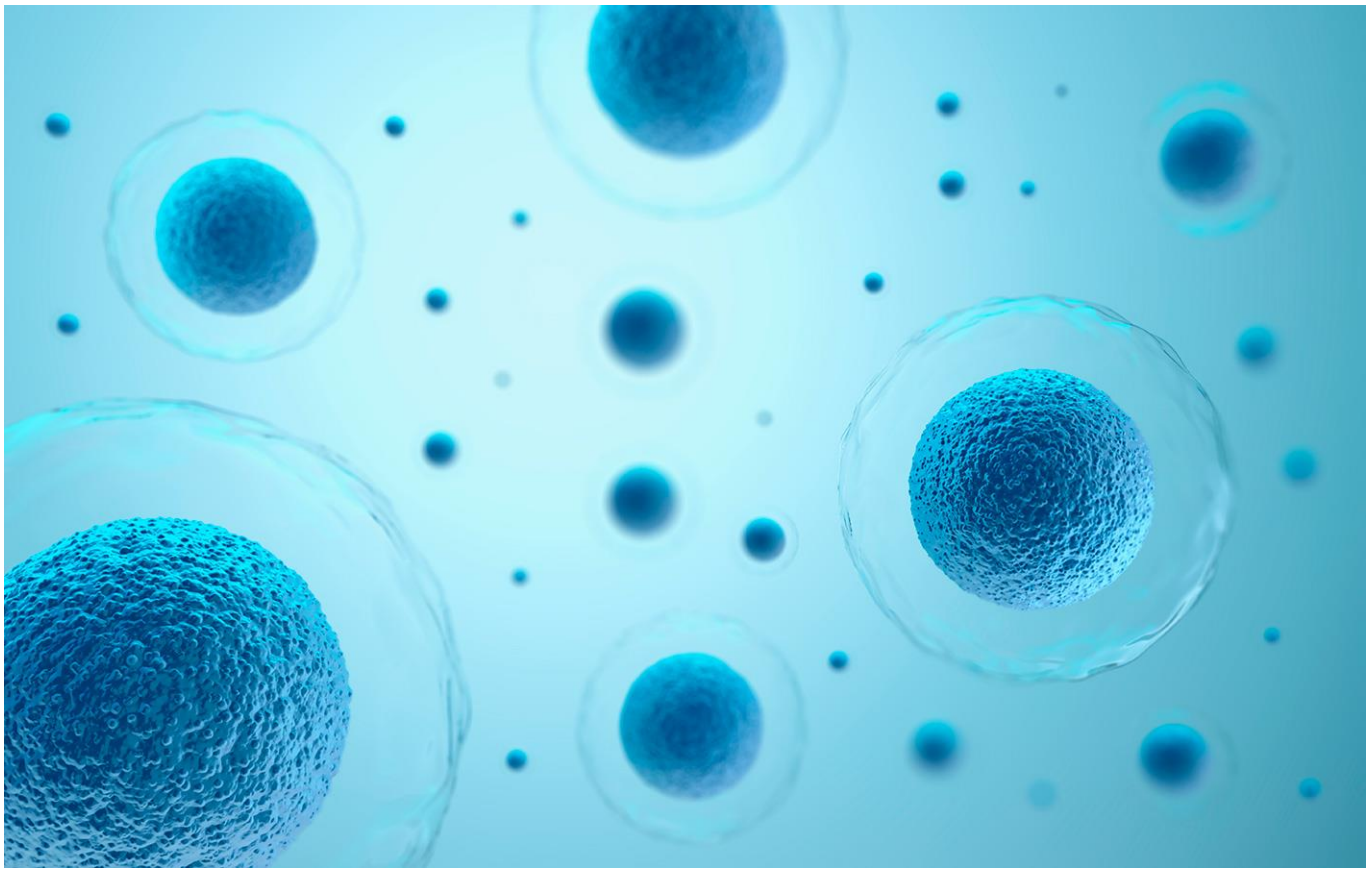
Avancerede terapier (ATMP)

En kortlægning af potentialer og udfordringer ved introduktion af nye behandlingsmuligheder i Danmark – Sammenfatning



Sarah Wadmann og Betina Højgaard

VIVE

Avancerede terapier (ATMP) – En kortlægning af potentialer og udfordringer ved introduktion af nye behandlingsmuligheder i Danmark – Sammenfatning

e-ISBN: 978-87-7119-988-8
Forsidefoto: Anusorn
Projekt: 302000
Finansiering: Pfizer Danmark

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DET NATIONALE FORSKNINGS- OG ANALYSECENTER FOR VELFÆRD

Forord

Udviklingen af nye lægemidler og andre medicinske teknologier skaber både nye behandlingsmuligheder og en række regulatoriske udfordringer. I denne rapport kortlægger VIVE de evalueringsmæssige, finansieringsmæssige og organisatoriske udfordringer og muligheder, som kan opstå, når nye gen- og celleterapier samt vævsteknologier introduceres i sundhedsvæsenet.

Det er VIVEs forhåbning, at rapporten kan være med til at skabe et bedre vidensgrundlag for dialog mellem politiske og administrative beslutningstagere, klinikere, virksomheder og patientorganisationer om introduktion af nye lægemidler i sundhedsvæsenet.

Undersøgelsen er finansieret af Pfizer Danmark og udarbejdet af Sarah Wadmann og Betina Højgaard fra VIVE. Nina Louise Aagaard og Morten Koburg Thomsen fra VIVE har bistået med visualiseringer og sproglig kommunikation i rapporten.

Undersøgelsen er blevet til med hjælp fra en række eksperter, som har deltaget i interviews. VIVE retter tak til alle interviewpersoner, som har bidraget med tid og ekspertise. VIVE ønsker også at takke to eksterne reviewere for deres værdifulde kommentarer og forslag til rapporten.

