character. Scientific and manufacturing challenges regarding platforms, techniques, raw materials and mechanisms of action were found to be specific to GCTs. Clinical and scientific challenges linked to orphan drug- and new indication were determined as non-GCT specific. Smaller developers expressed more difficulties in the regulatory domain compared to large companies. This was attributed to less familiarity with regulatory trajectories and evidence requirements. Large companies seemed more successful in bringing products to the market by utilizing their generic development expertise and resources. The research conducted in this Chapter provides a timely cross-section of companies developing GCTs in Europe. The classification of challenges and periodic reassessment allows tracking of the developer landscape over time.

Complementary to **Chapter 2.1**, in **Chapter 2.2 and 2.3** economic challenges specifically for smaller and academic cell-based therapy (CBT) developers were addressed. CBTs are more often developed in the public domain by small or academic developers. Especially autologous products and therapies intended to treat small populations ask for small scale and personalised manufacturing development which is costly and requires significant investment. As a result, biomedical researchers and clinicians are increasingly faced with cost considerations which generally is not a part of their routine activities. To facilitate costing of small-scale CBT manufacturing and development, in **Chapter 2.2** a uniform and transparent framework and methodology was developed and validated using eight different CBTs as case studies from four facilities across Europe.[2] This framework and methodology were translated into a tool which is made available in the public domain. In **Chapter 2.3** the feasibility of the CBT costing framework and methodology developed in **Chapter 2.2** was assessed to estimate manufacturing development costs.[3] By demonstrating feasibility of its use outside its initial context, broader application of this framework may be possible as well as incorporation of cost insights earlier on in CBT development, prospective as well as in retrospect. To add, cost reduction should not be the primary objective when applying costing frameworks. Their use lies in providing economic insights and substantiating cost consequences of

manufacturing (development) strategies by facilitating transparent methods, replicable cost estimates and building economic capabilities.

The third Chapter of this thesis takes a regulatory and health technology assessment body perspective. First, in **Chapter 3.1** clinical and regulatory success in Europe from 2009 to 2018 of gene- and cell-based therapies were assessed, quantified and compared to other medicinal product groups.[4] The quantification showed that the implementation of Advanced Therapy Medicinal Product (ATMP) specific marketing authorization regulation did not slow down or hamper the development and success rates of GCTs compared with conventional medicinal and orphan medicinal products. These findings refutes concerns of a low number of centrally marketed GCTs in Europe when compared with clinical trial activity.[5,6] Our analysis shows that following the enactment of ATMP-regulation in 2007, an initial adjustment period of regulatory change occurred. In response, regulatory challenges figured prominently in meetings and publications shortly after 2007. As a result, stakeholders actively engaged with each other to exchange views and practices of GCT development in the new regulatory environment. From 2013 onwards, an increase in positive opinions was seen suggesting a positive learning curve for developers and regulators with regard to submissions. Continued development and regulatory success is dependent on regulation and regulators being adaptive to rapid technological advancement and new information about benefits and risks accruing over the drug life cycle. In so doing, regulation can simultaneously contribute to minimizing risks for patients, balancing the values and interests of stakeholders, and enabling further GCT innovation.

In **Chapter 3.1** key considerations in HTA of GCTs in Scotland, the Netherlands and England were identified and thereafter classified using the EUnetHTA core model domains. In the Netherlands, and England most key considerations were identified in the clinical effectiveness (EFF) and cost and economic effectiveness (ECO-) domains. In Scotland the social aspects-domain yielded most key considerations, followed by ECO- and EFF-domains. It was observed that conditions varied when orphan- or end-of-life criteria were applied. Last, a trend was seen in the ratio of arguments pro- and contra reimbursement between positive, negative and restricted recommendations. Positive recommendations showed a higher percentage of pro key considerations across jurisdictions and negative recommendations a higher percentage of contra key consideration. Restricted recommendations showed an approximately equal percentage of pro- and contra- considerations. The research in **Chapter 3.2** is the first empirical review of HTA-reports in which key considerations are identified and classified using the EUnetHTA core model. Although further validation may be needed, more widespread application of this approach will allow for comparison of key considerations outside the GCT field, such as past medical innovations, orphan medicinal products and others. This can contribute to a better understanding and empirically substantiation of how considerations in health technology assessment differ over time and between jurisdictions. Additionally, more insights in weighing of considerations and experienced uncertainties, (i.e., evidentiary, methodological and others) may guide methodological research, trial designs and submission guidance's among others.

Chapter 4 assessed cost-effectiveness, value, and affordability of gene therapies. First, in **Chapter 4.1** a systematic review identified the methodological considerations discussed in literature when conducting economic evaluations (EEs) of gene therapies, as these are considered to be substantially different from other medicinal products. Identified considerations described payment

models, definition of perspectives, addressing uncertainty, data extrapolation, discount rates, novel value elements, and use of indirect and surrogate endpoints. Additionally, we found that the previously identified considerations, to date, have hardly been applied and explored in peer-reviewed published evaluations. The few EEs that did explore these elements show that these elements have considerable impact on the outcomes of the EEs. Similar to findings **in Chapter 2.1, 3.1 and 3.2**, few of the identified considerations were found to be not specific for gene therapies. Examples are indirect comparison and small sample size in orphan indication, application of novel elements and use of surrogate or novel endpoint. It was concluded that accepted EE methods can broadly be applied to GTs, but few elements may need adjustment (discounting rate, different perspectives and scenarios that explore the impact of payment models, and treatment waning). This study provides a prioritised list for further research to determine appropriateness and application of individual methodological considerations.

The learnings from **Chapter 4.1** were applied in **Chapter 4.2**, in which a cost-effectiveness analysis was conducted in a case study of a gene therapy in development for hemophilia A in the Netherlands. The gene therapy, valoctocogene roxaparvovec (Roctavian®) or valrox, is in development for patients with severe Hemophilia A without inhibitors. Valrox was compared to Dutch standard of care being prophylactic FVIII and prophylactic emicizumab (Hemlibra®). The results of the analysis showed that on a population level prophylactic FVIII and prophylactic emicizumab compared to valrox yielded an increase in quality adjusted life years against less costs. **Chapter 4.2** also demonstrated and quantified considerable uncertainty in study outcomes when applying payment models and scenario analyses. In addition, the study incorporated novel measures applicable for analysis of curative therapies, such as treatment durability (defined as initial treatment effect and treatment waning) and break-even-time (time in years from treatment for future benefits to offset upfront payment). Inclusion of these novel elements can inform conditions set to payment models. More research is needed to better quantify uncertainties and characterize the impact on decision making.

Challenges in GCT development

A high presence of SMEs was identified in the GCT-field (**Chapter 2.1**), higher compared to the small-molecule and biotechnology industry.[1,7] Previous research established that the majority of developers in the GCT field are not companies but hospitals, and academic facilities.[1] More so, hospitals and academic developers were found to dominate early stage development.[8] This suggests that in the GCT field small developers (e.g., SMEs, academia and hospitals) drive innovation and early development. This is in line with research describing previous waves of biomedical innovation in which it was observed that innovation predominantly occurs in academia.[9]

The findings of this thesis corroborate and extend previous findings that translational capabilities needed to cross the valley of death are less developed amongst SMEs and academic developers.[10,11] Development by SMEs and academic developers is associated with specific challenges such as limited funding and limited ability to draw on experience – clinical, regulatory or economic - compared to larger pharmaceutical developers (**Chapter 3.1**).[11,12] Our research showed higher incidence of especially regulatory challenges (**Chapter 2.1**) amongst SMEs and less developed insights in development costs and cost-consequences of early development strategies amongst

academic developers (**Chapter 2.2 & 2.3**).[1,2,13] The strength and expertise of SMEs and more so of academic developers lies in the underlying science and technology. Integrating, building and reconfiguring internal and external capabilities within an organisation in alignment with its (changing) environment - also known as dynamic capabilities[14] - asks for considerable and strategic investments of both money and time. However, smaller developers often have less capital spending and cannot accept as much financial risk as large pharmaceutical companies.

Chapter 2.1 and 2.2 showed small and academic CBT developers often underestimated consumed and required resources in manufacturing (development).[2,3] Development and application of the costing framework and methodology showed the developers included in the studies structurally undervalued their resources, leading to overly optimistic budgeting and low (external) price setting. The unaccounted costs were often seen to be absorbed by facility budgets or start-up subsidies in the short term. However, in the long term systematic undervaluation can considerably hinder translation of CBTs as funds may run dry which is likely to impact financial viability of facilities. This may lead to discontinuation of product development for other reasons than promising (pre-) clinical results.[15] Therefore, insights in resource use and cost-consequences of development strategies early on in development are important to increase successful translation of CBTs, attract appropriate funding and ensure financial stability.

More diversity is not only seen among developers, but also amongst authorities involved in development, regulation and HTA. For example, because GCTs may consist of live tissues or have gene editing properties, development requires interactions with new or extra authorities. To transport or conduct research with genetically modified organisms (GMOs) in humans specific licenses and permits need to be granted[16]. Interpretation, experience, and organization of required authorities may differ per country.[17] For CBTs, a similar situation was described regarding customs and transporting of human tissue between Member States and outside (**Chapter 2.1**). Identification and interaction with these authorities, their offerings, services, and legal remits requires intricate familiarization and experience with the GCT- and drug development field by developers.

When assessing the development of the first GCTs reaching advanced development milestones it is observed that most of the products have advanced via (public-private) partnerships. For example in the case of Strimvelis® (autologous CD34+ enriched cell fraction containing CD34+ cells transduced with retroviral vector encoding for the human adenosine deaminase deficiency [ADA] cDNA sequence), the treatment was originally developed by San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), located at in an academic hospital in Milan, Italy.[18] Via a collaboration with GlaxoSmithKline (GSK) the therapy was advanced. In this collaboration GSK provided developmental experience and financial security via milestone payments whereas SR-Tiget provided the science and technology.[19] Similar collaborations were seen in the development of Imlygic® (talimogene laherparepvec), MACI® (autologous cultured chondrocytes) and Holoclar® (ex vivo expanded autologous human corneal epithelial cells containing stem cells).

As described in **Chapter 3.1**, strategic partnerships between smaller (academic) developers and larger companies are an example to advance the GCT field.[4,20] In such partnerships, academic developers and SMEs provide an innovation (e.g., a product or technology) and strong scientific and technological expertise. Larger developers can draw on resources, experiences, and capabilities

from prior development trajectories, and contribute experience in navigating the regulatory and health technology assessment (HTA) landscape whilst providing some financial stability. This observation is in line with the idea that large pharmaceutical companies are increasingly becoming 'network integrators' instead of having solely research and development as core business.[21,22] As network integrator a company can take several roles (e.g. investor, regulatory expert, economic expert, lobbyist etc.) to help smaller or less experienced developers to navigate the increasingly complex environment of regulations, policies, health business and politics.[21]

Another strategy gaining traction is the use of shared (public-private) development facilities.[23] These facilities can provide infrastructure and expertise for translation and early-phase manufacturing to help overcome development challenges (e.g., safety, effectiveness, scalability). Examples of such facilities are Cell and Gene Catapult in the United Kingdom or California Institute of Regenerative Medicine (CRM) in the United States. The case studies in **Chapter 2.3** were (partially) developed in a shared facility and showed that timely involvement of regulatory and quality experts contribute to shortening development timelines.[3] In both case studies regulatory and quality experts were involved in the stage just before the manufacturing process capability was validated on production equipment (Technology Readiness Level: TRL 6) and onwards.[24] This point was considered optimal by the scientists affiliated to the shared facility because manufacturing processes were likely to change during process validation (TRL 4 and 5). This 'optimal point' may differ between product (types) and developers, however regulatory and quality input is required sufficiently early to avoid the necessity to re-do costly work if requirements are not appropriately addressed.

