Improving patient access to gene and cell therapies for rare diseases in Europe

A review of the challenges and proposals for improving patient access to advanced therapeutic medicinal products in Germany

V1

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Chaired by:

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Reader notes:

This document contains country-specific insights on challenges and potential solutions to access to advanced therapeutic medicinal products (ATMPs) for patients with rare diseases.

The purpose of the document is to provide a starting point for country-specific engagement and discussion within multi-stakeholder meetings.

The challenges and solutions were discussed and prioritised with members of the RARE IMPACT Working Group in face to face meetings and WebEx video conferences between September 2018 and September 2019. Country-specific challenges/solutions have drawn on global recommendations previously published by the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) and the Alliance for Regenerative Medicine (ARM), both members of the Working Group.

The challenges and solutions contained within this document are those that have been proposed as priorities for discussion with local stakeholders by members of the Working Group – the report does not include all challenges identified during the secondary research or Working Group meetings.

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Executive Summary

The RARE IMPACT initiative was launched at the European Conference on Rare Diseases and Orphan Products (ECRD) in 2018. It is a multi-stakeholder initiative working to improve patient access to gene and cell therapies (or advanced therapy medicinal products [ATMPs]).[1] This patient-focused initiative aims to both assess challenges and propose actionable solutions to concerns regarding patient access to these transformative rare disease treatments in Europe. Through engagement with health technology assessment (HTA) agencies, regulatory bodies, payers, patient groups, clinicians, manufacturers and other experts across Europe, RARE IMPACT partners have proposed ideas to provide better patient access to ATMPs in Europe.

Currently, ATMPs have been assessed positively in Germany and patients have received good access to these treatments in recent years. Affordability has not been a major impediment to patient access and the health system has managed to secure ATMP access within existing protocols for assessment and reimbursement. However, with more ATMPs due to be launched in the coming years, there are potential barriers to sustainable patient access to ATMPs for which there is now an opportunity to address.

The primary challenge to ensuring sustainable patient access to ATMPs relates to the assessment at the national level. The Arzneimittelmarkt-Neuordnungsgesetz (AMNOG; English translation: Pharmaceuticals Market Reorganisation Act) process is highly structured and emphasises methodological consistency and rigour. There is relatively little flexibility to account for the particular characteristics of ATMPs that place constraints on trial design and evidence availability at launch. The challenges concern the greater evidential uncertainty due to single arm or synthetic control arm studies, small patient numbers in trials, the use of surrogate endpoints and a lack of established comparators.

The most direct response to this challenge would be to allow more flexibility in the AMNOG assessment methodology to reflect the challenges of evidence generation for ATMPs in small populations. This would be especially beneficial in respect to indirect comparisons with appropriate comparator and extrapolation of surrogate data to downstream outcomes. Greater methodological flexibility could be permitted in accordance with the relative paucity of existing data on the disease, endpoints and current standard of care.

Under new legislation the Gemeinsamer Bundesausschuss (G-BA; English translation: Federal Joint Committee) can now request additional data collection for orphan products with conditional approval. The change will introduce a data collection period of 18 months post-launch and enable the Gesetzliche Krankenversicherung (GKV; English translation: Statutory health insurance) to trigger a price negotiation if the G-BA deem the additional data collected to be unsatisfactory. This may pose a challenge in that there is a very limited opportunity to collect meaningful data within an 18-month period. It is therefore necessary for the G-BA to provide guidance on real-world evidence generation needs at early scientific advice meetings, rather than at the time of assessment. It is also important that the process of evidence generation and price negotiation is adaptive and iterative to accurately reflect the cumulative weight of evidence over time.

For these reforms to be effective the quality of data collected needs to be maximised. There is a need for German health authorities to consider how healthcare providers can be encouraged to generate the data required, given no current obligation to participate in data collection. Similarly, patient education is required on the importance of post-treatment follow-up to ensure data collection is meaningful. This is particularly important for potentially curative treatments where patients may not feel the need to continue attending clinic.

[1] Medicines for human use developed from genes, cells or tissues are classified as ATMPs by the European Medicines Agency (EMA)

Innovative funding schemes, such as outcome-based payment agreements, are likely to be an important part of this new process. Such agreements have already been developed for CAR-T in Germany, in which the manufacturer agreed to a rebate for some of the treatment cost if the survival outcomes of the therapy are not met. It should be noted that this model was agreed with a single coalition of payers (Gesellschaft für Wirtschaftlichkeit und Qualität für Krankenkassen) and further encouragement should be given to extend the participation for future ATMPs.