Mickael Bech
Forsknings- og analysechef for VIVE Sundhed
2021

English Summary

Scientific and technological developments in medicine pave the way for new kinds of treatment, including advanced therapy medical products (ATMPs). ATMPs are medicines for human use based on genes, tissues or cells. A characteristic of these treatments is that they consist of biological material that is modified to replace a missing function or repair a pathological dysfunction in the patient. The aim is to slow down or stop disease development in the early stages or increase the body's capacity to regenerate – in some cases offering new treatment options for patients who previously had no prospect of active treatment. Often, the treatments are to be administered only once and, typically, they carry a promise of long-lasting therapeutic effects.

Yet ATMPs also bring challenges. The introduction of these new treatments requires high upfront costs for the public healthcare providers because of necessary investments in infra-structure (e.g. equipment, storage and treatment capacity) and a high price per dose compared to other kinds of medicine. Often, clinical effects and adverse effects are very uncertain – particularly long-term effects. Furthermore, ATMPs come with new logistical and infrastructural demands and require more complex procedures for quality control than most other types of medicine. Public decision-makers are therefore faced with challenging issues related to the use of adequate evaluation methods, sustainable payment models and organizational conditions to enable the uptake of these treatments. These challenges put pressure on pharmaceutical companies, public authorities, healthcare payers and other stakeholders to develop joint solutions.

The aim of this report is to map and discuss challenges and possibilities pertaining to the evaluation, financing and organisation of treatment with ATMPs in the Danish healthcare system, in order to support informed dialogue among stakeholders about possible solutions and needs for further research. Furthermore, Swedish and English experiences with ATMPs are briefly compared with the current state of affairs in Denmark. Sweden and England were chosen because these countries have taken a proactive approach to examining challenges and possible solutions related to the introduction of ATMPs, which Denmark might learn from, and at the same time exhibit political and organizational similarities with Denmark, which provides for easier transfer of experiences.

It is outside the scope of this report to provide a comprehensive mapping of ethical and legal challenges related to the introduction of ATMPs. Ethical and legal concerns are mainly touched upon when they arise in relation to the evaluation, financing and organisation of ATMP treatment. It is also outside the scope of this report to recommend specific solutions to the challenges identified. Rather, the report provides recommendations about which themes and questions stakeholders might debate in a search for joint solutions.

The report mainly builds upon a literature review. To supplement the literature review, nine expert interviews were conducted to ensure up-to-date information about existing practices related to the evaluation, financing and organisation of treatment with ATMPs in Denmark, Sweden and England. In Denmark, interviews were conducted with clinicians who are experienced in ATMP treatment, the regional authorities who own and fund the hospitals where ATMP treatment is conducted, the public procurement organisation, Amgros,

and the pharmaceutical industry association. In addition, interviews were conducted with researchers and representatives from health technology assessment (HTA) institutions in Sweden and England.

Evaluation

The methodological challenges that arise in relation to the evaluation of advanced therapies are not novel ones. However, the methodological challenges tend to be more pronounced for the advanced therapies, which makes it relevant for stakeholders to revisit some classical methodological discussions about the evaluation of the clinical effectiveness and cost-effectiveness of pharmaceuticals and consider whether methodological adaptions might be warranted. The methodological discussions of relevance to advanced therapies centre mainly around four questions:

The first question is that of how to handle uncertainty regarding clinical effects. Due to small patient populations, a lack of control groups in clinical studies and uncertain long-time effects, the documentation of clinical effects and adverse effects for ATMPs is often characterised by great uncertainty. The uncertainties about the size and duration of clinical effects also introduce uncertainty in the evaluation of the cost-effectiveness of these treatments. Accordingly, HTA institutions and public decision-makers are faced with major challenges when they are to decide whether ATMPs offer reasonable value for money and forecast the budget implications of their introduction and take-up in clinical practice. There are no immediate methodological tools that HTA bodies can implement to effectively eliminate these uncertainties. However, methods exist that can reduce the risk of bias in clinical effectiveness evaluations, which rest on observational data. In addition, methods exist that can be used to systematically examine and present the uncertainties for decision-makers. The Danish Medicines Council provides a detailed account of the requirements for the use of these methods in its revised methods guidelines. The ability of national HTA bodies and decision-makers to re-quire a certain level of clinical documentation also depends on regulatory processes at the EU level. When new therapies are granted a conditional marketing authorisation by the European Medicines Agency (EMA), it also puts pressure on national bodies to accept preliminary documentation of clinical effects and adverse effects. Therefore, the methodological requirements made at the national level should not be considered isolated from regulatory developments at the supranational level.

The second question is whether productivity costs and benefits should be included in health economic evaluations of new therapies. Therapies that are administered early in life and can be expected to have long-lasting effects, like some gene therapies, are likely to be particularly sensitive to the choice of whether to include productivity effects. The Danish Medicines Council adopts a 'limited societal perspective' in its economic evaluations. This means that all health-related costs and benefits are included, irrespective of where they fall (e.g. effects on home nursing, general practitioner services, specialised healthcare services or caregiver resources), while productivity effects are not included. There is no conclusive methodological answer as to which analytical perspective to adopt in health economic evaluations. This is an analytical choice, which also reflects societal values, including ideas about equality, since the inclusion of productivity effects might discriminate against people who are not part of the workforce (e.g. due to old age). The methodological

discussion therefore links to questions about political priorities. The methods guidelines of the Medicines Council do not explicate the reasons for the choice of analytical perspective, making it difficult for external parties to discern which rationales and values inform the evaluations.