Considerations in market authorization of GCTs

To accommodate GCTs within the existing regulatory system for marketing authorization the Advanced Therapy Medicinal Product (ATMP) regulation was enforced.[25] The research in **Chapter 3.2** quantified clinical and regulatory success and showed overall no indication of substantial lower regulatory success rates for GCTs compared to non-GCTs, new active substances (NAS) and orphan products in the decade following the enactment of the ATMP-regulation.[4] However, when assessing the cumulative number of MAAs we roughly observe two phases of regulatory GCT-activity in Europe with varying market authorization success. The analysis shows an initial phase directly following the enactment of the ATMP-regulation (2009–2013) and a subsequent phase from 2013 up to and including 2019. In the initial phase several negative opinions and applicant withdrawals were seen. From 2013 onwards, while more MAAs were submitted, the number of negative opinions and applicant withdrawals remained stagnant. This implies that around 2013, GCT developers started to benefit from the clarity provided by the new regulations and subsequent guidance changes. This was interpreted as institutional learning of the EMA and the Committee of Advanced Therapies (CAT) – the EMA-committee responsible for assessing the quality, safety and efficacy of GCTs (**Chapter 3.1**). Around the same time developers started to benefit from collective learning and enhanced dynamic capabilities suggesting adaption to regulatory change.[14]

Previous research assessing regulatory change to accommodate GCTs under current decision making frameworks describes the global regulatory landscape as diverse.[26] Coppens et al. concludes that this diverse landscape may impose serious hurdles - especially regarding regulatory and quality requirements - for the field to mature from early clinical to late stage development. Yet,

it was just concluded that the regulatory success rate based on centralized Market Authorisation calculated in **Chapter 3.1** do not show alarming low rates of clinical and regulatory success.[4] Part of the discrepancy may be explained by the observation that the regulatory challenges in **Chapter 2.1,** were not often related to centralized European procedures.[1] Instead, the majority of identified regulatory challenges were experienced on an EU Member State level.[1] Medicinal product regulations in Europe cover a variety of overlaying jurisdictions and authorities across its, at time of the research, 28 Member States.[27] Medicinal product regulation also remains dependent on national laws and even when EU regulations are in place Member States often have substantial discretion to add additional or different provisions. These provisions can have an historic origin (i.e., may already be in place) or newly mandated. Consequently, similar GCTs may be subject to different national laws and requirements across Europe. These differences in the regulatory landscape have been reported to be time consuming, add cost to development and influence competitive advantage[1,28]. In addition, there have also been discussions about the added value of national regulatory pathways next to a centralized authorisation procedure.[29,30]

An example of a regulatory challenge attributed to the diverse regulatory landscape is the genetically modified organism (GMO) legislation. The GMO legislation was implemented to assess the environmental risks of GMOs which include genetically modified foods, recombinant DNA research and gene therapy clinical trials.[16] In addition to the challenges associated with the additional permit processes, developers mentioned that the process is not integrated with the benefit-risk assessment conducted by the EMA and generally done by authorities mainly involved in environmental affairs.[31] For example, in the United Kingdom applications for GMO-permits for research purposes, including clinical trials, are processed by the Department for Environment, Food and Rural Affairs and the permit is granted by the Secretary of State for the Environment.[31] Depending on biological characteristics and outcome of the environmental risk assessment, GMO clinical trials are regulated under the contained use or under the deliberate release framework. The latter is a different, and mostly described as a more lengthy, assessment by developers.[31] To contrast, in the Netherlands, all applications fall under the deliberate release framework and are processed by a '*GMO-office*'. The permit itself is issued by Ministry of Infrastructure and Water Management.[31] These examples only span two Member States, more descriptions of regulatory variance and its implications have been described in more detail elsewhere.[17,32–34]

Similar to the observed regulatory variance and interpretation of the GMO-legislation, **Chapter 2.1** also identified challenges related to Member State differences in GMP-requirements, customs and transporting regulations of human tissue, implementation of Hospital Exemption and (additional) requirements for clinical trials with paediatric populations.[1] These findings are in line with literature, which provides multiple comprehensive overviews of jurisdictional differences, challenges and implications for GCT development.[17,32,33,35–37] Dis-harmonization between Member States has been described in drug development outside of the GCT field. However, the combination of the more diverse development landscape, the inclusion of authorities previously not involved in drug development (e.g. the GMO-legislation), implementation of new regulations and modification of acting regulations indicate to impact GCT-development more than development of more conventional medicinal products.[1,16,33] More specific, developers have indicated it impacts development logistics, development time, cost, and adds considerable managerial burden.[1]

Given that the EMAs assessment committees (e.g., CAT and CHMP) consist of delegates of the 28 Member States, the described impact of a diverse regulatory landscape may be somewhat surprising. Centralization of knowledge was the primary reason to subject GCTs to a centralized European procedure (**Chapter 3.1**).[4] One reason could be that accommodation to regulatory change originating on an EU level, may be delayed on a Member State level with inter-Member-State differences.[26] The time it takes to align EU and national provisions may therefore affect development timelines, national local business climate as well as patient access to products. In response several (multi-stakeholder) initiatives have successfully started to address Member State variance, such as efforts to harmonize GMO-legislation and reform GMP-requirements among others.[31,38,39] From the developers' perspective, respondents indicated in **Chapter 2.1** that seeking frequent and early interactions with EU and national competent authorities helped attenuate regulatory challenges. Also, building and retaining internal GCT regulatory and manufacturing expertise contributed to addressing regulatory hindrences.

Considerations in market access of GCTs

The work in **Chapter 4.1** suggests that economic evaluations of gene therapies are not radically different from evaluations of more conventional medicinal products, but that a number of methodological elements may need adjustment.[40] These elements are: innovative payment models to address uncertainty and upfront payment, (differential) discounting, and novel value elements. The methodological considerations within the elements, however, do not necessarily show alignment. This can partially be explained by inconsistent use of terminology. For example, when addressing payment models, more specific performance based contracts were also described as mile-stone based contracts, value-based contracts, pay-for-performance schemes, performance-based risk-sharing arrangements, often without a clear definition and including an array of conditions. Additionally, different payment models showed to have impact on specific measures such as budget impact (e.g., annuity payment), uncertainty (e.g., outcome-based) (**Chapter 4.2**). This suggests that (design of) different models – or the conditions they consist of - could be used to achieve specific goals such as spreading cost, risk-sharing or decreasing uncertainty.

To continue, other methodological considerations addressing the same theme were found to be contradictive, for example around the (re)definition of perspectives. Carr et al opted for wider inclusion of only personal, social, and economic benefits besides treatment cost[41], where others propose inclusion of, among others, infrastructural and capital cost.[42–44] Although, assessment of considerations was outside the remit of the study described in **Chapter 4.1**, the work does provide a timely overview and prioritization of discussions in literature.[40] This overview will facilitate continuation of discussions to determine appropriateness and impact of individual or combined methodological considerations. In these discussions the stakeholders utilising the economic evaluations (e.g., HTA-bodies, decision makers, developers, researchers) as well as those involved in the evidence generation (e.g., clinicians, regulators, authorities, researchers patients) needed to conduct these analyses should be included. As this thesis, and previous work, has demonstrated that choices in early development have an effect down-stream (**Chapter 2 and 3.1**).[26,45,46]

In **Chapter 4.2** learnings from the review of methodological considerations (**Chapter 4.1**) were applied in a case study assessing cost-effectiveness of a novel gene therapy in severe Hemophilia

A in the Netherlands. When developing the cost-effectiveness model, the generic steps of developing a decision model as described by Briggs et al. could broadly be applied, supporting the earlier finding that economic evaluation of gene therapies are not radically different from other products.[47] In addition, the study incorporated two novel measures which were not identified in the systematic review in **Chapter 4.1**: break-even time and treatment durability. Contrary to chronic treatments, if a gene therapy proves to be less effective than claimed the treatment cannot be discontinued, nor can the cost be recouped.[40] The upfront treatment cost under traditional payment agreements is irreversible.[48] At time of admission this irreversible cost vastly exceeds the immediate health benefits. Cost savings (net monetary benefits, NMB) and health gains (net health benefits, NHB) recouped over time will slowly compensate the 'investment'. However, when this happens is highly uncertain, given evidentiary uncertainties at time of decision and limited experience with gene therapies. In **Chapter 4.2** the time it takes for the investments to equal the net benefits (NHB=0 & NMB=0) was estimated as the 'break-even time'. Treatment durability was added to incorporate the gene therapy specific effect measures treatment waning and initial response. Inclusion of the combined treatment durability measure allowed for adoption of an existing disease specific model by incorporating a gene therapy arm, as is demonstrated in **Chapter 4.2.** It also proved useful to assess impact of alternative assumptions which could help inform decision making, or at least better characterise uncertainty and impact. To clarify, the combined measure includes treatment waning and initial response which are clinical measures often individually reported in gene therapy trials. However, because of small sample size and limited follow-up they are often reported with large confidence intervals.[49,50] Including these individual parameters allowed to explore effectiveness scenario's as well as translation to a clinical meaningful concept, i.e., treatment durability.

Although one-off administered curative therapies are considered costly, several treatments demonstrating considerable benefit have been reported to be cost-effective or in the case of the analyses in **Chapter 4.**2 even cost-saving (i.e., dominated).[51,52] However, budget impact and timing of payment may still cause affordability challenges amongst payers.[53] To illustrate, a cost-effectiveness analysis of the gene therapy onasemnogene abeparvovec (Zolgensma®) indicated for spinal muscular atrophy type 1 (SMA1), included in **Chapter 4.1**, estimated undiscounted incremental benefit of 27.5 life years and 10.4 (discounted) quality adjusted life years (QALYs) compared to nusinersen (Spinraza®).[40,51] Applying an estimated price of $2.5 to $5.0 million US dollars the study concludes the intervention is cost-effective. The reported estimated base case incremental cost-effectiveness ratio (ICER) of $31,379/QALY is well below accepted US willingness-to-pay thresholds and therefore suggests good value for money. However, whether a payer can afford the high-upfront price of $2.5-5.0 million US dollars per patient remains to be seen. Therefore, when interpreting economic evaluations of curative or one-off administered therapies, additional outcomes such as budget impact and cost over time should be included to assess affordability. The concise budget impact analysis in **Chapter 4.2** demonstrates payment models may be able to spread costs to some extent.

The analysis in **Chapter 3.2** showed GCTs were routinely subjected the formal HTA, of which economic evaluations often are a part. The review of HTA-reports yielded some GCT-specific considerations, but most identified key considerations overlapped with known considerations for orphan medicines and conditional approved products (e.g., small sample size, limited follow-up,

indirect comparisons). Although, a majority of the considerations and associated challenges are not unique to GCTs, these products seem to experience more barriers and accumulated uncertainty in their assessment. From the reports it was derived that due to little experience in the assessment of GCTs, the interpretation and characterisation of uncertainty was found challenging by the HTA-bodies. Although additional risk mitigating measures and studies seemed to, in part, address uncertainties flagged by the HTA-bodies to some extent, the evidence available at time of decision remained limited. Ongoing early clinical research shows developers are exploring larger indications, which may partially address issues linked to orphan indications. However, GCTs indicated for larger populations reaching development milestones will likely intensify the budget impact and reimbursement discussions, and introduce new challenges. Previous waves of biomedical innovations have shown that over times prices go down as volumes increase, however this is less likely to be the case for GCTs as personalised and costly manufacturing dictate higher target prices.[53]

To add, the comprehensive quality and manufacturing sections seen in market authorization dossiers reflect adoption of assessment of to the novel characteristics of GCTs. In the HTA-reports this adoption was to some extent reflected in the key considerations regarding the technical and organisational domain describing impact of lengthy manufacturing processes and measures needed for proper transportation and admission (**Chapter 3.2**). But the length and comprehensiveness of these domains did not match the sections included in market authorisation dossiers. Moreover, it seemed the domains describing technical and organisational challenges did not bare much weight in the assessment. This could mean that HTA of GCTs is not considerably affected by their unique characteristics or that the impact may be underestimated.

Last, the analysis in **Chapter 3.1 and 3.2** may indicate that a *second generation* of GCTs has arrived. This second generation is developed while the ATMP-regulation was in place. Organisational learning and clarity provided to developers seems to have resulted in evidence generation better aligned with regulators and authority needs. At the same time developers have cultivated dynamic capabilities to identify, shape and substantiate value propositions for HTA-bodies, while HTA-bodies gained experience and became more comfortable with (novel) uncertainties in the assessments.