Given the particular characteristics of ATMPs in rare diseases, and the implications for the assessment of benefit, it is particularly important that the patient perspective is incorporated into the assessment process. Greater input would be helpful in understanding the burden of disease, interpreting novel endpoints and the magnitude of benefit, and understanding the impact on quality of life. Patient involvement in determining evidence requirements post-launch and interpreting evolving data would be very valuable and might assist with optimising patient compliance with follow-up assessments.

While affordability is currently not an issue, future funding challenges for ATMPs in Germany relate to the ability of existing structures to allow sustainable reimbursement strategies for ATMPs, which in many cases require large one-time payments. Annuity payments have been recognised as being a potential solution to the problem of large upfront costs and uncertain long-term outcomes. While such arrangements are conceptually attractive, they face practical challenges. Clarification should be sought from sick funds and accounting standards bodies if the concern about annuity payments is a legal/regulatory constraint or institutional preference. If the former, further engagement with accounting bodies and government financial regulators may be necessary to understand the opportunity for exemptions for ATMPs or contractual structures that are compliant. If the latter, further dialogue is necessary with sick funds to help them appreciate the benefits of minimising health outcome uncertainty through risk-sharing contracts. In addition, it may be helpful to create standardised annuity contracts that can be used across sick funds to minimise institutional concern about these novel deal structures.

The distribution of patients requiring a high-cost ATMP and the ability of German patients to switch insurance raises some concerns amongst sick funds about the affordability of ATMPs in future. To mitigate against the risk of patient movement, a framework for risk-sharing could be proposed and utilised amongst a consortium of insurers, such has been done with CAR-T. Risk-sharing in the form of collectivisation, such as the use of 'high-risk funds', allows initial costs to be collectivised and insured. In this way, individuals' freedom to choose their insurance company is not compromised, while at the same time the fund balances expenses and amortisation. In order to ensure access beyond an initial willing group of insurers, a standardised and expanded approach could be developed for individual ATMPs or groups of ATMPs.

To date, German patients have been able to travel to cross-border treatment centres to receive ATMPs that are not available in Germany. However, this access is funded by sick funds on a case-by-case basis meaning there is a risk of variable patient access to ATMPs. Currently the G-BA does not assess ATMPs provided outside of Germany through the AMNOG process. Were this to change it might provide assurances for sick funds on the benefit of the product regardless of its availability within Germany or in cross-border scenarios. Alternatively, developing guidelines for sick funds to standardise the approach to decisions on funding for cross border ATMPs would benefit patients and remove uncertainty over availability.

The interpretation of hospital exemption legislation in Germany may pose a challenge to patient access as it currently stands (although this issue tends to apply more to cell therapies), where treatments approved through the central authorisation process of the European Medicines Agency (EMA) may have to compete with products developed under the hospital exemption directive. To address this, internal guidance could be issued to treating centres on when treatments with Marketing Authorisation should supersede those developed under hospital exemption in order to protect the integrity of the regulatory and assessment processes of the EMA and the AMNOG process. As Germany are taking over the

presidency of the European Council, there is the potential that clarification or amendments to the hospital exemption directive could be sought. Any amendment should provide clear direction on when treatments with Marketing Authorisation supersede treatments developed under hospital exemption.

Accessibility of treatments for patients in Germany is very good and poses only minor challenges to patient access. These primarily revolve around the issue that some potential aspects of ATMPs may lead to delays in access, such as the requirement for additional assessment if a novel procedure or diagnostic accompanies the ATMP. These delays could be mitigated with better clarity around assessment needs of a new product and stakeholder communication well in advance, which would allow for better preparation and streamlining of the complex process.

An overview of challenges and proposals for improving patient access to ATMPs in Germany

Domain (Impact)*	Challenge	Proposed solution	Feasibility**
Assessment 	**AS1.** The type of evidence available for ATMPs in rare diseases at the time of assessment is not always aligned with AMNOG requirements	**AS1a.** Allow more flexibility in G-BA/IQWIG methods to reflect the challenges of evidence generation for ATMPs in small populations. **AS1b.** G-BA to provide guidance on real-world evidence generation at early scientific advice meetings, rather than waiting until post approval benefit assessment. **AS1c.** Greater level of patient involvement in the assessment process.	++ ++ ++
	AS2. The AMNOG orphan drug exemption is being scrutinised; ATMPs will reach the €50m annual sales threshold earlier/faster than chronic treatment options for rare disease.	**AS2.** Develop an adaptive process of evidence generation and re-assessment by supporting greater uptake of outcomes-based agreements that allow the exemption to be maintained but reflect the reality of data collection timelines for ATMPs.	+
Affordability 	**AF1.** Free selection of health insurers means return on ATMP investment are not guaranteed, making insurers less willing to fund one-off ATMPs.	**AF1.** Seek to establish a framework for risk sharing between insurers (as has been done in the past, and currently with CAR-T).	++
	AF2. Large one-time costs pose a challenge to individual sick funds. Annuity payments may require reform of sick fund accounting processes.	**AF2.** Implement modified/innovative annuity payments.	++
	AF3. ATMPs can be caught between the AMNOG and NUB processes. As access in the NUB process is a case-by-case basis, it creates potential inequality.	**AF3.** Allow broad access under the NUB process with list price reimbursement (with clawback) until price has been negotiated following benefit assessment	+
Availability 	**AV1.** Patients have received access to treatment via cross-border initiatives in the past, but these pathways are uncertain in the future.	**AV1.** Develop guidelines for sick funds to standardise approach to cross-border coverage.	++
	AV2. Interpretation of the hospital exemption legislation means approved ATMPs may have to compete with products developed under hospital exemption.	**AV2.** Issue local guidance to treating centres on limiting the use of hospital exemption once Marketing Authorisation has been granted for an ATMP. Germany should use position	+