The third question is whether and how other types of treatment effects than the prolongation and quality of life should be considered in health economic evaluations. Again, this question involves not only methodological considerations but also raises questions about political priorities. When treatment effects are measured as quality-adjusted life-years (QALY), the ability of treatments to influence the longevity and quality of life is taken into account. Yet public decision-makers may also find it relevant to consider other types of treatment effects. In relation to ATMPs, the question has been raised whether priority should be given to innovative treatments that represent new treatment principles or are targeted particularly rare or severe conditions – which also raises questions about how to define and operationalise criteria such as 'innovativeness', 'rarity' and 'severity'. In relation to these considerations, it is also important for stakeholders to reflect on how such criteria are to be applied in the evaluations. Criteria, like rarity or severity, may be integrated into the economic evaluation (e.g. as QALY modifiers), expressed as differentiated cost-effectiveness thresholds or taken into account in a deliberative process. Each approach has its pros and cons. Internationally, there are examples of disease severity being operationalised in health economic evaluations in ways that favour end-of-life treatment. Potentially, this practice discriminates against treatments that are administered early in life and can be expected to have long-lasting effects. In Denmark, the Medicines Council can take into account a principle of 'severity' in the evaluation of new treatments. This principle is not integrated into the economic evaluation methods but can be considered in the deliberative processes of the Council. Due to a very broad definition, the principle is open to considerable interpretive flexibility.

The fourth question is how to handle the fact that it may take a long time for treatment benefits of some ATMPs to arise. In health economic evaluations, future effects are often discounted based on two assumptions: 1) that decision-makers and citizens prefer benefits to occur as early as possible and to pay for them as late as possible, and 2) that consumption is expected to grow over time (positive wealth effect). The practice of discounting can make it more difficult for preventive and long-lasting treatments to demonstrate benefits compared to treatments that provide immediate health benefits. Stakeholders may therefore consider whether current practices of discounting should be revised. Questions to consider include whether the same or differential discounting rates should be applied for costs and benefits, and which rationales should guide the level of the rate to be applied. The current practice of the Medicines Council is to apply the same discounting rate for costs and benefits (3.5%). The rate follows the general discounting rate defined by the Ministry of Finance. The rationale guiding the choice of discounting rate is not explicated in the methods guideline of the Medicines Council.

Financing

The introduction of ATMPs requires high upfront investments by the healthcare systems. Payments for medicine are typically to be made at treatment onset. In the case of one-

time treatments, the price per dose is considerably higher than for other types of treatment, and the payer is not able to recover the costs should the treatment not work as intended. Moreover, it often requires considerable infrastructural investments before the first patient can be treated (e.g. investments in new equipment, special storage capacity, the development of new procedures, staff education and certifications). In principle, these challenges are not new to public decision-makers. However, the known challenges are intensified because of the high budget implications and late manifestation of treatment benefits for some types of ATMP. Three main questions arise against the backdrop of these challenges:

The first question is which criteria are to guide the decisions of public authorities to enter into negotiations about managed entry agreements (MEAs). MEAs refer to agreements in which a manufacturer and a payer/procurer define conditions that can help manage uncertainty about the effectiveness and/or budget implications of a new treatment. Multiple kinds of MEAs exist, which can help address various types of decision uncertainties and which are more or less demanding to manage in practice. Hence, it is pertinent for stakeholders to consider which type of agreements are suitable in which cases. In Denmark, most experience has been obtained with MEAs that address uncertainty about budget implications. A model for reimbursement with evidence generation has recently been agreed upon by the regional authorities. It will enter into force by January 2022. Initial experience has been gained with performance-based payment. Performance-based payment implies that the payment for a given treatment is conditional on the ongoing documentation of pre-defined treatment effects.

The second question is whether the budget implications for payers and providers may become so extensive that it might reduce the introduction of new cost-effective treatments. The prospect of an increase in the number of marketed ATMPs can prompt considerations about the division of financial responsibility between political-administrative levels of management. In Denmark, the regional authorities have so far been able to secure access to the ATMPs that have been recommended as standard treatment by the Danish Medicines Council. There is one historical example of the central government authorities issuing a guarantee to the regional authorities that pharmaceutical expenses that exceeded the allocated budget would be covered by state funds. However, a similar guarantee of coverage has not since been granted by the centralised government authorities, signalling that pharmaceutical expenses constitute part of the regional healthcare budgets on par with other types of expenses. Hence, stakeholder considerations about potential co-funding of ATMPs or other high-cost treatments by state funds also prompt questions about which is the appropriate political-administrative level at which priorities among various types of healthcare services are to be made.

The third question concerns which options public authorities may employ to influence the pricing of new high-cost treatments, like ATMPs. In Denmark there is no tradition for direct price regulation of pharmaceuticals. Instead, agreements made between the pharmaceutical industry association, the Ministry of Health and the regional authorities place certain limits on the pricing of newly marketed pharmaceuticals. In addition, a Nordic collaboration among public procurement organisations has been established to explore options for joint procurement agreements. The expectation is that increasing the market size may allow rebates to be more easily negotiated. At the EU level, the pricing of new pharmaceuticals

can be affected indirectly by the regulation of intellectual property rights because of the impact on market competition. Accordingly, it can be relevant for stakeholders to explore possibilities of reducing economic barriers for accessing the market for ATMPs. For instance, it might be possible to establish leasing or royalty models for the use of the technology platforms that are used in the development of new gene therapies.

Organisation

The implementation processes for ATMPs in Denmark resemble those of other highly specialised treatments: the regional authorities are responsible for ensuring the capacity, education and other resources that are necessary to introduce new treatments. The main challenges for the public authorities are that new treatments are being introduced at a high pace and that ATMPs come with complex supply chains and monitoring requirements. The complexity of ATMP treatment places great infrastructural demands on the healthcare system. Two main questions appear pertinent for stakeholders to consider:

The first question is to what extent the requirements for quality control and certification processes can be harmonised to reduce the resource demand for hospitals and provide for less complex negotiations of procurement agreements among manufacturers and healthcare payers. The requirements arise at different levels: some relate to EMA regulation, others to national legislation and others again to specific manufacturers. Any harmonisation attempts should therefore take into account considerations of how product-specific requirements that are regulated through contracts between manufacturers, payers and providers can be distinguished from more general requirements that can be addressed through national or supranational regulation.