Limitations

For the studies presented in this thesis, several limitations are to be addressed. First the GCT field is a novel field allowing for the observation of a small research population with limited follow-up time. Also, the GCT field is a rapidly evolving field. The conducted studies and their outcomes should be interpreted in the context of the time in which they were performed. To clarify, the results presented in this work represent a timely snapshot of the GCT field - including the GCTs, developers and decision framework. The composition of the field, its developers and policies are likely to change over time. Even within the timeframe captured in this work, changes in developmental capabilities, policies and challenges were observed. In addition, the novelty of the field also caused little availability of comparative and confirmative evidence. This was especially the case for studies assessing development costs and health technology assessment (**Chapters 2.2, 2.3** and **3.2**). To address this, the outcomes of **Chapter 3.2** were contextualised with work available outside the GCT field. In addition, throughout this thesis it was aimed to report the rationale and methods – new and more

established - as transparent as possible. This was done to comply with good research practices as well as to facilitate their application in future research and increase comparability or results. In **Chapter 2.2** the developed framework and methodology was translated into a tool, which is made available in the public domain.

Next, regulatory and policy research (**Chapter 3.1 and 3.2**) in general is associated with several limitations. The underlying assumption of policy decisions is that regulatory and HTA assessments themselves are done in a consistent way. This is likely not to be the case, as policies, decision frameworks and composition of committees change over time. This may be more applicable to HTAs than regulatory reviews, as HTAs are conducted on a national level introducing intra-authority variance. This has implications for **Chapter 3.2**. Also, this study included HTA-reports of only three HTA-bodies based in the north-west of Europe. These findings may therefore have limited generalisability to other parts of Europe. This notion is confirmed by literature describing differences in HTA-frameworks across Europe.[54,55] Similarly, the development cost studies described in **Chapter 2.2 and 2.3** are also performed in facilities located predominantly in north-west Europe which may limit generalisability of costing insights. However, the framework and methodology developed in these studies is likely to be geographically transferable.[56]

To continue, the different Chapters in this research address specific parts in drug development and the stakeholders involved. The research assessing development challenges (**Chapter 2**) was conducted in close collaboration with different types of developers; small, large, public and private. The research assessing market authorisation and market access was based on secondary data such as literature and public policy documents (**Chapter 3 and 4**). These may be subject to selection and information bias as the HTA-reports and policy documents reflect mere a summary of stakeholders discussions in **Chapter 3,** and the peer-reviewed literature included in the review described in **Chapter 4.1** may not be complete or reflective of discussions elsewhere.

The way forward

How gene and cell-based therapies compare to other medicinal products

The notion that GCTs are different from more conventional medicinal products is often mentioned in literature as well as throughout this thesis.[26,57] From the research it may derive that the product characteristics of GCTs are different (e.g., live cell and tissues). However, when placing GCTs in a wider historic context it is also observed that they follow an established pattern of incremental technology development and diffusion.[58,59]

What we now consider to be conventional medicinal products (e.g., monoclonal antibodies and proteins) were at some point in time also new and characterised as considerably different. However, through combined efforts maturation, dissemination and implementation of these innovations has been achieved.[9,60] Consequently, I propose to consider GCTs from here on forward not as considerably different but considerably new. This may nudge all stakeholders involved in GCTs development to view these products not as an isolated medicinal product group, but seek and

incorporate learnings from the past and permit horizontal and/or vertical transfer of (novel) policies, methods and frameworks.[61–63]

Taking a broader perspective and combining the thesis-findings with current and past learnings in drug development, it was observed that the challenges show considerable overlap with other domains, and have root-causes originating outside the GCT-field. The observation that GCTs so far predominantly address orphan and new indications has already been mentioned. These medicinal product groups themselves are associated with their own set of developmental challenges.[64,65] Similar can be said for drug development by small and medium-sized enterprises (SME's) and academic facilities.[11,66,67] When assessing considerations and uncertainties, it can therefore be beneficial to delineate more generic development challenges and GCT-specific challenges. **Chapter 2.1** showed generic challenges seem to reside more in the clinical, scientific, and financial domain, and more GCT-specific challenges were found in the technical and regulatory domain. However, periodic re-assessment of development challenges and their origin - amongst all stakeholders including authorities – should be performed as the GCT field is highly dynamic. For instance, a shift towards larger (non-orphan) indications, are likely to introduce (new) challenges. **Chapter 2.1** describes a framework to categorise challenges and a developer cohort which can act as a baseline. Identification, categorisation and tracking of challenges may help developers to inform development strategies, identify knowledge gaps and facilitate targeted knowledge dissemination. Similarly, it may prompt authorities to (re)design of policies and accommodate organisational readiness.

Informing decision making

The research conducted in this thesis shows that regulatory change was needed to adopt to new evidentiary requirements necessary to demonstrate and assess quality, safety and efficacy of GCTs. Developers have started to benefit from clarity provided by European regulators.[4] However, continued efforts are needed to align national provisions and provide similar clarity on a Member State level. Continued efforts are also needed to assess impact of modified evidentiary requirements in market authorization on downstream decision makers (e.g., HTA-bodies). The impact of, for example, acceptance of market authorisation applications based on less evidence (such as a single Phase I or I/II clinical trial) in expedited pathways have shown to considerably increase uncertainties.[68] Additionally, other regulatory activities such as availability of regulator imposed post-approval studies have been described to impact, and in some cases, even alter outcomes of relative effectiveness assessments.[69] Therefore, regulatory changes should be accompanied with a downstream impact assessment.

Although, assessment of appropriate application of the methodological considerations in economic evaluations is outside the remit of the study in **Chapter 4.1**, the work does provide a timely overview and prioritization of discussions in literature. This discussion should be continued to determine appropriateness and application of individual methodological considerations. In these discussions the stakeholders utilising the economic evaluations (e.g., HTA-bodies, decision makers, developers, researchers) as well as those involved in the evidence generation (e.g., clinicians, regulators, authorities, patients) needed to conduct these analyses should be included.

The large confidence intervals and high impact of (small) variations in inputted parameters in economic evaluations may raise questions around the usability of the estimated outcomes in decision making (**Chapter 4.1 and 4.2**). Future research could extend on the work in **Chapter 4.2** and explore additional measures or analyses to better inform a broader set of policy decisions. Additional measures such as break-even time could inform conditional reimbursement models. Also, expected value of information analyses (EVI) – which are an extension to probabilistic cost-effectiveness analyses – provide information on the strategy when a 'wrong' strategy is adopted, which is not captured in sensitivity analyses.[70] EVIs inform the decision maker about the expected cost of uncertainty and parameters for which additional research is most useful (expected value of perfect information or EVPI) or which may contribute most to uncertainty (partial EVPI).[70,71] This may be useful to design coverage with evidence development payment models but can also be applied earlier on in decision making. For example, in the case study described in **Chapter 4.2,** the EMAs decision to request additional data led to withdrawal of the market authorization by the developer. An EVI and forgone health assessment could quantify monetary and health won or lost by delaying market authorization and can be weighed against estimated benefits at time of decision. EVIs, can provide additional insight in implications of decision strategies and added, or foregone, value to obtain additional evidence.

Advancing development capabilities and strategies

The GCT field is characterized by a diverse developer landscape with high presence of smaller innovators who have limited capabilities and experience with regulatory and health economic assessments. The European drug development field may also seem complex to newcomers. However, it is increasingly confirmed in-depth knowledge of its stakeholders, regulations, pathways, and policies is essential to successfully surpass drug development milestones. To facilitate this, authorities – especially regulatory authorities - provide a variety of services for developers to inform and interact with decision makers. Also, inclusion and notifying new and established developers about (regulatory) changes is a task for (industry) umbrella associations. To facilitate economic capabilities of smaller developers a framework and methodology was developed, which has been translated into a costing tool. This publicly available tool allows for direct application in practice and requires very little economic experience. Structural application of costing tools are a first step in including cost-conscious considerations in manufacturing development. Whereafter, the cost-consequences of development strategies over time can be assessed. This can be done both prospective as well as retrospective. We therefore encourage developers to use and test our tool and share their findings, best practices as well as less successful learnings. Consistent use of same methods will increase comparability of results as well as provide insight of cost-drivers, generalisability and transferability of results, and business model opportunities. Although smaller developers may be hesitant towards including cost-consideration in development for different reasons, research in this thesis as well as elsewhere has demonstrated that to ensure translation of GCTs towards viable medicinal product, it is key to include regulatory and economic considerations in early development.[26,72,73]

When assessing the current state of academically developed GCTs, especially in the case of CBTs, plentiful early clinical development activity is seen.[13,74] However, a considerable number of CCTs have been tested in exploratory clinical trials, but show little follow-up in the form of phase I/II trials.[13,75] The combination of small indications, autologous therapies and high-risk supply chain may

result in an unattractive business case for larger commercial developers, but create opportunities for academic facilities without instigating competition.[76] It requires further exploration of how to best organise development trajectories and incentivize academic and commercial GCT development in a complementary fashion to also ensure development of GCTs with less commercial potential.

A way forward is to direct efforts to insights into GCTs that are best suited to continue development in an academic environment versus a more commercial environment, keeping in mind that the answer to this question is likely to change as the field evolves. A case is increasingly been made to further explore academic development for small-indications and autologous products. However, several challenges are also flagged in academic development: adoption of GMP requirements tailored to GCTs in an existing hospital environment are costly and time consuming, finding and retaining adequate personnel and funding (both initial and sustained).[13,77,78] Other discussions in literature propose moving towards small to mid-size shared facilities which are seen as a better strategic investment compared to large facilities.[77] Here it is suggested products to be moved from an academic setting to a private setting once the demand exceeds facility capacity. The research in **Chapter 2.3** showed utilizing such a shared facility and timely inclusion of its in-house regulatory and quality expertise can save considerable time and costs as well as increase development success. However, other considerations will also contribute such as intellectual property, occupation of services and return on investment potential. Further exploration of the feasibility and the role of shared facilities in GCT development is needed. This includes assessment of but is not limited to suitability of products, place in the product development trajectory, point of engagement and exploration of sustainable and cost-conscious business models.

Institutional readiness

The rise of GCTs started with the emergence of radical innovative technologies predominantly from small and academic developers followed by entrance of more and larger competitors and incremental innovation. As mentioned before this pattern has previously been seen in the rise of biotechnology, but also more recent in development of Non-Biological Complex Drugs (NBCD).[45] This pattern is described in a wider context in innovation science as the innovation life cycle.[79,80] From literature it can be derived that challenges in early development of innovative medicinal product groups describe similar findings around scientific, technical and organizational dependencies, regulatory adoption and adjustment to uncertainty.[45,65,81] Given continued scientific advances, biomedical innovations will continue to emerge and progress toward clinical application. The ability and extent to which an organization can adapt to embrace a new technology can be described as *institutional learning* and *institutional readiness*.[82–84] Internalizing organizational learning to increase institutional readiness, amongst developers as well authorities, will help accommodate translation of future biomedical innovations.

This thesis described three domains in which translation challenges occur in GCT development: (i) Translation from the laboratory to the clinic (development), (ii) regulation via centralized market authorization and (iii) market access defined as health economics and health technology assessment towards implementation in healthcare services. These three domains have been adopted from innovation challenge research applied to GCTs.[72,85] However, market access after product reimbursement is obtained, is not the same as patient access. To ensure patient access via inclusion

of GCTs in healthcare services clinical adoption is needed.[86] Although clinical adoption itself is out of scope of this thesis due to taking the three-domain approach, it could be said that clinical adoption may be underexposed in this thesis. It is important to realize that additional efforts may be needed to accommodate GCT logistics, manufacturing and quality control all the way to the point of admission due to the fragile product nature.[87,88] This notion is important to ensure facilities and healthcare systems are not caught off-guard by the variety and complexity of these therapies.[86] Successful incorporation of GCTs into healthcare services could be disruptive and may require stakeholders to venture outside their comfort zone and jointly seek solutions.[72,89] In clinical adoption, it is evident that commercial developers are exploring the role of network integrator and are starting to offer patient enrolment and logistic support services to ensure timely and proper tissue procurement. Also, these systems will need to be somehow incorporated in treatment algorithms and facility logistics. Clinical adoption comes with its own challenges and can be regarded as a field of study of its own.[72]

Research recommendations

In order to advance the development, market authorization and market access of GCTs towards integration in health care systems the following research recommendations are proposed:

- Periodic (re-)assessment of challenges experienced by GCT-developers, for example by following up with the cohort of companies compiled in this thesis, to inform development strategies, identify knowledge gaps and facilitate knowledge dissemination. In addition, challenges can be assessed which are experienced by other stakeholders involved in GCT-developers such as regulators, HTA-bodies, clinicians, and patients.
- More research is needed into challenges identified in recurring phases of innovation and dissemination of technologies in the pharmaceutical policy field in Europe by learning from GCTs and past biomedical innovations. Learnings will contribute to internalizing organisational learning amongst developers and authorities.
- To accommodate and coordinate the multi-level regulatory environment in the European Union more insight is needed in the implementation of regulations on a European level and the implications for individual Member States. In doing so, the alignment between the European regulatory framework and national provisions should be considered as well as variance in national provisions between Member States.
- In light of evidentiary uncertainty caused by small (finite) samples in HTA, the implications of expedited pathways for down-stream decision makers should be explored further. This includes coordination between regulators and HTA-bodies and is also seen outside of the GCT-field.
- Further explore appropriateness and impact of methodological elements in economic evaluations of gene therapies, such as inclusion of additional value elements, value-based pricing, methodologies to address indirect comparisons and small samples, payment mechanisms to ensure sustainable healthcare system funding and consensus on use of surrogate endpoints and indirect comparisons. Development and implementation of methodological recommendations should occur in collaboration with payers and authorities whose decisions these evaluations aim to inform.
- To strengthen economic capabilities of small and academic developers, implication and interpretation of the CBT costing framework and methodology could be explored.