Domain (Impact)*	Challenge	Proposed solution	Feasibility**
		to seek clarity of the hospital exemption directive to ensure products with Marketing Authorisation supersede hospital exemption products.	
Accessibility 	**AC1.** Advanced therapies may require novel administration devices or protocols and these may require a separate HTA assessment before the medicinal product itself can be appraised.	**AC1.** Clarity on likely assessment needs in advance to allow manufacturers to prepare for assessment.	+

Notes: *The Working Group assessment of the relative impact of the challenge of each domain on patient access is represented by Harvey balls from highest (represented by a full blue Harvey ball) to lowest (represented by an empty, white Harvey ball); **Feasibility: Working Group assessment of feasibility of solutions to be implemented. + low feasibility, ++ medium feasibility, +++ high feasibility.

The collaboration

RARE IMPACT is a collaboration of three not-for-profit organisations, two trade associations and 18 manufacturers of ATMPs brought together by EURORDIS, a non-governmental patient-driven alliance of patient organisations. The overarching objective of the collaboration is to ensure European patients with rare diseases obtain quick access to gene and cell therapies and to create a sustainable model for manufacturers and payers to maintain patient access and innovation. To achieve this objective, the collaboration has established the following goals:

- Identify challenges that are preventing rare disease patients accessing ATMPs
- Propose actionable solutions to address these challenges
- Utilise these ideas within multi-stakeholder discussions within individual countries and in pan-regional forums

The approach

A framework for categorising barriers to patient access was developed and validated by the collaboration. The framework includes four categories, described in Table 1 below.

Table 1. Framework applied to structuring identified challenges

Category	Description
Assessment (magnitude of benefit)	Challenges related to the assessment of the benefit of ATMPs within pricing and reimbursement processes. This includes topics such as evidence uncertainty, generating comparative data, use of surrogate endpoints and assessment pathways.
Affordability (price, cost and funding	Challenges concerning the pricing, funding and affordability of ATMPs, including the application of innovative payment models.
Availability (legally available)	Non-regulatory challenges to the product being available within countries, such as those related to cross-border healthcare and hospital exemptions.
Accessibility (accessible by patients)	Administrative, service capacity and geographic challenges that delay or prevent patient access to ATMPs.

Identification of challenges and proposals for improving patient access

Primary and secondary research was conducted to identify challenges to patient access to ATMPs and potential solutions. Secondary research was conducted to create a database of conceptual and country-specific challenges. This research included:

- A targeted literature search
- Reviewing outputs from other initiatives (e.g., ARM's "Recommendations for Timely Access to ATMPs in Europe" and EUCOPE's "Gene & Cell Therapy – Pioneering Access for Ground-Breaking Treatments")
- Assessing pathways through which patients access ATMPs in the countries of interest
- Reviewing HTA and pricing and reimbursement (P&R) decisions for existing ATMPs

Challenges and potential solutions were supplemented, assessed and prioritised through a review process including:

- Members of the Working Group (including EURORDIS, trade associations, affiliated NGOs and 18 member companies)
- Country-specific patient associations
- Country level decision makers, such as policymakers, HTA bodies and budget holders
- Experts and advisors, such as healthcare professionals, patient representatives, P&R system experts, ATMP technical experts, economists and academics

In Germany, stakeholders engaged included representatives from:

- DAK-Gesundheit
- Allianz Chronischer Seltener Erkrankungen (ACHSE; Alliance for Chronic Rare Disease)
- Independent experts and consultants

Following stakeholder engagement, the challenges and solutions were refined and prioritised to reflect the perceived importance in improving patient access and feasibility of implementation. Therefore, the challenges in this report are not exhaustive of all identified through primary and secondary research but represent the most important issues as determined by stakeholders.

The outputs from this process have been summarised in this report as a basis for discussion within multi-stakeholder meetings in each country and at the European level.