The second questions is to what extent the existing data infrastructure and data legislation can support the diagnostic practices that are necessary to introduce new gene therapies and follow up on clinical effects of ATMPs more generally. If gene therapies are to be administered before the onset of symptoms, it calls for consideration about how more widespread screening for hereditary diseases may be organised and which dilemmas may raise. As gene sequencing become a more widespread practice, this also raises questions about the rationales guiding particular regulatory principles. For instance, it becomes uncertain how the regulatory distinction in Danish law between 'wet' data (biological material) and 'dry' data (information) should be interpreted: Do the 'wet' data 'dry up' as a consequence of gene sequencing? In addition, the assumption that health data is information about individuals (who hold individual rights) is challenged by more widespread use of genetic data, which can also convey information about the disease risk of patients' relatives. Finally, if MEAs are to be used on a larger scale, stakeholders are advised to explore the practical and regulatory opportunities and challenges related to the repurposing of patient data to inform MEAs, including considerations about the quality of data and patients' self-determination.

English and Swedish experiences and developments

In both England and Sweden, public authorities have acted proactively to explore whether existing principles and practices for the evaluation of new treatments are suitable in light of the challenges raised by the development of precision medicine, including ATMPs. Neither country plans to make fundamental changes of the methods used by HTA bodies to

evaluate new therapies, but both are considering some general adjustments that are of relevance to – but not exclusive for – ATMPs.

In England, an existing practice of the National Institute for Health and Care Excellence (NICE) is to apply different evaluation programmes (with different methods and criteria) for different kinds of medical technologies. Of particular relevance to ATMPs is the evaluation programme for highly specialised treatments, which is targeted at treatments for very rare diseases. In this evaluation programme, exemptions from the use of standard economic evaluation methods can be made, and higher costs per QALY can be accepted if the QALY gain is of a particular size. Some of the new gene therapies have qualified for evaluation in the highly specialised treatments programme. In Sweden, the national HTA body, Tandvårds-Läkemedelförmånsverket (TLV), do not plan to introduce differentiated evaluation programmes.

In both England and Sweden, the national HTA bodies explore options for introducing new methods that can be used to systematically examine and quantify decision uncertainties.

In England, a general methods review undertaken by NICE has led to a proposal to replace the use of a QALY modifier that gives particular priority to end-of-life treatment with another QALY modifier for severe diseases that does not discriminate against treatments administered early in life. In Sweden, higher cost-effectiveness thresholds are applied for particularly severe diseases. Decisions about when to apply these higher thresholds are made through deliberation.

In both England and Sweden, the methods reviews have addressed the issue of discounting. In England, a general lowering of the discount rate from 3.5% to 1.5% is being considered, while no changes in the discounting rate appear to be under way in Sweden.

In England, considerable experience has been obtained with the use of MEAs. In particular, MEAs have been used for cancer treatments, owing to the setting up and revision of the national Cancer Drug Fund (CDF), which provides earmarked funding for new cancer treatments during a managed access period. In August 2021, it was decided to extend the CDF to include also earmarked funds for 'innovative medicines' beyond cancer care. MEAs have been made for several of the new gene and cell therapies that are being introduced into the English healthcare system. Typically, MEAs are considered if the manufacturer can make probable that substantial decision uncertainties can be addressed within a limited time horizon (max five years) and has made a price suggestion that makes it possible for NICE to recommend the treatment as standard treatment after the managed access period (given that the uncertainties are addressed). In the experience of NICE, it is challenging to withdraw reimbursement for treatments when the decision uncertainties are not addressed in a satisfactory manner.

In both England and Sweden, there is limited experience with the use of performance-based payment. In England, it is the experience of NICE that these agreements are difficult to manage in practice. In Sweden, the first performance-based agreement is being negotiated during the autumn of 2021. The agreement concerns the gene therapy onasemnogene abeparvovec-xioi (Zolgensma).