- Replicability of identification of key consideration and categorisation using the EUnetHTA core model could be explored. Additionally, this approach could be applied outside of the GCT field to further research interpretation and weighing of considerations in HTA.
- It requires further exploration of how to best organise development trajectories and incentivize academic and commercial GCT development in a complementary fashion as well as ensure development of GCTs with less commercial potential.
- Market access after product reimbursement is obtained, is not the same as patient access. More work is needed in the challenges and solutions to accommodate clinical adoption of GCTs to ensure patient access via inclusion of these innovative products in healthcare services.

General conclusion

This thesis demonstrates that new product characteristics of GCTs do not fit particularly well within established development, regulatory and HTA-frameworks for conventional medicinal products. Novel GCT characteristics asked for redesign of established medicinal product handling, manufacturing and quality assurance which is accompanied by increased development cost and higher risk. The novelties also require capability building in interaction between developers demonstrating and authorities assessing product quality, safety and efficacy. The novel characteristics seemed to affect the health technology assessment (HTA) to a lesser extent. However, the intended curative effects, originating from new mechanisms of action, and higher target prices continue to raise concerns amongst payers and HTA-bodies how to address budget impact and affordability as more GCTs reach late clinical development.

The conducted research provides a cross section of (early) development challenges of GCTs and how they affect down-stream development spanning from manufacturing to reimbursement. It provided empirical findings from a systems and developer perspective as well as cost and cost-effectiveness tools and methods to classify challenges and considerations in HTA to accommodate timely, safe and sustainable patient access to these therapies. This research, therefore, contributes to the fit between these transformative therapies and existing development, regulatory and HTA frameworks, which is not only relevant for GCTs but could also be applicable to future biomedical innovations.

References

1. ten Ham RMT, Hoekman J, Hövels AM, Broekmans AW, Leufkens HGM, Klungel OH. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Mol Ther - Methods Clin Dev*. 2018;11(December):121-130. doi:10.1016/j.omtm.2018.10.003

2. ten Ham RMT, Hövels AM, Hoekman J, et al. What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings. *Cytotherapy*. 2020;22(7):388-397. doi:10.1016/j.jcyt.2020.03.432

3. ten Ham RMT, Nievaart JC, Hoekman J, et al. Estimation of manufacturing development cost of cell-based therapies: A feasibility study. *Cytotherapy*. 2021;In Print.

4. ten Ham RMT, Hövels AM, Klungel OH, Leufkens HGM, Broekmans AW, Hoekman J. Development and Regulation of Gene and Cell-Based Therapies in Europe: A Quantification and Reflection. *Trends Pharmacol Sci*. 2020;41(2):67-71. doi:10.1016/j.tips.2019.11.007

5. Hanna E, Rémuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. *J Mark Access Heal Policy*. 2016;4(1):31036. doi:10.3402/jmahp.v4.31036

6. Morrow D, Ussi A, Migliaccio G. Addressing Pressing Needs in the Development of Advanced Therapies. *Front Bioeng Biotechnol*. 2017;5(9):1-6. doi:10.3389/fbioe.2017.00055

7. Stakeholders and Communication Division. *SME Office Annual Report 2017*. Vol 2017. London, UK; 2018. https://www.ema.europa.eu/en/documents/report/small-medium-sized-enterprise-sme-office-annual-report-2017_en.pdf.

8. de Wilde S, Guchelaar H-J, Zandvliet ML, Meij P. Clinical development of gene- and cell-based therapies: overview of the European landscape. *Mol Ther - Methods Clin Dev*. 2016;3(July):16073. doi:10.1038/mtm.2016.73

9. Sood A, Tellis GJ. Technological evolution and radical innovation. *J Mark*. 2005;69(3):152-168. doi:10.1509/jmkg.69.3.152.66361

10. OECD. Policy note: Improving the business environment for SMEs through effective regulation. In: *SME Ministerial Conference*. Mexico City, Mexico; 2018:1-11. https://www-oecd-org.proxy.library.uu.nl/cfe/smes/ministerial/documents/2018-SME-Ministerial-Conference-Parallel-Session-1.pdf.

11. Mangematin V, Lemarié S, Boissin J, et al. Development of SMEs and heterogeneity of trajectories: the case of biotechnology in France. *Res Policy*. 2003;32(4):621-638. doi:10.1016/S0048-7333(02)00045-8

12. Regnstrom J, Koenig F, Aronsson B, et al. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur J Clin Pharmacol*. 2010;66(39). doi:0.1007/s00228-009-0756-y

13. de Wilde S, Guchelaar HJ, Herberts C, et al. Development of cell therapy medicinal products by academic institutes. *Drug Discov Today*. 2016;21(8):1206-1212. doi:10.1016/j.drudis.2016.04.016

14. Teece D, Pisano G. The Dynamic Capabilities of Firms. In: Holsapple CW, ed. *Handbook on Knowledge Management*. Vol. 2. Berlin, Heidelberg: Springer Berlin Heidelberg; 2003:195-213. doi:10.1007/978-3-540-24748-7_10

15. Lièvre M, Ménard J, Bruckert E, et al. Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility. *BMJ*. 2001;322(7286):603-605. doi:10.1136/bmj.322.7286.603

16. European Commission. Genetically Modified Organism (GMO) aspects for investigational medicinal products. https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en. Published 2020. Accessed November 9, 2020.

17. Bachtarzi H, Farries T. The Genetically Modified Organism Medicinal Framework in Europe, United States, and Japan: Underlying Scientific Principles and Considerations Toward the Development of Gene Therapy and Genetically Modified Cell-Based Products. *Hum Gene Ther Clin Dev.* 2019;30(3):114-128. doi:10.1089/humc.2019.042

18. Monaco L, Faccio L. Patient-driven search for rare disease therapies: the Fondazione Telethon success story and the strategy leading to Strimvelis. *EMBO Mol Med.* 2017;9(3):289-292. doi:10.15252/emmm.201607293

19. Aiuti A, Roncarolo MG, Naldini L. Gene therapy for ADA-SCID, the first marketing approval of an ex vivo gene therapy in Europe: paving the road for the next generation of advanced therapy medicinal products. *EMBO Mol Med.* 2017;9(6):737-740. doi:10.15252/emmm.201707573

20. Thomas CJ, McKew JC. Playing well with others! Initiating and sustaining successful collaborations between industry, academia and government. *Curr Top Med Chem.* 2014;14(3):291-293. doi:10.2174/1568026613666131127125351

21. Rafols I, Hopkins MM, Hoekman J, et al. Big Pharma, little science?: A bibliometric perspective on Big Pharma's R&D decline. *Technol Forecast Soc Change.* 2014;81:22-38. doi:https://doi.org/10.1016/j.techfore.2012.06.007

22. Garnier J-P. Rebuilding the R&D engine in big pharma. *Harv Bus Rev.* 2008;86(5):68—70, 72—6, 128. http://europepmc.org/abstract/MED/18543809.

23. de Wilde S, Veltrop-Duits L, Hoozemans-Strik M, et al. Hurdles in clinical implementation of academic advanced therapy medicinal products: A national evaluation. *Cytotherapy.* 2016;18(6):797-805. doi:10.1016/j.jcyt.2016.02.010

24. Mankins JC. *Technology Readiness Levels.* Vol April 6. Washington, DC; 1995. http://www.artemisinnovation.com/images/TRL_White_Paper_2004-Edited.pdf.

25. The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council. *Off J Eur Union.* 2007;324((EC)1394/2007):121-138. http://data.europa.eu/eli/reg/2007/1397/oj.

26. Coppens DGM. Regulating gene and cell-based therapies as medicinal products. 2020. https://dspace.library.uu.nl/handle/1874/390654.

27. Christiansen T. Governance in the European Union. In: Cini M, Borragán NP-S, eds. *European Union Politics.* Vol 2006. 6th editio. New York: Oxford University Press; 2016:1-19,417. doi:10.1093/hepl/9780198708933.003.0007

28. Coppens DG, Gardarsdottir H, de Bruin ML, Meij P, Leufkens HG, Hoekman J. Regulating advanced therapy medicinal products through the Hospital Exemption: an analysis of regulatory approaches in nine EU countries. *Regen Med.* 2020;15(8):rme-2020-0008. doi:10.2217/rme-2020-0008

29. Coppens DGM, Hoekman J, De Bruin ML, et al. Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries. *Cytotherapy.* 2020;22(10):592-600. doi:10.1016/j.jcyt.2020.04.092

30. Alliance for Regenerative Medicine. *Position on Hospital Exemption.* Vol 28.; 2017. https://alliancerm.org/sites/default/files/ARM_position_on_HE_final.pdf.

31. Kenter MJH. Is it time to reform oversight of clinical gene therapy in the EU? *Br J Clin Pharmacol.* 2019;85(1):8-10. doi:10.1111/bcp.13795

32. Anliker B, Longhurst S, Buchholz CJ. Umweltrisikobewertung GVO-haltiger Arzneimittel. *Bundesgesundheitsblatt-Gesundheitsforsch - Gesundheitsschutz.* 2010;53(1):52-57. doi:10.1007/s00103-009-0986-2

33. Iglesias-Lopez C, Obach M, Vallano A, Agustí A, Montané J. Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States. *Crit Rev Toxicol.* 2019;49(7):580-596. doi:10.1080/10408444.2019.1689380

34. Bruetschy C. The EU regulatory framework on genetically modified organisms (GMOs). *Transgenic Res.* 2019;28(Suppl 2):169-174. doi:10.1007/s11248-019-00149-y

35. Marti A. Requirements for Clinical Trials with Gene Therapy and Transplant Products in Switzerland. In: Galli MC, Serabian M, eds. *Regulatory Aspects of Gene Therapy and Cell Therapy Products: A Global Perspective*. Cham: Springer International Publishing; 2015:131-145. doi:10.1007/978-3-319-18618-4_7

36. Wilson JM. Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency. *Mol Genet Metab.* 2009;96(4):151-157. doi:10.1016/j.ymgme.2008.12.016

37. Tsai H, Liu L, Dusting G, et al. Pro-opiomelanocortin gene delivery suppresses the growth of established Lewis lung carcinoma through a melanocortin-1 receptor-independent pathway. *J Gene Med.* 2012;14(1):44-53. doi:10.1002/jgm

38. European Comission. *Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products*. Vol Volume 4. Brussels; 2017. doi:10.1093/oxfordhb/9780199546282.013.0024

39. Alliance for Regenerative Medicine, European Federation of Pharmaceutical Industries and Associations, EuropaBio. *Call for More Effective EU Regulation of Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms*.