ASSESSMENT

Impact: 

Challenge		Potential solution		Feasibility
AS1.	The type of evidence available for ATMPs in rare diseases at the time of assessment is not always aligned with AMNOG requirements.	**AS2a.**	Allow more flexibility in G-BA/IQWIG methods to reflect the challenges of evidence generation for ATMPs in small populations.	++
		AS2b.	G-BA to provide guidance on real-world evidence generation at early scientific advice meetings, rather than waiting until post approval benefit assessment.	++
		AS1c.	Greater level of patient involvement in the assessment process.	++
AS2.	The AMNOG orphan drug exemption is being scrutinised; ATMPs will reach the €50m annual sales threshold earlier/faster than chronic treatment options for rare disease.	**AS2.**	Develop an adaptive process of evidence generation and re-assessment by supporting greater uptake of outcomes-based agreements that allow the exemption to be maintained but reflect the reality of data collection timelines for ATMPs.	+

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working Group identified assessment challenges:

Challenge AS1.

The type of evidence available for ATMPs in rare diseases at the time of assessment is not always aligned with AMNOG requirements.

The key challenges for ATMPs in Germany relate to ATMP assessment. The AMNOG process is highly structured and emphasises methodological consistency and rigour. There is relatively little flexibility to account for the particular characteristics of ATMPs and constraints on trial design and evidence availability at launch. These challenges are similar in nature to those that are currently faced by orphan drugs in Germany, but often amplified in the case of ATMPs. They concern the greater evidential uncertainty due to single arm or synthetic control arm studies, small patient numbers in trials, the use of surrogate endpoints and a lack of established comparators.

Gathering evidence on the long-term benefit of ATMPs is difficult and the G-BA and the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG; English translation: The Institute for Quality and Efficiency in Healthcare) apply firm rules on when it is acceptable to extrapolate from surrogate trial endpoints to outcomes, such as survival. For such extrapolation to be accepted, it is necessary that the relationship between the surrogate and the outcome has been demonstrated to a very high level of statistical proof, something that is particularly difficult in disease areas with small populations and potentially limited existing observational data from which to assess correlation.

Single arm studies and unblinded trials are also considered to be insufficiently robust to allow for the inference of added benefit. Yet regulators are often reluctant to permit controlled trials in highly morbid populations with no other effective treatment options, and blinding is extremely difficult given the nature of the intervention for cell and gene therapies.

Although indirect treatment comparisons (ITCs) are permitted, G-BA methods guidance is quite strict and indirect comparisons from single-arm studies less likely to be accepted. The appropriate comparator can be hard to identify in rare, heterogeneous diseases where no established standard of care exists. As well as making it harder to identify an appropriate comparator for a controlled study, it also makes it more challenging to undertake indirect comparisons with the G-BA defined appropriate comparator. Matched indirect comparisons of patients in single arm studies with those from observational data sets are complicated by the lack of robust natural history datasets in rare diseases and the heterogeneity of treatments that patients are receiving in clinical practice.

Despite these challenges, ATMPs have been positively assessed through the AMNOG process and patient access has been achieved. This is largely due to the orphan drug exemption which allows for drugs with orphan designation to be automatically granted additional benefit if projected 12-month outpatient sales are less than €50m (note: if sales exceed €50m over a 12-month period, manufacturers are required to submit a full benefit dossier for assessment and enter new negotiations with GKV). For example, Yescarta achieved an unquantifiable additional benefit with a data package that included a single-arm trial and ITC over other historical controls. However, the €50m annual sales threshold may complicate the situation for ATMPs, given their high one-off prices, in contrast to more conventional treatments, where cost may be spread over multiple years.

The law for security in pharmaceutical supply that was passed in June 2019 will impact ATMP assessment. Under new legislation the G-BA can now request additional data collection for orphan products with conditional approval within a given timeframe, which will be considered during subsequent benefit assessment. The G-BA will determine how this data collection is conducted. This is being put in place to help the G-BA manage uncertainty in the data available at the time of launch, but the proposed data collection period of 18 months may not capture the potential long-term benefit of ATMPs. Despite the additional benefit for orphan drugs provided for in law, if the G-BA determines the data collected to be unsatisfactory (regardless of whether the data was collected by the manufacturer or no new information can be obtained), prices will have to be re-negotiated.

Proposed solution AS1a

Allow more flexibility in G-BA/IQWIG methods to reflect the challenges of evidence generation for ATMPs in small populations.

The most direct response to this challenge would be to allow more flexibility in the IQWIG/G-BA assessment methodology to reflect the challenges of evidence generation for ATMPs in small populations. In particular, greater flexibility would be beneficial in two key areas: indirect comparison with appropriate comparator and extrapolation of surrogate data to downstream outcomes.