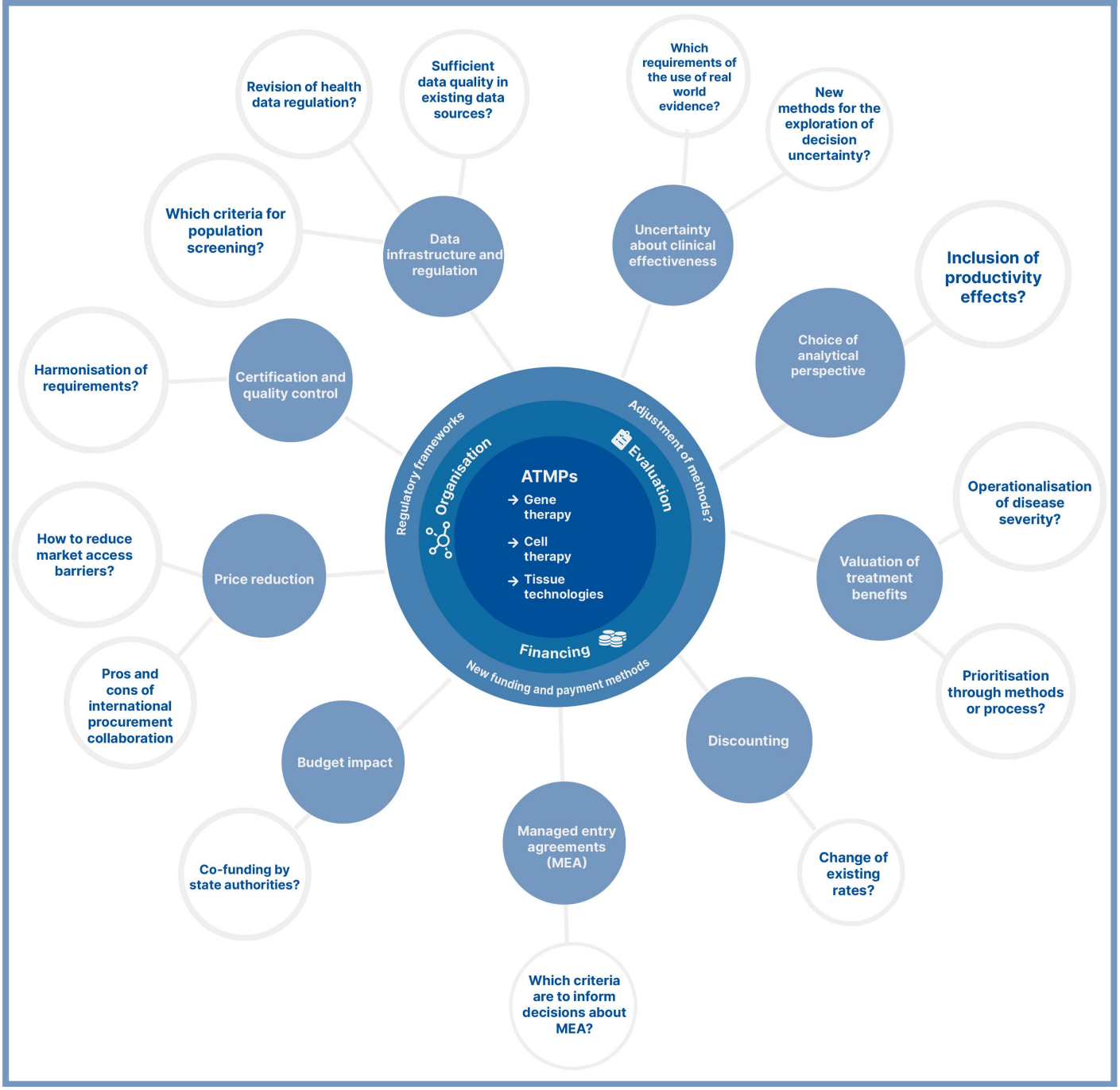
While highly specialised and high-cost treatments, like ATMPs, are typically funded at the national level in England, the funding responsibility is more decentralised in Sweden. In Sweden, public debate has been raised about the risk of geographical inequality in treatment access related to the centralised model for the delivery and financing of highly specialised healthcare.

England and Sweden both invest in capacity and healthcare infrastructure that is necessary to introduce and undertake treatment with ATMPs. In England, designated Centres of Excellence have been appointed through a nationally coordinated process, while there appears to have been some challenges to ensuring national coordination in Sweden. Some underestimation of the need for treatment capacity in England might have caused some slow-down of the take up of new ATMPs.

In both countries, a need to ensure better data quality and opportunities for combining data sources is identified to support post-marketing monitoring of clinical effects. Initiatives have been made in both countries to review existing regulation of health data.

The figure below sums up central themes and questions related to the evaluation, financing and organisation of ATMP treatment, which we suggest stakeholders to consider and debate.

Themes and questions to be discussed by stakeholders during the development of solutions to challenges related to the evaluation, financing and organisation of treatment with advanced therapies.



Sammenfatning

Den videnskabelige og teknologiske udvikling på det medicinske område baner i stigende grad vejen for nye typer behandlinger, herunder nye gen- og celleterapier samt vævsteknologier. Disse nye typer behandlinger er kendetegnet ved, at de består af biologisk materiale, som er blevet modificeret med henblik på at opnå en funktion hos patienten, som vil erstatte manglende funktion eller reparere sygdomsgivende dysfunktion. Ofte er der tale om engangsbehandlinger, som har til formål at bremse sygdomsudvikling i et tidligt stadie og/eller øge kroppens muligheder for at reparere sig selv. Håbet er, at behandlingerne har langvarige, sygdomsmodificerende effekter og potentielt kan erstatte behov for kontinuerlig behandling. I nogle tilfælde udgør de nye lægemidler også behandlingsmuligheder for patienter, som ikke tidligere har haft udsigt til behandling.

Imidlertid kommer de avancerede terapier også med en række udfordringer. Det er forbundet med høje startomkostninger for det offentlige sundhedsvæsen at tage de nye behandlinger i brug, fordi prisen pr. dosis er høj sammenlignet med andre lægemidler, og fordi det er nødvendigt at investere i infrastruktur (fx udstyr og opbevarings- og behandlingskapacitet). Ofte er der betydelig usikkerhed om behandlingernes kliniske effekter og bivirkninger – særligt langtidseffekterne. Endelig stiller de nye terapier andre krav til logistik, kvalitetskontrol og infrastruktur end mange andre typer lægemidler. For offentlige beslutningstagere kan det skabe udfordringer med at sikre passende evalueringsmetoder, holdbare finansieringsmodeller og organisatoriske rammebetingelser, som sikrer, at behandlingerne kan leveres i praksis. Disse udfordringer stiller krav til lægemiddelproducenter, offentlige myndigheder og indkøbere om at udvikle løsninger.

Formålet med denne rapport er at kortlægge og diskutere de evalueringsmæssige, finansieringsmæssige og organisatoriske udfordringer og muligheder, som gen- og celleterapier samt vævsteknologier giver anledning til, når de introduceres i det danske sundhedsvæsen. På den baggrund skal rapporten understøtte vidensbaseret dialog mellem interessenter på lægemiddelområdet om mulige løsningsforslag og eventuelle behov for yderligere undersøgelser. Derudover perspektiveres der til svenske og engelske erfaringer med introduktion af avancerede terapier. Sverige og England er valgt, fordi der er en række politiske og organisatoriske lighedspunkter med Danmark, som kan gøre det lettere at overføre erfaringer, samtidig med at de to lande har haft en proaktiv tilgang til at afdække udfordringer og mulige løsninger for introduktion af avancerede terapier, som Danmark potentielt kan lære af.