40. ten Ham RMT, Klungel OH, Leufkens HGM, Frederix GWJ. A Review of Methodological Considerations for Economic Evaluations of Gene Therapies and Their Application in Literature. *Value Heal.* 2020;23(9):1268-1280. doi:10.1016/j.jval.2020.04.1833

41. Carr DR, Bradshaw SE. Gene therapies: The challenge of super-high-cost treatments and how to pay for them. *Regen Med.* 2016;11(4):381-393. doi:10.2217/rme-2016-0010

42. Drummond MF, Neumann PJ, Sullivan SD, et al. Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy. *Value Heal.* 2019;22(6):661-668. doi:10.1016/j.jval.2019.03.012

43. Ettinger WH, Flotte TR. The role of gene and cell therapy in the era of health care reform. *Hum Gene Ther.* 2011;22(11):1307-1309. doi:10.1089/hum.2011.2526

44. Raymakers AJN, Regier DA, Peacock SJ. Modelling uncertainty in survival and cost-effectiveness is vital in the era of gene therapies: the case of axicabtagene ciloleucel. *Heal Policy Technol.* 2019;8(2):103-104. doi:10.1016/j.hlpt.2019.05.009

45. Klein K. Regulation in the dynamic environment of complex medicines. 2019. https://dspace.library.uu.nl/handle/1874/385131.

46. Vreman RA, Leufkens HGM, Kesselheim AS. Getting the Right Evidence After Drug Approval . *Front Pharmacol* . 2020;11:1365. https://www.frontiersin.org/article/10.3389/fphar.2020.569535.

47. Briggs A, Claxton K, Sculpher M, et al. *Decision Modelling for Health Economic Evaluation*. 2nd Editio. (Gray A, Briggs AH, eds.). Oxford, UK: Oxford University Press; 2006.

48. Claxton K, Palmer S, Longworth L, et al. Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. *Health Technol Assess (Rockv).* 2012;16(46). doi:10.3310/hta16460

49. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. *N Engl J Med*. 2020;382(1):29-40. doi:10.1056/NEJMoa1908490

50. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med*. 2017;377(18):1713-1722. doi:10.1056/nejmoa1706198

51. Malone DC, Dean R, Arjunji R, et al. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. *J Mark Access Heal Policy*. 2019;7(1):1601484. doi:10.1080/20016689.2019.1601484

52. Machin N, Ragni M V., Smith KJ, et al. Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Large B-Cell Lymphoma. *JAMA Pediatr*. 2019;2(12):1-44. doi:10.1001/jamapediatrics.2018.2530

53. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. *J Mark Access Heal Policy*. 2015;3(1):29321. doi:10.3402/jmahp.v3.29321

54. Allen N, Pichler F, Wang T, Patel S, Salek S. Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. *Health Policy (New York)*. 2013;113(3):305-312. doi:10.1016/j.healthpol.2013.09.007

55. Allen N, Walker SR, Liberti L, Salek S. Health Technology Assessment (HTA) Case Studies: Factors Influencing Divergent HTA Reimbursement Recommendations in Australia, Canada, England, and Scotland. *Value Heal*. 2017;20(3):320-328. doi:10.1016/j.jval.2016.10.014

56. Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride J-E. Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. *Curr Med Res Opin*. 2007;23(4):671-682. doi:10.1185/030079906X167327

57. Iglesias-López C, Agustí A, Obach M, Vallano A. Regulatory framework for advanced therapy medicinal products in Europe and United States. *Front Pharmacol*. 2019;10:1-14. doi:10.3389/fphar.2019.00921

58. Nightingale P, Martin P. The myth of the biotech revolution. *Trends Biotechnol*. 2004;22(11):564-569. doi:10.1016/j.tibtech.2004.09.010

59. Kubinyi H. Drug research: myths, hype and reality. *Nat Rev Drug Discov*. 2003;2(8):665-668. doi:10.1038/nrd1156

60. Bayon Y, Vertès AA, Ronfard V, et al. Turning Regenerative Medicine Breakthrough Ideas and Innovations into Commercial Products. *Tissue Eng - Part B Rev*. 2015;21(6):560-571. doi:10.1089/ten.teb.2015.0068

61. Yutin N. Horizontal Gene Transfer. In: Maloy S, Hughes K, eds. *Brenner's Encyclopedia of Genetics (Second Edition)*. Second Edi. San Diego: Academic Press; 2013:530-532. doi:https://doi.org/10.1016/B978-0-12-374984-0.00735-X

62. Medicine I of. Gene Transfer Research: The Evolution of the Clinical Science. In: Lenzi RN, Altevogt BM, Gostin LO, eds. *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee*. Washington, DC: The National Academies Press; 2014:134. doi:https://doi.org/10.17226/18577

63. Lawrence JG. Horizontal and Vertical Gene Transfer: The Life History of Pathogens. In: Russell W, Herwald H, eds. *Concepts in Bacterial Virulence*. Volume 12. Basel: Karger; 2005:255-271. doi:10.1159/000081699

64. Putzeist M, Mantel-Teeuwisse AK, Aronsson B, et al. Factors influencing non-approval of new drugs in Europe. *Nat Rev Drug Discov*. 2012;11(12):903-904. doi:10.1038/nrd3894

65. Putzeist M, Heemstra HE, Garcia JL, et al. Determinants for successful marketing authorisation of orphan medicinal products in the EU. *Drug Discov Today*. 2012;17(7-8):352-358. doi:10.1016/j.drudis.2011.10.027

66. Viganò M, Giordano R, Lazzari L. Challenges of running a GMP facility for regenerative medicine in a public hospital. *Regen Med*. 2017;12(7):803-813. doi:10.2217/rme-2017-0051

67. Informatics PE. SMEs in Pharma and Biotech - Size Matters | PerkinElmer. Inside Informatics. http://blog.cambridgesoft.com/post/2015/12/02/smes-in-pharma-and-biotech-size-matters.aspx. Published 2015. Accessed January 3, 2019.

68. Vreman RA, Naci H, Goettsch WG, et al. Decision Making Under Uncertainty: Comparing Regulatory and Health Technology Assessment Reviews of Medicines in the United States and Europe. *Clin Pharmacol Ther*. 2020;0(0). doi:10.1002/cpt.1835

69. Bloem LT, Vreman RA, van Oirschot S, et al. The Role of Regulator-Imposed Post-Approval Studies in Health Technology Assessments for Conditionally Approved Drugs. *Int J Heal Policy Manag*. 2020;(x):1-9. doi:10.34172/ijhpm.2020.198

70. Oostenbrink JB, Al MJ, Oppe M, Rutten-van Mölken MPMH. Expected Value of Perfect Information: An Empirical Example of Reducing Decision Uncertainty by Conducting Additional Research. *Value Heal*. 2008;11(7):1070-1080. doi:https://doi.org/10.1111/j.1524-4733.2008.00389.x

71. Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. *Health Technol Assess*. 2004;8(31):1-103, iii. doi:10.3310/hta8310

72. Gardner J, Faulkner A, Mahalatchimy A, Webster A. Are there specific translational challenges in regenerative medicine? Lessons from other fields. *Regen Med*. 2015;10(7):885-895. doi:10.2217/rme.15.50

73. Wilde SP de. Translation of academic medicinal products towards clinical practice. 2018. https://scholarlypublications.universiteitleiden.nl/handle/1887/59755.

74. Eder C, Wild C. Technology forecast : advanced therapies in late clinical research , EMA approval or clinical application via hospital exemption. *J Mark Access Heal Policy*. 2019;7(1). doi:10.1080/20016689.2019.1600939

75. Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical development of advanced therapy medicinal products in Europe: Evidence that regulators must be proactive. *Mol Ther*. 2012;20(3):479-482. doi:10.1038/mt.2012.13

76. McKernan R, McNeish J, Smith D. Pharma's developing interest in stem cells. *Cell Stem Cell*. 2010;6(6):517-520. doi:10.1016/j.stem.2010.05.012

77. Bersenev A, Fesnak A. Place of academic GMP facilities in modern cell therapy. In: *Methods in Molecular Biology*. Vol 2097. ; 2020:329-339. doi:10.1007/978-1-0716-0203-4_21

78. Meij P, Veltrop LA, Wilde SPDE. *Advanced Therapy Medicinal Products Naar de Reguliere Klinische Zorg: Knelpunten En Mogelijkheden*. Leiden, the Netherlands; 2016. https://docplayer.nl/19697069-Advanced-therapy-medicinal-products-atmps-naar-de-reguliere-klinische-zorg-knelpunten-en-mogelijkheden.html.

79. Andersen B. The hunt for S-shaped growth paths in technological innovation: A patent study. *J Evol Econ*. 1999;9(4):487-526. doi:10.1007/s001910050093

80. Abernathy WJ, Utterback JM. Patterns of industrial innovation. *Technol Rev*. 1978;80:40-47.

81. Zwart-van Rijkdom JEF. Assessment and diffusion of biotechnology drug. 2002. https://dspace.library.uu.nl/handle/1874/331.

82. Gardner J, Webster A, Barry J. Anticipating the clinical adoption of regenerative medicine: Building institutional readiness in the UK. *Regen Med.* 2018;13(1):29-39. doi:10.2217/rme-2017-0121

83. Uzkurt C, Kumar R, Ensari N. Assessing organizational readiness for innovation: An exploratory study on organizational charachteristics of innovativeness. *Int J Innov Technol Manag.* 2013;10(4). doi:https://doi.org/10.1142/S0219877013500181

84. Rashman L, Withers E, Hartley J. Organizational learning and knowledge in public service organizations: A systematic review of the literature. *Int J Manag Rev.* 2009;11(4):463-494. doi:10.1111/j.1468-2370.2009.00257.x

85. Gardner J, Webster A. The social management of biomedical novelty: Facilitating translation in regenerative medicine. *Soc Sci Med.* 2016;156:90-97. doi:10.1016/j.socscimed.2016.03.025

86. Sharpe M, Barry J, Kefalas P. Clinical Adoption of Advanced Therapies: Challenges and Opportunities. *J Pharm Sci.* 2020;Online ahe:1-8. doi:10.1016/j.xphs.2020.08.027

87. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. *Cell Stem Cell.* 2016;19(3):293-297. doi:10.1016/j.stem.2016.08.012

88. Bennett C. *Cell Therapy Manufacturing: The Supply Chain Challenge.*; 2018. https://www.genengnews.com/insights/cell-therapy-manufacturing-the-supply-chain-challenge/.

89. O'Donnel D. The Cell Therapy Supply Chain: Logistical Considerations for Autologous Immunotherapies. BioProcess International. https://bioprocessintl.com/manufacturing/cell-therapies/the-cell-therapy-supply-chain-logistical-considerations-for-autologous-immunotherapies/. Published 2015. Accessed October 5, 2020.

6

Summaries

6.1

Summary

Gene and cell-based therapies (GCTs) are highly innovative therapies and hold great promise in the treatment and potential cure of high burden and chronic diseases. However, it is reported that these products experience translational challenges in successfully surpassing development milestones towards market authorisation and market access.

The aim of this thesis is to assess gene and cell-based therapy development challenges and how these challenges play a role in marketing authorization and market access, as well as develop tools and methods to mitigate market access challenges for developers.

Challenges in the development of gene and cell-based therapies

Based on a survey among European commercial GCT developers**, Chapter 2.1** showed that the European GCT field is still in early stages of development with a high representation of small and medium-sized enterprises (SMEs). Most often mentioned were regulatory challenges (n=82, 34%), more specific related to country-specific requirements (n=40, 16%), followed by manufacturing (n=37, 15%), and clinical trial design (n=19, 8%) which were classified as technical and clinical challenges respectively. Large companies were observed to be more successful in bringing products to the market by utilizing their general development expertise and resources. Smaller developers expressed more difficulties in the regulatory domain. Examples are less familiarity with regulatory trajectories and evidence requirements. A distinction was made between challenges specific for GCTs and with a more generic character. Scientific and manufacturing challenges regarding platforms, techniques, raw materials and mechanisms of action were found to be specific to GCTs. Orphan drugs and new indication linked challenges were determined as not GCT specific. The research conducted in this chapter provides a timely cross-section of the private GCT developers in Europe. The transparent description of challenge classification allows for periodic (re-)assessment of development challenges experienced by the cohort described in this research as well as elsewhere.