Greater flexibility could be afforded in the assessment of indirect comparisons with appropriate comparators according to the relative availability of natural history data – in diseases in which least data is available and where standard of care is heterogeneous, more flexibility could be permitted. Similarly, interpretation of the validity of matching criteria should be relative to the availability of observational data.

A second change could be to allow greater flexibility in extrapolation of short-term surrogate data to long-term ‘patient relevant’ outcomes in situations where it is not possible to generate outcomes data within a trial (e.g., because endpoints are not well established or the disease course is too long).

Both of these topics should be a key area of discussion between G-BA and manufacturers during early scientific advice. It would also be helpful for the G-BA/IQWIG to provide greater guidance on requirements for indirect comparisons and data extrapolation for ATMPs in rare diseases, based on the experience to date. Cross European collaboration on such methodological guidance would improve the consistency of data analysis requirements and enhance the potential for larger, regional data sets that might provide greater certainty.

Feasibility: ++
Stakeholders: G-BA, IQWIG
Timeframe: 12–18 months

Proposed solution AS1b

G-BA to provide guidance on real-world evidence generation at early scientific advice meetings, rather than waiting until post approval benefit assessment.

Under the new law for security in pharmaceutical supply, it is understood that the G-BA will need to inform the manufacturer of the areas of evidential uncertainty to be addressed, allowing the manufacturer to design post-launch data collection accordingly. However, if this guidance is only provided at the time of initial benefit assessment, then there is very limited opportunity to collect meaningful data within, say, a 24-month period, due to the complexity of setting up data collection processes. For German real-world data to be used effectively within the pricing and reimbursement process, planning for collection must begin before launch so that all patients treated after marketing approval can be incorporated into the sample. It is therefore necessary for the G-BA to provide guidance on real-world evidence generation at early scientific advice consultations, rather than waiting until post approval benefit assessment.

In addition, for these reforms to be effective the quality of data collected needs to be maximised. There is a need for German health authorities to consider how healthcare providers can be encouraged to generate the data required, given no current obligation to participate in data collection. With small patient populations, it is important to attain high rates of compliance to make the data meaningful. Similarly, patient education is required on the importance of post-treatment follow-up to ensure data collection is meaningful. This is particularly important for potentially curative treatments where patients may not feel the need to continue attending. Finally, while the priority will be to obtain insight into the outcomes of German patients on treatment, the G-BA should also consider larger real-world data sets aggregated from patients across Europe within subsequent benefit assessments.

Feasibility: ++
Stakeholders: G-BA, trade associations, individual manufacturers, clinicians and registry administrators
Timeframe: Real-world evidence guidance at joint scientific advice (0–3 months), education on data generation (immediate)

Proposed solution AS1c

Greater level of patient involvement in the assessment process.

Given the particular characteristics of ATMPs in rare diseases, and the implications for the assessment of benefit, it is particularly important that the patient perspective is incorporated into the assessment process. Greater input would be helpful in understanding the burden of disease, interpreting novel endpoints and the magnitude of benefit, and understanding the impact on quality of life. Patient involvement in determining evidence requirements post-launch and interpreting evolving data would be very valuable and might assist with optimising patient compliance with follow-up assessments.

Feasibility: ++
Stakeholders: G-BA, patient associations
Timeframe: 0–12 months

Challenge AS2

The AMNOG orphan drug exemption is being scrutinised; ATMPs will reach the €50m annual sales threshold earlier/faster than chronic treatment options for rare disease.

Scrutiny of the orphan drug exemption was a catalyst for the development of the law for security in pharmaceutical supply. Without the orphan drug exemption, securing reimbursement for ATMPs in rare diseases would be difficult as the data package available at launch is likely to be insufficient for demonstrating additional benefit in accordance with strict AMNOG evidential requirements.

Under the orphan drug exemption products are not required to undergo a full benefit assessment unless a €50m annual sales cap is triggered. Previously, this sales cap was based on the annual outpatient sales of a product. It is now based on the overall revenue (inpatient and outpatient). The €50m sales cap is likely to problematic for ATMPs as a bolus of prevalent patients at the time of launch means these products are more likely to surpass the sales threshold in the first-year post-launch than orphan medicines for which cost is spread over multiple years.

Proposed solution AS2

Develop an adaptive process of evidence generation and re-assessment by supporting greater uptake of outcomes-based agreements that allow the exemption to be maintained but reflect the reality of data collection timelines for ATMPs.

The maintenance of the orphan drug exemption is critical to ensure patients with rare diseases in Germany continue to have access to innovative medicines. The new legislation offers an opportunity to maintain the orphan exemption but allow for further data generation and greater confidence in the alignment between price and benefit.