Det har været uden for rammerne af denne rapport at lave en selvstændig afdækning af etiske og juridiske problematikker. Etiske og juridiske problematikker berøres kort i forbindelse med afdækningen af de evalueringsmæssige, finansieringsmæssige og organisatoriske udfordringer. Det falder uden for rapportens rammer at komme med anbefalinger til konkrete løsningsforslag. Derimod kommer vi med anbefalinger til temaer, som med fordel kan diskuteres af interessenterne på lægemiddelområdet.

Afdækningen bygger fortrinsvis på litteraturgennemgang. Derudover er der gennemført ni ekspertinterviews med klinikere, regionernes indkøbsorganisation Amgros, Lægemid-

delindustriforeningen, Danske Regioner samt forskere og evalueringsinstitutioner i England og Sverige, som supplerer litteraturgennemgangen med opdateret viden om eksisterende praksisser vedrørende evaluering, indkøb, finansiering og organisering af behandling med avancerede terapier i Danmark, Sverige og England.

Evaluering

De evalueringsmæssige udfordringer, som avancerede terapier giver anledning til, er ikke nye problemstillinger. Udfordringerne kommer dog ofte og tydeligt til udtryk for disse typer behandlinger. Det gør det relevant for interessenterne på lægemiddelområdet at genbesøge nogle klassiske metodiske diskussioner om evaluering af lægemidlers effektivitet og omkostningseffektivitet – og overveje, om der er behov for metodiske tilpasninger. De metodiske diskussioner drejer sig særligt om fire spørgsmål:

Det første spørgsmål er, hvordan man kan håndtere usikkerhed om behandlingernes kliniske effekter, som er relateret til små patientpopulationer, fravær af kontrolgrupper i kliniske studier og ukendte langtidseffekter. Evalueringen af avancerede terapier vil typisk være præget af stor usikkerhed om effektstørrelser og -varighed samt bivirkninger. Disse usikkerheder om kliniske effekter skaber afledt usikkerhed om behandlingsomkostningerne. Det gør det vanskeligt for evalueringsinstitutioner og beslutningstagere at vurdere, om en ny behandling giver en rimelig værdi for pengene, og hvordan de offentlige sundhedsbudgetter vil blive påvirket af behandlingen. Der findes ikke metodiske løsninger, som kan fjerne disse usikkerheder. Der er dog metoder, som kan reducere risikoen for fejltolkninger ved effektanalyser, som bygger på observationelle data, og metoder, som kan bruges til at undersøge og præsentere usikkerhederne for beslutningstagere. Medicinrådet redegør detaljeret for brugen af disse metoder i dets nyeste metoderetningslinjer. Spørgsmålet om håndtering af usikkerhed om kliniske effekter er også relateret til de dokumentationskrav, som stilles i forbindelse med markedsføringsgodkendelse af nye lægemidler på EU-niveau. Da muligheden for at håndhæve nationale dokumentationskrav påvirkes af overnationale krav, må disse drøftes i sammenhæng.

Det andet spørgsmål er, hvorvidt arbejdsmarkedseffekter skal regnes med i de sundhedsøkonomiske analyser. Dette vil have særlig betydning for behandlinger, som gives tidligt i livet og kan forventes at have langvarige effekter, såsom nogle af de nye genterapier. Medicinrådet anvender et begrænset samfundsperspektiv i dets sundhedsøkonomiske analyser. Det indebærer, at alle sundhedsrelaterede udgifter og gevinster medregnes, uanset om de falder inden for det regionale sundhedsvæsen eller andre sektorer, men at arbejdsmarkedsrelaterede effekter og omkostninger ikke regnes med. Der er ikke noget entydigt metodisk svar på, hvilke typer udgifter og gevinster, der skal medtages i en sundhedsøkonomisk evaluering. Det er analytiske valg, som også afspejler samfundsværdier, herunder bestemte opfattelser af lighed, fordi valget af metode kan stille nogle patientgrupper bedre eller dårligere end andre. Denne diskussion kalder derfor på politisk prioritering. I medicinrådets metoderetningslinjer er der ikke givet begrundelser for, hvorfor bestemte typer omkostninger og gevinster skal in- eller ekskluderes i den sundhedsøkonomiske analyse. Dermed er det vanskeligt for udenforstående at gennemskue, hvilke samfundsværdier der ligger til grund for de metodiske valg.

Det tredje spørgsmål er, hvorvidt og hvordan der skal tages højde for andre typer behandlingsgevinster end livslængde og livskvalitet i de sundhedsøkonomiske analyser.

Igen kalder dette spørgsmål ikke blot på metodiske overvejelser, men også på politisk prioritering. Når behandlingsgevinster opgøres via kvalitetsjusterede leveår (QALY), tages der kun højde for effekter på livslængde og livskvalitet. Der kan imidlertid også være andre typer værdi, som beslutningstagere i det offentlige sundhedsvæsen finder det relevant at tage hensyn til. I relation til de avancerede terapier er der rejst diskussion om, hvorvidt der skal gives særlig prioritet til innovative lægemidler, som baner vejen for nye behandlingsprincipper, eller som er målrettet særligt sjældne eller alvorlige tilstande. Det rejser afledte spørgsmål om, hvordan kriterier for 'innovation', 'sjældenhed' og 'alvorlighed' i praksis kan operationaliseres og indgå i evalueringsprocesserne. Der er forskellige fordele og ulemper ved at lade kriterierne indgå som en integreret del af den sundhedsøkonomiske analyse (fx via QALY-vægte), definere forskellige grænseværdier for betalingsvilje eller tage hensyn til kriterierne i en åben diskussion mellem interessenter (deliberativ proces). I nogle sundhedsøkonomiske evalueringer operationaliseres sygdomsalvor på en måde, som favoriserer behandlinger, der gives til patienter, som har kort restlevetid. Dermed diskrimineres behandlinger, som gives tidligt i livet. Medicinrådets alvorlighedsprincip er ikke operationaliseret på en måde, så det kan indgå i sundhedsøkonomiske analyser. Den brede definition giver mulighed for stor fortolkningsfleksibilitet i rådets beslutningsprocesser.

