Ethical concerns of accepting off-label use of *rituximab* for multiple sclerosis

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Preface

National Institute of Public Health commissioned an assessment of ethical implications of rituximab use of the treatment of MS, as a support to "*Disease-modifying treatments for relapsing remitting multiple sclerosis (RRMS), including rituximab. A health technology assessment. Tjelle TE, Rose C, Ohm IK, Pike E, Håheim, LL Bidonde J, Fretheim A, Juvet LK, Disease-modifying treatments for relapsing remitting multiple sclerosis, including rituximab. A health technology assessment. Report from Norwegian Institute of Public Health, Folkehelseinstituttet, Oslo, June 2019"*.

This document was provided to meet the commission.

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Summary

In this document, the ethical concerns of accepting use of the off-label drug rituximab in treating multiple sclerosis, are presented and analysed. A structured framework for ethical analysis is used to present available evidence, clarified consequenses for concerned parties, identified conflicts of interests and ethical principles, pointed at areas that need clarification, and highlighted ethical trade-offs. In order to respond to the question: "*Is it ethically acceptable to include the off-label drug rituximab as a treatment option for MS?"*, decision makers need to decide whether it is ethical acceptable to 1) only accept RCT-evidence for effect and safety; 2) deviate from existing regulation of marketing authorization; 3) restrict the use of rituximab to assure that the pharmaceutical industry has incentives to develop innovations in the future; and 4) not save substantial costs, if that can be done without lowering the health level of MS-patients. The legitimacy of the decision-making process is not evaluated in this document.

Objective

The aim of this chapter is to identify and assess ethical dilemmas and principled value trade-offs by using an off-label drug, rituximab, in the treatment of multiple sclerosis.

Background

Multiple sclerosis (MS) is a complex and multifaceted disease, as is its treatment. For both patients, clinicians1 and the health authorities it is challenging to get an evidence-based overview of treatment options and potential burdens and benefits of the various drugs. Also, around 4% of the total drug-budget in Norway is for MS-medication2, which leads to public interest to ensure that these resources are used in an efficient and fair way. Careful and continuous evaluation of treatment alternatives are therefore necessary.

Bestillerforum commissioned the National Institute of Public Health to prepare a health technology assessment (HTA) on MS-treatments, including rituximab, which is currently used off-label for this indication. The mandate was to compare the effect, safety and cost-effectiveness of these disease-modifying medicines used for MS in Norway. Part of the mandate was to

[1] In this chapter, we use "clinician" for describing the group of medical experts, neurologists, prescribing doctors, physicians, or clinical professionals.
[2] The last available published data we found are from 2016 when costs for inhospital and «h-resept» for MS-drugs were 833 792 000 (Helsedirektoratet. Kostnader til legemidler i helseforetak. Analysenotat 1/2018SAMDATA spesialisthelsetjenesten. https://www.helsedirektoratet.no/search?searchquery=legemiddelkostnader%2020162018 p. Page 24-25) while the total public budget for drugs was 18,2 billions (https://www.apotek.no/fakta-og-ressurser/statistikk-for-2016)

evaluate legal and ethical aspects of using an off-label drug for an indication where registered drugs are available.

Off-label use means that the drug has been approved for use, but does not have market-authorisation for the specific disease in question (in this case MS). Medicines are used off-label on a daily basis in the health care system, e.g. for patient groups where there are no approved drugs available (2). Legally, off-label use is not a problem, as clinicians are allowed to prescribe a marketed drug for unapproved use, if they assess that it is medically relevant for their patient. However, controversies and practical challenges may arise when other well-documented and effective medicines with market authorisation are available for the given indication.

Rituximab is a well-known drug in use for several other indications than MS, including off-label use for various other diseases. As the patent for rituximab has expired, there is little financial incentive in investing in the clinical studies that would be needed for rituximab to be approved for MS. An increasing proportion of MS-patients in Norway are now using rituximab, so there is a need to clarify the status of the drug.