For this to work, the process of evidence generation and re-assessment should be ongoing and adaptive, rather than a one-off re-assessment followed by a binary decision. It also needs to reflect the reality of data collection timelines for ATMPs in rare diseases – 18 months is likely insufficient time to reach a definitive conclusion on a treatment's real-world effect. Changes to price and reimbursement status should therefore be incremental and iterative, reflecting the cumulative weight of evidence.

Innovative funding schemes, such as outcome-based payment agreements, are likely to be an important part of this new process. Such agreements have already been developed for CAR-T in Germany, in which the manufacturer agreed to a rebate for some of the treatment cost if the survival outcomes of the therapy are not met. This type of innovative payment model could provide an option for ATMPs with similar clinical and technical profiles. It should be noted that this model was agreed with a single coalition of payers (Gesellschaft für Wirtschaftlichkeit und Qualität für Krankenkassen [GWQ]) and further encouragement should be given to extend the participation for future ATMPs. GWQ have stated their willingness to engage in similar innovative strategies in the future.

Feasibility: +
Stakeholders: G-BA, sick funds, trade associations
Timeframe: Immediate

AFFORDABILITY

Impact: 

Challenge		Potential solution		Feasibility
AF1.	Free selection of health insurers means return on ATMP investment are not guaranteed, making insurers less willing to fund one-off ATMPs.	**AF1.**	Seek to establish a framework for risk sharing between insurers (as has been done in the past, and currently with CAR-T).	++
AF2.	Large one-time costs pose a challenge to individual sick funds. Annuity payments may require reform of sick fund accounting processes.	**AF2.**	Implement modified/innovative annuity payments.	++
AF3.	ATMPs can be caught between the AMNOG and NUB processes. As access in the NUB process is on a case-by-case basis, it can create inequality.	**AF3.**	Allow broad access under the NUB process with list price reimbursement (with clawback) until price has been negotiated following benefit assessment.	+

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working Group identified affordability challenges:

Challenge AF1

Free selection of health insurers means return on ATMP investment are not guaranteed, making insurers less willing to fund one-off ATMPs.

Patients in Germany have free choice of sick funds with which to seek insurance. Their ability to switch between plans means insurers may be unwilling to commit to the large upfront cost associated with ATMPs knowing that the 'return' on that investment, in the form of healthier members, might be accrued by another fund.

Proposed solution AF1

Seek to establish a framework for risk sharing between insurers (as has been done in the past, and currently with CAR-T).

In practise, few patients switch between sick funds in Germany. To mitigate against the risk of patient movement, a framework for risk-sharing could be proposed and utilised amongst a consortium of insurers, which has been a successful strategy for the CAR-T treatment, Kymriah. Risk-sharing in the form of collectivisation, such as the use of 'high-risk funds', allows initial costs to be collectivised and insured. In this way, individuals' freedom to choose their insurance company is not compromised, while at the same time the fund balances expenses and amortisation. Similar systems were put in place in the past to redistribute risk of high-cost patients between sick funds (e.g., with haemophilia patients). Such a scheme could pose a potential solution, so that one insurer does not hold the entire risk and cost burden. Insurers have expressed a willingness to participate in such schemes in the future. While there are learnings from the CAR-T scheme, it was the coordination and willingness of the insurers to engage that ultimately led to a deal being struck. The pooled risk from the insurers side is matched with an outcomes-based approach from the manufacturers who have agreed a rebate with the insurers should

patients not reach pre-specified milestones following treatment. The barriers to annuity payments should also be addressed in order to provide further risk-sharing options to payers.

In order to ensure access beyond an initial willing group of insurers, a standardised and expanded approach could be developed for individual ATMPs or groups of ATMPs as has been seen with haemophilia products in the past.

Provision of data on when patients change health insurance companies could help indicate the magnitude of the issue, as findings from previous research have suggested that such change happens rarely and may not represent a significant problem.

Feasibility: ++
Stakeholders: GKV, individual sick funds, individual companies
Timeframe: Immediate – GKV have indicated a willingness to engage in innovative approaches to ensure access

The set-up of risk sharing frameworks is demanding, as calculation of the compensation mechanisms, inclusion and exclusion criteria and derived bonus is complex. It should be conducted based on existing data to create and test different models for sustainability. These proposed solutions do not necessarily require entire systematic restructuring.

Challenge AF2

Large one-time costs pose a challenge to individual sick funds. Annuity payments may require reform of sick fund accounting processes.

Larger one-time payments for ATMPs pose a potential cost challenge to individual sick funds. Annuity payments have been recognised as being a potential solution to the problem of large upfront costs and uncertain long-term outcomes. While such arrangements are conceptually attractive, they face practical challenges. In Germany, sick fund accounting processes may pose challenges to annuity payment models, which rely on the service being provided within one year, but payments being spread over multiple years. It is unclear how much flexibility sick funds have in deviating from these standard practices and whether the expressed reluctance is due to legal constraints or institutional conservatism.