Det fjerde spørgsmål er, hvordan man metodisk skal forholde sig, når der går lang tid, fra et lægemiddel gives, til gevinsterne opstår. I sundhedsøkonomiske evalueringer nedskrives værdien af fremtidige effekter (diskontering) ofte ud fra en antagelse om, at beslutningstagere og borgere foretrækker at få behandlingsgevinster her og nu og at betale for dem senere. Denne praksis kan stille forebyggende og langsigtede behandlinger ringere end behandlinger, som giver helbredsgevinster på den korte bane. Det er særligt en udfordring for nye genterapier, hvor der både er forventninger om langvarige effekter og høje startomkostninger. Det kalder på overvejelser om, hvorvidt der skal benyttes forskellige diskonteringsrater for effekter og omkostninger, og hvordan raten skal fastlægges. Medicinrådet benytter samme diskonteringsrate for gevinster og omkostninger (3,5 %). Raten følger Finansministeriets samfundsøkonomiske diskonteringsrate. Medicinrådets retningslinjer giver ingen begrundelse for valget af diskonteringsrate.

Finansiering

Introduktionen af nye avancerede terapier kræver høje startomkostninger i det offentlige sundhedsvæsen. Dels fordi der skal betales for hele behandlingen ved opstart, når der er tale om engangsbehandling; dels fordi det kan kræve investeringer i udstyr, opbevaringskapacitet, udvikling af procedurer samt certificeringer og uddannelse, før patienter kan behandles. Principielt afspejler disse finansielle udfordringer heller ikke nye udfordringer for offentlige beslutningstagere. Men udfordringerne forstærkes ved, at budgetkonsekvenserne er ganske høje sammenlignet med andre typer lægemiddelbehandlinger, og at gevinsterne først kan forventes flere år efter behandlingen. Det rejser tre spørgsmål.

Det første spørgsmål er, hvilke kriterier der skal guide beslutninger for offentlige indkøbere og producenter om at indgå forhandlinger om 'managed entry agreements'. Managed entry agreements henviser til aftaler, hvor producent og indkøber fastsætter betingelser, som skal bidrage til at håndtere usikkerhed om et lægemiddels effektivitet og/el-

ler budgetkonsekvenser. Der findes forskellige aftaletyper, som kan adressere forskellige typer beslutningsusikkerhed, og som er mere eller mindre krævende at implementere i praksis. For offentlige beslutningstagere kalder det på overvejelser om, hvilke aftaletyper der er velegnede i hvilke tilfælde. I Danmark er der fortrinsvis opnået erfaring med aftaletyper, som adresserer usikkerhed om budgetkonsekvenser. En model for ibrugtagning med evidensproduktion er netop blevet vedtaget af Danske Regioner. Modellen træder i kraft fra januar 2022. Der er begyndende erfaring med aftaler om resultatbaseret betaling. Resultatbaseret betaling vil sige, at betalingen afhænger af, om prædefinerede behandlingseffekter opnås for enkeltpatienter eller grupper af patienter.

Det andet spørgsmål er, om budgetkonsekvenserne for regionerne og hospitalerne vil blive så store, at det kan begrænse optaget af nye omkostningseffektive terapier. Udsigten til en stigning i antallet af gen- og celleterapier samt vævsteknologier kan skabe overvejelser om, hvorvidt der skal etableres mulighed for statslig medfinansiering – og i så fald efter hvilke kriterier. Hidtil har regionerne formået at sikre adgang til de specialiserede behandlinger, som er blevet anbefalet af Medicinrådet, inden for de eksisterende budgetrammer. Historisk har der været et eksempel på en statslig finansieringsgaranti på lægemiddelområdet, men signalet fra centralforvaltningen har siden været, at lægemiddeludgifter skal indgå i de regionale budgetter på linje med andre sundhedsudgifter. Overvejelserne om en eventuel statslig medfinansiering involverer derfor også spørgsmål om, hvor det politiske prioriteringsansvar placeres.

Det tredje spørgsmål er, hvilke muligheder der kan være for at påvirke prissætningen af nye lægemidler. I Danmark er der ikke tradition for direkte prisregulering af lægemidler, men aftaler mellem lægemiddelindustriforeningen, Sundhedsministeriet og regionerne sætter visse begrænsninger for prissætningen. Derudover indgår Danmark i nogle tilfælde indkøbsaftaler med andre nordiske lande for at skabe en bedre forhandlingsposition og dermed øge muligheden for at opnå rabatter. På EU-niveau kan prissætningen indirekte påvirkes gennem reguleringen af intellektuelle ejendomsrettigheder, fordi det påvirker mulighederne for konkurrence. Det kalder på overvejelser om, hvorvidt det er muligt at reducere økonomiske adgangsbarrierer for at træde ind på markedet for nye avancerede terapier, fx ved at etablere muligheder for at lave 'lejeaftaler' eller aftaler om betaling af 'royalties' af fremtidig fortjeneste for brug af de teknologiplatforme, som bruges til udvikling af nye genterapier.

Organisering

Principielt adskiller implementeringsprocesserne for ATMP's sig ikke fra indførelsen af øvrig højt specialiseret behandling: De enkelte regioner har ansvar for at sikre kapacitet, uddannelse og øvrige ressourcer til at igangsætte og skalere behandlingen. Udfordringen for offentlige beslutningstagere består i, at takten for introduktionen af nye behandlinger øges, og at de nye typer terapier kommer med særligt komplekse forsyningskæder og opfølgningsbehov, som stiller store krav til sundhedsvæsenets infrastruktur. Det rejser to spørgsmål.