Complementary to **Chapter 2.1**, in **Chapters 2.2 and 2.3** economic challenges specifically for smaller and academic cell-based therapy (CBT) developers were addressed. In **Chapter 2.2** a uniform and transparent framework and methodology to facilitate costing of small-scale CBT manufacturing was developed via a micro-costing study in four facilities across western Europe. Costs were divided into steps (tissue procurement, manufacturing, and fill-finish). The steps were each subdivided into cost categories (materials, equipment, personnel, and facility), and each category was broken down into facility running (fixed) costs and operational (variable) costs. The study also yielded a tool. This free tool allows for direct use of the costing framework and methodology in practice. CBTs developed in public domain are more often of personalized nature, asking for product specific manufacturing development which is costly and requires significant investments. As a result, biomedical researchers and clinicians are increasingly faced with cost considerations which generally is not a part of their routine activities but necessary to acquire funding and financial sustainability of facilities.

Manufacturing development of CBTs is a timely scientific and iterative process, which requires considerable investment. In **Chapter 2.3**, the feasibility of the CBT costing framework and methodology developed in **Chapter 2.2** was assessed in estimating manufacturing development

costs. This was done via a retrospective costing study using two CBTs as case studies. By demonstrating feasibility of its use outside its initial context, broader application of this framework may be possible as well as spill over of cost insights earlier on in CBT development. Cost reduction should not be the primary objective when applying costing frameworks. Their use lies in facilitating inclusion of cost considerations and cost-conscious decisions in product development and accommodating economic capabilities amongst smaller and academic developers.

Assessment of GCTs by regulators and health technology assessment bodies

In the third chapter of this thesis a regulatory and health technology assessment body perspective was taken. First, in **Chapter 3.1** clinical and regulatory success were assessed, quantified, and compared with other medicinal products from 2009 to 2013. The quantification of overall GCT development success in the EU (obtained by multiplying clinical success rate with regulatory success rate) was estimated to range between 5.2 and 16.3%. This estimate falls within Asher Mullard's rule of thumb in which it he stated that globally around 10% of drug projects in Phase I clinical trials receive market authorization. The quantification showed that the implementation of the regulatory policies did not slow down the development and success rates of GCTs compared with conventional medicinal products and orphan medicinal products, which contradicts concerns of low number of centrally marketed GCTs in Europe when compared with clinical trial activity. The assessment of regulatory activity shows that developers from 2013 onwards seemed to benefit from the new regulations and guidance's. Continued development and regulatory success is dependent on regulation and regulators being adaptive to rapid technological advancement and new information about benefits and risks accruing over the drug life cycle. In so doing, regulation can simultaneously contribute to minimizing risks for patients, balancing the values and interests of stakeholders, and enabling further GCT innovation.

Chapter 3.2 investigated the health technology assessment of GCTs in Scotland, the Netherlands, and England. Key considerations were systematically identified and thereafter categorized. Considerations (defined as a value judgement of the HTA-body on the presented dossier) were extracted from the reports and categorized using the domains of the EUnetHTA Core Model®v3. In the Netherlands, and England most key considerations were identified in the clinical effectiveness (EFF) and cost and economic effectiveness (ECO) domains. In Scotland the social aspects-domain yielded most key considerations, followed by ECO- and EFF-domains. It was observed that conditions varied, and more uncertainty was accepted when orphan- or end-of-life criteria were applied. Last, a trend was seen in the ratio of pro- and contra-arguments in the key considerations between positive, negative and restricted recommendations. Positive recommendations showed higher percentage of pro key considerations across jurisdictions and negative recommendations a higher percentage of contra key consideration. Restricted recommendation showed approximately equal percentage of pro- and contra-considerations.

The research in **Chapter 3.2** is the first empirical review of HTA-reports in which key considerations are identified and categorized using the EUnetHTA core model framework. It was concluded that

considerations outside the common described effectiveness and cost-effectiveness domains may bare considerable weight in formulation of the recommendation including ethical and legal aspects. Although further validation of the methodology may be needed, more widespread application of this new approach will allow for comparison for key considerations outside the GCT field, such as past medical innovations, orphan medicinal products and others. This will contribute to increasing understanding and empirical substantiation of health technology assessment, weighing of evidence and uncertainties.

Cost-effectiveness, value and affordability of gene and cell-based therapies

In **Chapter 4.1** methodological considerations discussed in literature addressing economic evaluations of gene therapies were identified in a systematic review. Considerations addressed payment models, definition of perspectives, addressing uncertainty, data extrapolation, discount rates, novel value elements, and use of indirect and surrogate endpoints. Next, the application of these considerations in literature was assessed to increase understanding and explore their impact. Application of novel methodological considerations was found sparce. However, when applied they showed considerable impact on study outcomes. It was concluded accepted economic evaluation methods can broadly be applied to GTs, but few elements may need adjustment. For now, it was recommended to include scenario analyses to explore impact of methodological choices and (clinical) uncertainties.

Cost-effectiveness, value, and affordability of gene therapies was assessed in **Chapter 4.2.** This was done via a case study of valoctocogene roxaparvovec (Roctavian®), or valrox, a gene therapy in development for patients with severe Hemophilia A without antibodies. The cost-effectiveness of this new technology was compared to prophylactic FVIII and prophylactic emicizumab (Hemlibra®) in the Netherlands. The results of the analyses showed that on a population level over 10 years incremental QALYs were achieved for less costs resulting in dominated ICERs in both comparisons. Additionally, we observed that payment models can impact annual budget impact, time of payment as well as uncertainty associated with annual spending. The cost-effectiveness and value based price of valrox was found to be linked to price discount of the comparator FVIII prophylaxis. These findings are in line with previous published analyses of gene therapies in severe hemophilia A in other jurisdictions. In line with **Chapter 4.1, Chapter 4.2** demonstrated and quantified considerable uncertainty on outcomes when applying payment models (one-off payment, annuity payment and outcomebased payment) and scenario analyses. The study also incorporated novel measures such as treatment durability (defined as initial treatment effect and treatment waning) and break-even-time (estimated time in years from treatment for future benefits to offset upfront payment). Inclusion of these novel elements can inform conditions set to payment models.

Discussion

The discussion describes development challenges and how these may affect market authorization and market access of GCTs. GCTs are different from more conventional medicinal products specifically regarding their mechanism of action, live starting materials, manufacturing and curative character. This causes additional translational challenges and required specialized technical and scientific development capabilities. Additionally, the developer landscape is more diverse with a high presence of small and academic developers which are known to have less capabilities in the development, regulatory authorization and economic domain. Challenges showed substantial overlap between development of GCTs and orphan products and novel indications. Combining these findings, it appears GCTs experience more challenges during development.

To accommodate GCT development, regulatory change occurred on a European level including enactment of a new regulations and adoption of guidance's and procedures. Additionally, GCTs are often eligible for non-GCT specific pathways. Especially adoption of and assessment of the quality and manufacturing of GCTs was found challenging, driven by unique product characteristics. However, quantification of regulatory success shows developers recently started to benefit from clarity provided by regulatory change. Health Technology Assessment methods and frameworks are largely applicable for the assessment of GCTs and seem to experience little impact of GCT characteristics. More challenging are evidentiary uncertainties and high prices leading to high budget impact and upfront irreversible payments. More research is needed to explore methodologies to address these uncertainties, for instance via innovative payment models.

GCTs follow an incremental path of technology development, similar to previous waves of medical innovations. Gatekeepers guarding the critical development milestones have to varying extent accommodated their policies, services and experience to foster the uptake of GCTs. Continued efforts are needed to further align GCT development, capabilities and (national) policies. Additionally, after market access clinical adoption is needed to achieve sustainable patient access.

Conclusion

This thesis demonstrated that new product characteristics of GCTs do not fit particularly well within established development, regulatory and HTA-frameworks for conventional medicinal products. Novel GCT characteristics ask for redesign of established medicinal product handling, manufacturing and quality assurance which is accompanied by increased development cost and higher risk. The novelties also require capability building in interaction between developers demonstrating and authorities assessing product quality, safety and efficacy. The novel characteristics seemed to affect the health technology assessment (HTA) to a lesser extent. However, the intended curative effects, originating from new mechanisms of action, and higher target prices continue to raise concerns amongst payers and HTA-bodies on how to address budget impact and affordability as more GCTs reach late clinical development.

The research provides a cross section of (early) development challenges of GCTs and how they affect down-stream development spanning manufacturing to reimbursement. This thesis describes empirical

findings from a systems and developer perspective. It also provides cost and cost-effectiveness tools and methods to classify challenges and considerations in HTA to accommodate timely, safe and sustainable patient access. This research, therefore, contributes to better understanding of the fit between these transformative therapies and existing development, regulatory and HTA-frameworks, which is not only relevant for GCTs but also for future biomedical innovations.

6.2

Samenvatting (Dutch Summary)

Gen- en celtherapieën (GCT's) zijn een zeer innovatieve geneesmiddelen. Ontwikkelaars, patiënten en behandelaars hebben hoge verwachtingen van de beoogde effecten, voornamelijk in de behandeling en mogelijke genezing van (chronische) ziekten met hoge ziektelast. De ontwikkeling van deze producten is echter onderhevig aan translationele uitdagingen die markttoegang, vergoeding en implementatie in de gezondheidszorg bemoeilijken.

Het doel van dit proefschrift is om uitdagingen in de ontwikkeling van GCT's te onderzoeken en in kaart te brengen welke rol deze spelen in het verkrijgen van markttoegang en vergoedingen. Ook is ten doel gesteld concrete handvatten en methodes te ontwikkelen voor GCT-ontwikkelaars, zodat beter kan worden omgegaan met de geïdentificeerde uitdagingen.

Uitdagingen in ontwikkeling van gen- en celtherapieën

In **Hoofdstuk 2.1** is gestart met het afnemen van een enquête onder Europese private GCT-ontwikkelaars met als doel het huidige veld en ervaren uitdagingen in kaart te brengen. Het Hoofdstuk laat zien dat het Europese GCT-veld zich nog voornamelijk in de vroege ontwikkelingsfase (fase I-II) bevindt. De enquête toont ook veel activiteit van kleine en middelgrote ondernemingen (MKB), meer dan bij de ontwikkeling van andere geneesmiddelgroepen. Meest genoemde uitdagingen door ontwikkelaars waren uitdagingen op het gebied van regulering (n = 82, 34%), vooral gerelateerd aan verschillende vereisten op nationaal niveau tussen landen (n = 40, 16%). Als tweede werden productie uitdagingen (n = 37, 15%) en moeilijkheden in opzet van klinische studies (n = 19, 8%) genoemd. Deze uitdagingen zijn respectievelijk geclassificeerd als technische en klinische uitdagingen. Een verschil in ontwikkelsucces kan worden gelinkt aan bedrijfsgrootte, waarbij grotere bedrijven succesvoller lijken te zijn in het op de markt brengen van producten. Dit lijkt te komen doordat zij kunnen voortbouwen op historisch opgedane kennis en ervaring, en toegang hebben tot meer middelen. Kleinere ontwikkelaars beschreven meer problemen te ervaren op het gebied van regelgeving. Dit is deels terug te leiden naar minder bekendheid met regulatoire trajecten en gevraagde bewijsvereisten. In de enquêteresultaten kan ook onderscheid gemaakt worden tussen uitdagingen specifiek voor GCT's en meer generieke (niet-GCT) uitdagingen. Wetenschappelijke en productie-uitdagingen met betrekking tot platforms, technieken, grondstoffen en werkingsmechanismen, zijn specifiek voor GCT's. Geïdentificeerde niet-GCT specifieke uitdagingen, zijn gerelateerd aan onder andere ontwikkeling van weesgeneesmiddelen en nieuwe indicaties.

De resultaten van deze studie leveren een actuele dwarsdoorsnede van het GCT-ontwikkelaars veld in Europa op, alsmede de uitdagingen die zij (hebben) ervaren gedurende de ontwikkeling. De methodes en uitdaging-classificaties zijn dusdanig beschreven dat zij periodieke (her-) evaluatie mogelijk maken.

Economische uitdagingen, specifiek voor kleinere en academische celtherapie (CT's) ontwikkelaars, zijn in **Hoofdstukken 2.2. en 2.3**, in aanvulling op **Hoofdstuk 2.1**, nader onderzocht. CT's die in het publieke domein zijn ontwikkeld, hebben vaak zeer complexe productieprocessen en zijn vaker patiënt specifiek (n=1). Deze specifieke en kleinschalige productie is erg kostbaar en vereist vooraf vaak aanzienlijke investeringen. Als gevolg hiervan worden biomedische onderzoekers en clinici steeds vaker geconfronteerd met economische overwegingen. Dit terwijl economische

vraagstukken eigenlijk geen deel uitmaken van hun routinematige activiteiten of training. Daarom is in toenemende mate inzicht in kosten belangrijk, ook voor kleinere en academische ontwikkelaars, om financiering van productie en ontwikkeling mogelijk te maken, en financiële duurzaamheid van faciliteiten te waarborgen.