Proposed solution AF2

Implement modified/innovative annuity payments.

Firstly, clarification should be sought from sick funds and accounting standards bodies if the concern about annuity payments is a legal/regulatory constraint or institutional preference. If the former, further engagement with accounting bodies and government financial regulators may be necessary to understand the opportunity for exemptions for ATMPs or contractual structures that are compliant. If the latter, further dialogue is necessary with sick funds to help them appreciate the benefits of minimising health outcome uncertainty through risk-sharing contracts. In addition, it may be helpful to create standardised annuity contracts that can be used across sick funds to minimise institutional concern about these novel deal structures.

Feasibility: ++
Stakeholders: G-KV, individual sick funds, individual companies
Timeframe: Immediate – G-KV have indicated a willingness to engage in innovative approaches to ensure access

Challenge AF3

ATMPs can be caught between the AMNOG and NUB processes. As access in the NUB process is on a case-by-case basis, it can create inequality.

There is a potential risk of ATMPs being caught between the AMNOG and NUB (new examination and treatment method) processes. The NUB process was introduced in 2005 to better integrate and fund innovative hospital products within the Diagnosis Related Groups (G-DRG) system. For new products that are not covered by the G-DRG, hospitals can apply individually for reimbursement through the NUB process. Products assessed through the NUB process may reach the market quicker, but it requires substantial effort from stakeholders and the product will be available only to the hospitals that applied for it. As access in the NUB process is on a case-by-case basis, it can create inequality.

Proposed solution AF3

Allow broad access under the NUB process with list price reimbursement (with clawback) until price has been negotiated following benefit assessment.

This risk of inequality could be addressed by expanding access to a particular ATMP in all hospitals if one hospital successfully applies for reimbursement via the NUB process. Additionally, the inequality risk can be avoided by paying the list price for the ATMP while being reimbursed via the NUB and then continuing payment as usual after benefit assessment has been conducted and G-DRG put in place. A clawback mechanism could be included that would cover any variation in the list price prior to benefit assessment and the negotiated price. Leveraging innovative payment models, which have been used successfully with CAR-Ts, and engaging with insurers on the formation of such schemes should be done as early as possible.

Feasibility: +
Stakeholders: G-KV, G-BA, individual sick funds, individual companies
Timeframe: Immediate

AVAILABILITY

Impact: 

Challenge		Proposed solution		Feasibility
AV1.	Patients have received access to treatment via cross-border initiatives in the past, these pathways are uncertain in the future.	**AV1.**	Develop guidelines for sick funds to standardise approach to cross-border coverage.	++
AV2.	Interpretation of the hospital exemption legislation means approved ATMPs may have to compete with products developed under hospital exemption.	**AV2.**	Issue local guidance to treating centres on limiting the use of hospital exemption once Marketing Authorisation has been granted for an ATMP. Germany should use position to seek clarity of the hospital exemption directive to ensure products with Marketing Authorisation supersede hospital exemption products.	+

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working Group identified availability challenges:

Challenge AV1

Patients have received access to treatment via cross-border initiatives in the past, these pathways are uncertain in the future.

The issue of availability is of relatively low concern in Germany, in comparison to assessment and affordability. To date, most patients in Germany can gain access to ATMPs in other countries as sick funds are usually approving such funding requests. However, there is no statutory requirement within cross-border legislation that mandates sick funds to cover such treatments and decisions are made on an individual patient and sick fund basis.

If in the future there are more ATMPs that require access via cross-border mechanisms, there is a risk of increasing variation in access for patients across sick funds. The sustainability of providing coverage in this manner for future ATMPs that require cross-border access is also questionable.

Proposed solution AV1

Develop guidelines for sick funds to standardise approach to cross-border coverage.

Developing guidelines for sick funds to standardise the approach to providing access to ATMPs in cross border scenarios would benefit patients and remove uncertainty over availability.

Currently the G-BA does not assess ATMPs provided outside of Germany through the AMNOG process. Were this to change it might provide assurances for sick funds on the benefit of the product regardless of its availability within Germany or in cross-border scenarios.

Feasibility: ++
Stakeholders: GKV, sick funds, individual companies, clinical experts, patient associations
Timeframe: Immediate

Challenge AV2

Interpretation of the hospital exemption legislation means approved ATMPs may have to compete with products developed under hospital exemption.

Article 28 (2) of the ATMP Regulation modified the Directive 2001/83/EC by adding the article 3(7), referred to as the 'hospital exemption' (HE). According to the legislation, it is permitted to use an ATMP without a Marketing Authorisation under certain circumstances. The purpose of this legislation is to provide unauthorised ATMPs to individual patients on a non-routine basis.