Det første spørgsmål er, i hvilken udstrækning kravene til kvalitetskontrol og sikker håndtering af de nye terapier kan harmoniseres for at strømline certificeringsprocesser for hospitalerne og forenkle forhandlingen af indkøbsaftaler for offentlige indkøbere og producenter. De øgede krav til logistik, kapacitet og kvalitetskontrol kræver ressourcer

for både producenter og det offentlige sundhedsvæsen, og kravene introducerer ny kompleksitet ved forhandling af indkøbsaftaler. Kravene opstår på flere niveauer (EU, nationale og virksomhedsspecifikke krav). Det kalder på overvejelser om, hvordan produktspecifikke krav, som kræver særlige aftaler mellem producenter, offentlige indkøbere og hospitaler, kan adskilles fra mere generelle krav, der kan imødekommes via nationale eller overnationale certificeringer eller akkrediteringer.

Det andet spørgsmål er, i hvilken udstrækning den eksisterende datainfrastruktur og det juridiske rammeværk kan understøtte de diagnostiske praksisser, som er nødvendige for indførelsen af nye genterapier, og muliggøre opfølgning på kliniske effekter af avancerede terapier. Hvis behandling med genterapier skal iværksættes før symptomdebut, kræver det overvejelser om, hvordan screening for arvelige sygdomme kan foregå, og hvilke dilemmaer der kan være forbundet hermed. Genomsekventering rejser også spørgsmål om rationalet bag visse principper i sundhedslovgivningen, herunder et regulatorisk skel mellem 'tørre' og 'våde' data og en antagelse om, at sundhedsdata er individuel information. Derudover kalder brugen af managed entry agreements på overvejelser om, hvilke praktiske og regulatoriske muligheder og udfordringer der er forbundet med at genbruge eksisterende datakilder til opfølgning på indkøbsaftaler, herunder overvejelser om datakvalitet og patienters selvbestemmelsesret.

Erfaringer fra England og Sverige

I både England og Sverige er man i gang med at vurdere, om de eksisterende evalueringsmetoder og finansieringsmodeller kræver tilpasning i lyset af udviklingen mod personlig medicin, herunder introduktionen af nye avancerede terapier. I ingen af landene lægges der op til grundlæggende ændringer af evalueringsmetoderne, men der er forslag om mindre justeringer.

I England findes der forskellige evalueringsprogrammer, hvor der benyttes forskellige evalueringsmetoder og -kriterier. Eksempelvis er der et særligt evalueringsprogram for højt specialiserede behandlinger, som er målrettet meget sjældne sygdomme, hvor der kan afviges fra sædvanlige sundhedsøkonomiske evalueringsmetoder og accepteres højere omkostninger pr. QALY. Dette evalueringsprogram har været anvendt for visse nye genterapier.

I begge lande overvejes det at indføre nye metoder til at undersøge og kvantificere beslutningsusikkerhed. I England foreslås det at operationalisere alvorlighed på en ny måde, som ikke favoriserer behandlinger, der gives i afslutningen af livet. I England foreslås en generel nedsætning af diskonteringsraten fra 3,5 % til 1,5 %, mens en ændring af diskonteringsraten ikke er på tale i Sverige.

I England er der forskellige 'ruter' for markedsadgang. Hvis nye behandlinger ikke kan anbefales som standardbehandling, kan der i nogle tilfælde laves aftaler om 'managed access'. Dette har været tilfældet for nogle nye gen- og celleterapier. Lægemidler, som indføres via managed access-aftaler, finansieres via en øremærket, national pulje. Tidligere kunne denne pulje kun benyttes til kræftbehandlinger, men den er netop udvidet til også at dække andre typer 'innovative behandlinger'. Aftaler om managed access kan benyttes, hvis producenten kan sandsynliggøre, at væsentlige beslutningsusikkerheder kan afhjælpes inden for en begrænset tidshorisont (maksimalt 5 år) og har tilbudt en pris, som gør

det muligt at anbefale lægemidlet som standardbehandling, efter managed access-perioden ophører. Tilbagetrækning af behandlinger, hvor beslutningsusikkerheden ikke reduceres tilstrækkeligt, er en væsentlig udfordring ved disse typer aftaler.

I både England og Sverige er der erfaringer med at forhandle indkøbsaftaler, som skal fordele økonomiske risici mellem producent og offentlig indkøber. Evalueringsinstitutioner og offentlige indkøbere i England er tilbageholdende med at benytte effektbaseret betaling, fordi denne typer aftaler opleves som meget komplekse at administrere i praksis. Der er dog opnået nogen erfaring. I Sverige er den første aftale om effektbaseret betaling ved at blive forhandlet.

I Sverige er der ingen statslig medfinansiering af lægemidler, herunder avancerede terapier. Der er rejst offentlig debat om risici for geografisk ulighed i adgang til behandling, hvis den meget decentrale model for finansiering og levering af behandling fastholdes.

I både England og Sverige investeres der aktivt i kapacitet til at udbyde behandling med gen- og celleterapi samt vævsteknologier inden for det offentlige sundhedsvæsen. I England har der været en centraliseret tilgang med udpegning af Centres of Excellence, mens der i Sverige har været visse udfordringer med at sikre national koordination. Underestimering af kapacitetsbehov har muligvis været en flaskehals for udbredelsen af de nye terapier i England.

I begge lande fremhæver evalueringsinstitutioner og myndigheder et behov for at sikre bedre datakvalitet og mulighed for at kombinere datakilder for at understøtte diagnostiske praksisser og opfølgning på behandlingseffekter af nye avancerede terapier. Der er taget initiativer til at gennemse eksisterende regulering af sundhedsdata i begge lande.

Tematikker og spørgsmål som interessenter på lægemiddelområdet med fordel kan drøfte som led i udviklingen af løsninger på udfordringer med evaluering, finansiering og organisering af behandling med avancerede terapier

VIVE

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