In **Hoofdstuk 2.2** is een raamwerk en methodologie ontwikkeld om de kostprijsberekening van kleinschalige CT-producties in kaart te brengen. Voor deze studie is kostendata verzamelt van de productie van 8 CT's, geproduceerd in 4 verschillende faciliteiten in West-Europa, in een *micro-costing* studie. De studie beschrijft hoe CT-productie kan worden onderverdeeld in generieke productiestappen (verkrijgen van startmateriaal, productie en afwerking). Deze stappen zijn elk onderverdeeld in kostencategorieën (materialen, apparatuur, personeel en faciliteit) en verder uitgesplitst in vaste kosten van de faciliteit en operationele (variabele) kosten. De methode is vertaald in een direct toepasbare *tool* om implementatie te faciliteren. De tool is kosteloos en publiekelijk beschikbaar gemaakt en bijgevoegd als supplement via de online *open access*-publicatie.

Waar in **Hoofdstuk 2.2** de nadruk op een bestaand CT-productieproces lag, is de aandacht in **Hoofdstuk 2.3** gericht eerder in het ontwikkeltraject; namelijk op productieontwikkeling. De wetenschappelijke kennis op het gebied van de ontwikkeling van CT-productieprocessen, neemt zeer snel toe en bouwt op elkaar voort. De ontwikkeling is zeer kostbaar en vereist aanzienlijke investeringen, ook vooraf en meer dan bij niet-CT's. In **Hoofdstuk 2.3** is onderzocht of het CT-kostenraamwerk en de methodologie, ontwikkelt in **Hoofdstuk 2.2,** toegepast kan worden om inzicht te krijgen in de ontwikkelkosten van het CT-productieproces. Dit is gedaan door middel van het uitvoeren van een retrospectieve *micro-costing* studie, waarbij twee CT's als casus hebben gediend. Dit haalbaarheidsonderzoek suggereert dat bredere toepasbaarheid van het kosten raamwerk en eerder ontwikkelde methode mogelijk is. Ook hebben de twee casussen gedemonstreerd dat het mogelijk is eerder in CT-productieontwikkeling zicht te verkrijgen in kosten en de economische consequenties van ontwikkelstrategieën. De auteurs benadrukken dat enkel kostenreductie niet het primaire doel is van het toepassen van het kostenraamwerk en methode. De meerwaarde ligt in het inzichtelijk maken van kostendrijvers, informeren van ontwikkel strategieën, efficiënt omgaan met schaarse middelen en het versterken van economische bekwaamheid bij kleinere en academische ontwikkelaars.

Beoordeling van gen- en celtherapieën door regulatoire- en vergoedingsautoriteiten

In het derde Hoofdstuk van dit proefschrift wordt het perspectief van de regulatoire instanties en vergoedingsautoriteiten ingenomen. In **Hoofdstuk 3.1** is het klinische en regulatoire succes van GCT's onderzocht, gekwantificeerd en vergeleken met enkele andere geneesmiddelgroepen in de periode van 2009 tot 2013. Het GCT-ontwikkelingssucces –verkregen door vermenigvuldiging van een klinische succespercentage met een regulatoire succespercentage- in de EU is geschat op 5,2% tot 16,3%. Deze schatting valt binnen de vuistregel, beschreven door Asher Mullard, waarin wordt gesteld dat wereldwijd ongeveer 10% van de geneesmiddelen in fase I studies marktautorisatie verkrijgt. De gelijkenis tussen de geschatte kwantificering en Mullard's vuistregel suggereert dat de implementatie van het nieuwe regelgevend kader in 2008, en het daaruit volgend beleid, het ontwikkelsucces van GCT's, in vergelijking met conventionele (wees)geneesmiddelen, niet hebben

vertraagd of verminderd. Deze observatie is in tegenspraak met eerder beschreven bezorgdheden in literatuur, over het lage aantal centraal Europees geautoriseerde GCT's in vergelijking met de het grote aantal klinische studies. Een visualisatie van de resultaten, waarbij regulatoire activiteit (markautorisatie aanvragen, positieve, negatieve en teruggetrokken marktautorisatie beoordelingen) van GCT's is uitgezet tegen de tijd van 2009 tot 2018, laat zien dat ontwikkelaars omstreeks 2013 beginnen te profiteren van het nieuwe regelgevend kader. Innovatie en regulatoir succes is afhankelijk van het aanpassingsvermogen van beleidsmakers en regulatoire instanties aan snelle technologische vooruitgang, en de capaciteit om nieuwe inzichten over effectiviteit en veiligheid gedurende de levenscyclus van geneesmiddelen te incorporeren in beleid. Alleen zo kan wet- en regelgeving bijdragen aan het minimaliseren van patiëntrisico's, terwijl tegelijkertijd stakeholder belangen worden behartigd en verdere innovatie van GCT's mogelijk worden gemaakt.

Hoofdstuk 3.2 onderzoekt de beoordeling van GCT's met marktautorisatie door vergoedingsautoriteiten in Schotland, Nederland en Engeland. De belangrijkste overwegingen die leidden tot het vergoedingsadvies (positief, negatief en voorwaardelijk positief), zijn systematisch geïdentificeerd en gecategoriseerd. De overwegingen (gedefinieerd als een waardeoordeel van de autoriteit over het gepresenteerde vergoedingsdossier) zijn geëxtraheerd uit vergoedingsdossiers en gecategoriseerd in domeinen zoals beschreven in het EUnetHTA Core Model®v3. Wanneer een overweging meer dan twee keer in verschillende dossiers werd gevonden, werd deze als 'belangrijk' aangemerkt. In Nederland en Engeland blijken de meeste belangrijke overwegingen zich te bevinden in het klinische effectiviteitsdomein (EFF) en kosten en economische effectiviteitsdomein (ECO). In Schotland leverde het sociale aspecten-domein (SOC) de meeste belangrijke overwegingen op, gevolgd door de ECO- en EFF-domeinen. Het toepassen van additionele beoordelingscriteria voor specifieke product- of patiëntgroepen lijkt de randvoorwaarden voor een positief vergoedingsadvies te beïnvloeden. Bijvoorbeeld de acceptatie van meer onzekerheden bij weesgeneesmiddelen of levensverlengende behandelingen. Ook is een trend waarneembaar in de verhouding tussen belangrijke voor- en tegen overwegingen tussen de vergoedingsadviezen. Positieve adviezen lieten een hoger percentage voor-overwegingen zien in alle drie de landen, en negatieve adviezen een hoger percentage tegen-overwegingen. Voorwaardelijk positieve adviezen toonden ongeveer evenveel pro- als contraoverwegingen in de dossiers.

Het onderzoek in **Hoofdstuk 3.2** is het eerste empirische overzicht waarin de belangrijkste overwegingen uit vergoedingsdossiers systematisch zijn geïdentificeerd en gecategoriseerd, met behulp van het EUnetHTA-model. De studie laat zien dat overwegingen buiten de geijkte effectiviteits- en kosteneffectiviteitsdomeinen, een aanzienlijk gewicht kunnen hebben bij het komen tot een vergoedingsadvies, zoals sociale, ethische en juridische aspecten. Hoewel verdere validatie van de methodologie nodig is, maakt de hier omschreven aanpak voor het eerst mogelijk om de inhoud van overwegingen onderliggend aan vergoedingsadvies, te identificeren en categoriseren. De systematische aanpak maakt vergelijking mogelijk tussen specifieke patient- en productgroepen binnen Europa, alsmede ook door de tijd. Daarmee draagt dit onderzoek bij aan het beter begrijpen van de empirische onderbouwing van vergoedingsbeslissingen, de onderliggende overwegingen en onzekerheden.

Kosteneffectiviteit, waarde en betaalbaarheid van gen- en celtherapieën

In **Hoofdstuk 4.1** worden in een systematisch literatuuroverzicht methodologische overwegingen beschreven met betrekking tot economische evaluaties van gentherapieën. Rationale hierachter is een heersende notie dat gentherapieën aanzienlijk verschillen van conventionelere geneesmiddelen, zoals moleculen en monoklonale antilichamen, en dat daardoor bestaande economische methoden niet (helemaal) passend zouden zijn. De methodologische elementen die in deze context in recente literatuur worden bediscussieerd zijn geïdentificeerd en gecategoriseerd, te weten: toepassing van betalingsmodellen, definitie van perspectieven, onzekerheden, extrapolatie van data, disconteren, nieuwe waarde-elementen en het gebruik van indirecte en surrogaateindpunten. De toepassing en impact van de elementen, zij het helemaal nieuw of aanpassingen aan bestaande methodologieën, is in hetzelfde Hoofdstuk ook onderzocht, middels een tweede literatuuroverzicht. De toepassing van bediscussieerde elementen is zeer schaars bevonden. Echter, wanneer ze zijn toegepast, is een grote impact te zien op de uitkomst van de economische evaluaties. **Hoofdstuk 4.2** concludeert dat de huidige aanvaarde methoden voor economische evaluaties in grote lijnen passend lijken voor de evaluatie van gentherapieën, maar dat enkele elementen wellicht aanpassing behoeven. Meer onderzoek is nodig naar de precieze aanpassingen, en de gevolgen hiervan. Deze studie geeft een actueel overzicht van elementen en argumenten in de wetenschappelijke discussie omtrent methoden voor economische evaluaties van gentherapieën, en biedt daarmee een startput voor verder onderzoek. Voor nu adviseren de auteurs scenarioanalyses op te nemen in evaluaties om de impact van methodologische keuzes en (klinische) onzekerheden te kwantificeren en interpreteren.

De kosteneffectiviteit, waarde en betaalbaarheid van gentherapieën zijn nader onderzocht in **Hoofdstuk 4.2**. Dit is gedaan aan de hand van het een casus met valoctocogene roxaparvovec (Roctavian®), of valrox, een gentherapie in ontwikkeling voor patiënten met ernstige hemofilie A zonder antilichamen. De kosteneffectiviteit van deze nieuwe technologie is vergeleken met factor VIII (FVIII) profylaxe en emicizumab (Hemlibra®) profylaxe in Nederland. De resultaten van beide analyses toonde aan dat op populatieniveau gedurende 10 jaar incrementele *quality adjusted life years* (QALY's) werden behaald tegen lagere kosten, wat resulteerde in een gedomineerde incrementele kosteneffectiviteits ratio's (*ICER's*). Resultaten laten ook zien dat betalingsmodellen van invloed kunnen zijn op *budget impact*, tijdstip van betaling en onzekerheid van geschatte kosten. Ook is in deze studie de *value-based price* van valrox geschat, welke een sterk verband toont met de kosten en kortingen van FVIII-profylaxe. Deze bevindingen komen overeen met eerder gepubliceerde analyses van gentherapieën bij ernstige hemofilie A in andere landen. In lijn met **Hoofdstuk 4.1**, tonen de resultaten van **Hoofdstuk 4.2** aanzienlijke onzekerheden bij het toepassen van betaalmodellen *(one-off payment, annuity payment en outcomebased payment)* in verschillende uitgevoerde scenarioanalyses. In de studie is ook tot nieuwe nieuwe uitkomst gekomen zoals *treatment durability* (gedefinieerd als het initiële effect van de behandeling en de mate waarin de effectiviteit afneemt over tijd) en *break-even-time* (geschatte tijd in jaren waarin toekomstige baten opwegen tegen de vooraf gemaakte kosten). Het exploreren en toepassen van deze nieuwe elementen kan bijdragen aan het informeren van besluitvorming en betaalmodellen.