The varying interpretation of this EU legislation means it could be used as a way to circumvent the applicable legal instruments for the marketing of safe and effective ATMPs. This could act as a disincentive for manufacturers to develop ATMPs to regulatory and manufacturing standards as the commercial opportunity could be challenged by unauthorised, individual products with no requirement to undergo the regulatory rigour to achieve Marketing Authorisation. In Germany, there is an established definition of the 'non-routine' products that should qualify for hospital exemption. Where there is medical justification for an individual patient, ATMPs that are manufactured in small quantities can be considered outside of normal assessment procedures. Alternatively, ATMPs which have not yet been manufactured in sufficient quantities to obtain the necessary data to enable a comprehensive assessment are also considered 'non routine'. This definition allows flexibility of the interpretation of the EU directive and opens ATMPs with marketing authorisation to competition from products developed under the hospital exemption.

Proposed solution AV2

Issue local guidance to treating centres on limiting the use of hospital exemption once Marketing Authorisation has been granted for an ATMP. Germany should use position to seek clarity of the hospital exemption directive to ensure products with Marketing Authorisation supersede hospital exemption products.

The German authorities should issue guidance to hospitals on when hospital exemptions can be used and limiting the use of hospital exemption products when an ATMP has been made available following Marketing Authorisation. This would align more closely with the spirit of the EU directive on hospital exemptions.

With a position as a leader in patient access in Europe and as holders of the presidency of the European Council from July – December 2020, Germany is well placed to address uncertainty in the EU directive. Issuing European-level guidance specifically defining the scope and requirements for hospital exemptions for ATMPs may clarify when ATMPs with Marketing Authorisation are prioritised for use. The guidelines should also address the possible interference of hospital exemption with recruitment of patients in clinical trials for the same indication. This echoes the ARM position on hospital exemptions.

Feasibility: +
Stakeholders: G-BA, clinical experts, patient associations, treating centres, trade associations, EU parliament
Timeline: 6–18 months

ACCESSIBILITY

Impact: 

Challenge		Potential solution		Feasibility
AC1.	Advanced therapies may require novel administration devices or protocols, and these may in some cases require a separate HTA assessment before the medicinal product itself can be appraised.	**AC1.**	Clarity on likely assessment needs in advance in order for manufacturers to prepare.	+

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working group identified accessibility challenges:

Challenge AC1.

Advanced therapies may require novel administration devices or protocols, and these may in some cases require a separate HTA assessment before the medicinal product itself can be appraised.

Similar to availability, the issue of accessibility is relatively minimal in Germany, in comparison to assessment and affordability. One existing issue is that ATMPs themselves are novel and may require novel surgical or non-surgical administration devices or protocols. In some cases, these may require a separate HTA assessment before the medicinal product itself can be appraised. Although German agencies are very active in early scientific advice, the current HTA legislation is constraining in terms of the route the products will take. As ATMPs are novel treatments, a lack of knowledge, experience or education regarding what exactly is needed may undermine the process.

Proposed solution AC1.

Clarity on likely assessment needs in advance in order for manufacturers to prepare.

Clear outlines of assessment needs should be provided in advance in order for manufacturers to prepare and target their preparations to the complexity of assessment protocols and requirements. A recent proposal (termed the “FKG”) from the German government is seeking to reform the AMNOG process so all ATMPs will undergo a benefit assessment.

Feasibility: ++
Stakeholders: Federal government, G-BA
Timeline: 6–18 months

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Appendix

Country profile

Market type	Comparative clinical effectiveness
Position in launch sequence	Early
Previous experience with ATMPs	Yes

	Status	Note
Strimvelis	No G-BA assessment	Patients have access via cross-border initiatives[1]
Holoclar	No G-BA assessment	The treatment method goes beyond the scope of pharmaceutical legislation. Examination is required[2]
Zalmoxis	Significant added benefit[3]	€130,000 per infusion (max. 4 infusions)
Glybera	Initially "Unquantifiable added benefit" [4a]. Position changed to "hospital-only product" allowing direct price negotiations[4b,]	The price was approximately €900,000 following an agreement with DAK[4b]
Imlygic	Added benefit not proven[5]	Continuous treatment, active comparators including nivolumab, pembroliumab and ipilimumab[5]
Provenge	No G-BA assessment	Withdrawn from EU market
MACI	No G-BA assessment	Suspended for use in the EU
ChondroCelect	No G-BA assessment	Withdrawn from EU market
Yescarta	Unquantifiable added benefit[6]	List price €327,000
Kymriah	Unquantifiable added benefit[7]	List price €320,000
Luxturna	Approved[8]	
Alofisel	Approved[9]	

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