Discussie

De discussie beschrijft hoe uitdagingen in de ontwikkeling van GCT's de invloed kunnen hebben op marktautorisatie en markttoegang. GCT's zijn in sommige opzichten aanzienlijk verschillend van conventionelere geneesmiddelen. De verschillen zit hem met namen in werkingsmechanismen, (levende) startmaterialen, productieproces en vaak curatieve karakter en zorgen voor extra translationele uitdagingen. Het adresseren van deze deels nieuwe translationele uitdagingen vereist gespecialiseerde, technische en wetenschappelijke kennis, en ontwikkelingcapaciteiten. Verder is gevonden dat de samenstelling van het GCT-ontwikkelaarslandschap zeer divers is. In vergelijking met de ontwikkeling van andere geneesmiddelen is er een zeer hoog percentage kleine en academische ontwikkelaars actief. Van dit type ontwikkelaars is bekend dat ze minder ontwikkelde translationele, regulatoire en economische capaciteiten hebben. Daarnaast laten de gevonden uitdagingen een aanzienlijke overlap zien met uitdagingen ook beschreven in de ontwikkeling van onder andere weesgeneesmiddelen en nieuwe indicaties. Deze observaties in ogenschouw nemend, lijkt het erop dat er meer uitdagingen worden ervaren bij de ontwikkeling van GCT's.

Om GCT-ontwikkeling te faciliteren, heeft op Europees niveau regulatoire verandering plaats gevonden waaronder invoering van een nieuw regelgevend kader en herziening van richtlijnen en procedures. Daarnaast kunnen GCT's ook vaak profiteren van algemenere, niet specifiek voor GCT's in het leven geroepen, (versnelde) regulatoire procedures. Vooral de aanpassing aan, en beoordeling van productkwaliteit en productie van GCT's bleek uitdagend voor zowel ontwikkelaars als beoordelende (lokale) instanties . Dit komt voornamelijk door de unieke producteigenschappen. Uit de kwantificering van het ontwikkelsucces blijkt dat ontwikkelaars slechts recentelijk zijn begonnen te profiteren van duidelijkheid die wordt geboden door het nieuwe regelgevend kader.

De methoden en kaders in vergoedingsbeoordelingen lijken echter grotendeels passend voor op GCT's en worden weinig beïnvloed door de specifieke product karakteristieken. Uitdagender zijn de onzekerheden in (lange termijn) bewijs en de hoge kosten voorafgaand aan de baten, die voortkomen uit de beoogde curatieve effecten. Meer onderzoek is nodig om specifieke methodologische elementen verder te verkennen om de geïdentificeerde onzekerheden te adresseren, een voorbeeld is invloed van en ontwerp van innovatieve betaalmodellen.

Vanuit een breder perspectief volgen GCT's een incrementeel en iteratief en innovatie pad, vergelijkbaar is met eerdere biomedische innovaties. Poortwachter instanties die de belangrijke ontwikkeling mijlpalen bewaken, hebben in verschillende mate hun beleid, diensten en procedures aangepast om de ontwikkeling van GCT's te faciliteren en incorporeren. Verdere inspanningen zijn echter nodig om GCT-ontwikkeling, specifieke translationele capaciteiten en (nationaal) beleid, verder op elkaar af te stemmen. Daarbij is het belangrijk te realiseren dat, maar dan bij eerdere biomedische innovaties, klinische implementatie na markttoegang essentieel is om toegang voor patiënten tot deze innovatieve therapieën te waarborgen.

Conclusie

Dit proefschrift toont aan dat de nieuwe en specifieke productkenmerken van gen- en celtherapieën (GCT's) niet goed passen in de gevestigde geneesmiddel ontwikkelings-, regulatoire- en vergoedings-kaders. De nieuwe eigenschappen vragen om evaluatie en gedeeltelijk herontwerp van gevestigde processen, productie en kwaliteitsborging, en gaan gepaard met een toename in ontwikkelkosten en risico's. De nieuwe technologien vragen ook om het op- en uitbouwen van capaciteiten en interacties bij zowel de ontwikkelaars, die kwaliteit, effectiviteit en veiligheid van producten dienen aan te tonen, als autoriteiten, die belast zijn met de beoordeling ervan. Vergoedingsbeoordelingen lijken minder beïnvloed te worden door de nieuwe product karakteristieken. Hier spelen in toenemende mate de beoogde curatieve effecten, voortkomend uit de nieuwe werkingsmechanismen, en hogere ontwikkel- en productiekosten een grotere rol.

Het onderzoek biedt een actuele dwarsdoorsnede en overzicht van uitdagingen in de (vroege) ontwikkeling van GCT's en hoe deze de verdere ontwikkeling van productie tot vergoeding beïnvloeden. Het werk beschrijft empirische bevindingen vanuit een systeem- en ontwikkelaarsperspectief. Ook biedt dit proefschrift concrete kosten- en kosteneffectiviteitstools en –methoden die gebruikt kunnen worden om uitdagingen en overwegingen voor markttoegang te identificeren en classificeren. Dit is van belang om patiënten tijdige, veilige én blijvende toegang tot deze innovatieve en veelbelovende therapieën te bieden. De studies dragen bij aan meer inzicht in de fit tussen innovatie therapieën en bestaande ontwikkelings-, regulatoire- en vergoedingskaders. Dit is niet enkel van belang voor de verdere ontwikkeling van GCT's, maar ook relevant voor toekomstige biomedische innovaties.

7

Addendum

7.2

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7.3

List of publications

Related to this thesis

Renske MT ten Ham, Jarno Hoekman, Anke M Hövels, Andre W Broekmans, Hubert GM Leufkens, Olaf H Klungel. *Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe.* Mol Ther Methods Clin Dev 2018;11:121-130

Renske MT ten Ham, Anke M Hövels, Olaf H Klungel, Hubert GM Leufkens, Andre W Broekmans, Jarno Hoekman. *Development and regulation of gene and cell-based therapies in Europe: a quantification and reflection.* Trends in Pharmacological Sciences. 2020;41(2):67-71

Renske MT ten Ham, Anke M Hövels, Jarno Hoekman, Geert WJ Frederix, Hubert GM Leufkens, Olaf H Klungel, Inge Jedema, Sabrina AJ Veld, Tanja Nikolic, Melissa van Pel, Jaap J Zwaginga, Fong Lin, Anna L de Goede, Gerty Schreibelt, Sandy Budde, I Jolanda M de Vries, Gwen M Wilkie, Harry Dolstra, Hans Ovelgönne, Pauline Meij, Joanne C Mountford, Marc L Turner, Marcel HN Hoefnagel. *What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings.* Cytotherapy 2020;22(7):388-397

Renske MT ten Ham, Olaf H Klungel, Hubert GM Leufkens, Geert WJ Frederix. *A review of methodological consideration in gene therapy economic evaluations and their application in literature.* Value in Health. 2020;23(9):1268-1280

Renske MT ten Ham, Julianne C Nievaart, Jarno Hoekman, Rachel S Cooper, Geert WJ Frederix, Hubert GM Leufkens, Olaf H Klungel, Hans Ovelgönne, Marcel HN Hoefnagel, Marc L Turner, Joanne C Mountford. *Estimation of manufacturing development cost of cell-based therapies: A feasibility study.* 2021. Cytotherapy. Accepted

Unrelated to this thesis

Vanessa Shih, **Renske MT ten Ham**, Christine Bui, Dan Tran, Jie Ting, Leslie Wilson. *Targeted therapies compared to dacarbazine for yreatment of BRAF(V600E) metastatic melanoma: A cost-effectiveness analysis.* Journal of Skin Cancer. 2015:1-8

Amr AMA Makady, **Renske MT ten Ham,** Anthonius de Boer, Hans Hillege, Olaf H Klungel, Wim G Goettsch. *Policies for use of real-world data in health technology assessment - A comparative study of six HTA-agencies.* Value in Health. 2017;20(4):520-532.

Rachel RJ Kalf, Amr AMA Makady, **Renske MT ten Ham**, Kim Meijboom, Wim G Goettsch. *Use of social media in the assessment of relative effectiveness: Explorative review with examples from oncology.* JMIR. 2018;4(1)

Merel van Nuland, Rick A Vreman, **Renske MT ten Ham**, Aurelia HM de Vries Schultink, Hilde Rosing, Jan HM Schellens, Jos H Beijnen, Anke M Hövels. *Cost-effectiveness of monitoring*

endoxifen levels in breast cancer patients adjuvantly treated with tamoxifen. Breast Cancer Res Treat. 2018;172(1):143-150

Renske MT ten Ham, Jeanette M Broering, Matthew R Cooperberg, Peter Carroll P, Leslie S Wilson. *Understanding the major factors affecting response shift effects on health-related quality of life: What the then-test measures in a longitudinal prostate cancer registry.* Clin Genitourin Cancer. 2019;18(1):e21-e27.

Chang W Jeong, Janet E Cowan, JM Broering, **Renske MT ten Ham,** Leslie S Wilson LS, Peter R Carroll, MR Cooperberg. *Robust health utility assessment among long-term survivors of prostate cancer: results from the cancer of the prostate strategic urologic research endeavor registry.* Eur Urol. 2019 Dec;76(6):743-751.

Chang Wook Jeong, Annika Herlemann, Janet E Cowan, Jeanette M Broering, **Renske M T ten Ham**, Leslie S Wilson, Peter R Carroll, Matthew R Cooperberg. *The relative impact of urinary and sexual function versus bother on health utility for men with prostate cancer.* JNCI Cancer Spectrum. 2020;4(5):pkaa044.

Renske MT ten Ham, Merel van Nuland, Rick A Vreman, Lourens G de Graaf, Hilde Rosing, Alwin M Bergman, Alwin DR Huitema, Jos H Beijnen, Anke M Hövels. *Cost-effectiveness assessment of monitoring abiraterone levels in metastatic castration-resistant prostate cancer patients.* Value in Health. 2021;24(1):P121-P128.

Joost W Geenen, Rick A Vreman, Cornelis Boersma, Olaf H Klungel, Anke M Hövels, **Renske MT ten Ham**. *Increasing the information provided by probabilistic sensitivity analysis: The relative density plot.* Cost Effectiveness and Resource Allocation. 2020;18:54

Awards and Distinctions

Publication selected as Trends Editors Pick 2020

Awarded publication: *Development and Regulation of Gene and Cell-Based Therapies in Europe: A Quantification and Reflection.*

Publication selected as Editors pick Value in Health Nov 2020

Awarded publication: *A Review of Methodological Considerations for Economic Evaluations of Gene Therapies and Their Application in Literature.*

Best Scientific Poster

TOPRA Conference 2019
Awarded poster: *Challenges in Advanced Therapy Medicinal Product Development*

7.4

About the author

Renske ten Ham was born on December 1st, 1989 in Harare Zimbabwe as the elder twin to Marloes and daughter of Rita and Peter. She received a BSc in pharmaceutical sciences in 2012 and a PharmD in 2015 from Utrecht University in the Netherlands. More recent Renske received an MSc in Health Technology Assessment (HTA) in 2020 from the University of Glasgow in Scotland.

During her studies Renske conducted research at the University of California, San Francisco (UCSF), where she was involved in several prostate cancer mapping, utility measurement and cost-effectiveness projects. She also spend time at the Dutch National Healthcare Institute (Zorginstituut Nederland) contributing to the IMI GetReal consortium.

After graduating Renske worked as a consultant for a US based life science research and consulting firm. Her main focus was Global Market Access, Health Economics and Outcome Research.

In December 2016 Renske started working at Utrecht University on the studies presented in this thesis as a PhD student at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute of Pharmaceutical Sciences. The research was conducted under supervision of prof. dr. O.H. Klungel, prof. dr. H.G.M. Leufkens, dr J. Hoekman, dr. G.W.J. Frederix and dr. A.M. Hövels. Renske combined research with a teaching and organisational responsibilities within the European Program for Pharmacovigilance and Pharmacoepidemiology (Eu2P-program).

Over the years, Renske chaired several boards and committees. She was president of the pharmaceutical student association for pharmacy student at Utrecht University. Also, she was the initiator and founder of the International Society of Pharmacoeconomics and Outcome Research (ISPOR) Student Chapter at Utrecht University. More recent Renske was president of 'young-NVTAG' as well as a board member of the parent organization NVTAG (Dutch Association of Medical Technology Assessment) in which she organized multiple events to inform and bring together the Dutch HTA community. Throughout the years has remained an active ISPOR member and currently has a leadership role within the special interest group for personalised medicine & advanced therapies.

Besides her professional career Renske is a sports enthusiast who, among other sports, gained several national titles in different disciplines in Dutch women's' Rugby.

"Uncertainty is the only certainty there is,
and knowing how to live with insecurity is the only security."
John Allen Paulos (1945 -)