In the public discussions on use of rituximab as MS-treatment several areas of disagreement have emerged. Controversies concerned issues like whether we can accept a drug without evidence on effect and safety from randomised controlled trials (RCT) with MS-patients, various questions considering resource-use and fairness issues, questions concerning how to respect patient autonomy, and challenges in shared decision-making. Various stakeholders have diverging views in these questions. Representatives from the pharmaceutical industry do not support use of rituximab for the treatment of MS, unmistakably stated through their withdrawal of funds and supports for conferences and travels for clinicians and researchers when it became clear that rituximab was being prescribed by Norwegian clinicians (1). Clinicians express diverging views on issues like the effectiveness and safety of rituximab. They also discuss the consequences that accepting rituximab will have for the pharmaceutical industry, future innovation of new drugs, as well as the governments´ economical motives. In these disputes, clinicians´ bindings to the pharmaceutical industry has been pointed at, leading to questions about impartiality and self-interest. While the patient-organization has expressed reservations about the use of rituximab and has questioned whether this is only to save money, many patients want rituximab, and even shift from the hospital where they get their treatment in order to be treated by clinicians who prescribe it. In such a complex and demanding situation, systematic evaluation and clarifications of ethical issues and trade-offs can help guide a discussion about what is at stake, which can illuminate acceptable solutions or options.

Method

In this chapter, a stepwise model for ethical case analysis was used, building on Kymlica's ethical case analysis, and further described by Miljeteig et al (2). A similar method is used by clinical ethics committees in Norway. The seven-step analysis relies upon systematic evaluation of an identified ethical dilemma and is used as a tool for a more transparent, explicit, and less-partial analysis. It is particularly suited for priority-setting dilemmas, with emphasis on interests at stake and outcomes for the affected stakeholders.

By responding to seven structured questions (Box 1), the available evidence, clarified options for concerned parties, identified conflicts of interests and ethical principles, pointed at areas that need clarification, and highlighted the trade-offs are assessed. Conclusion is not provided in this document.

Background information was collected from literature review, participation in meetings with clinicians and the NIPH-project group, public meetings with clinicians and pharmaceutical industry representatives, interviews with clinicians and patient representatives, and published material in the mass media. Evaluation of the legitimacy of the decision-making process was not the objective for this chapter, and was not conducted.

Gather information. If insufficient information, ask for more.

Step I: What is the ethical dilemma, and what are alternative actions?

Step II: What do we know about the outcomes of alternatives?

Step III: What laws, rules or guidelines regulate the decision?

Step IV: Who are the involved stakeholders?

Step V: What are the stakeholders' potential burdens and benefits?

Step VI: What and who´s interests are in conflict?

Step VII: What are the values and principles at stake?

Discuss what is most important in the case; clarify trade-offs and suggest acceptable solutions.

*B**ox 1:** The 7-step method of ethical analysis*

Results

The steps in the ethical analyses described under Methods are presented below.

Step I: What is the ethical dilemma, and what are alternative outcomes?

The main ethical dilemma in this problem is:

Is it ethically acceptable to include the off-label drug rituximab as a treatment option for MS?

Alternatives outcomes are: (1) Yes, rituximab should be provided as MS-treatment; and (2) No, it should not be provided as MS-treatment

Step II: What is the evidence for the alternative outcomes?

In this step of the analysis outcomes are evaluated. The effectiveness, safety and costs of rituximab and other MS-drugs are presented in detail in a separate report by the Norwegian

Institute of Public Health (NIPH).[3] What became explicit when reviewing the evidence presented in the report, and the background information, were the two main areas of disagreement concerning possible outcomes, namely: a) The quality of the study design and the level of evidence of effect and safety of rituximab used as treatment for MS-patients and b) Effect of accepting off-label drug like rituximab on innovation and the industry´s investment in research and development of new and better drugs.

What is the quality of the study design and the level of evidence of effect and safety of rituximab used as treatment for MS-patients?

Sufficient evidence provided through one or more RCTs is required for market authorisation of a drug (3). In the following section, we will focus on scientific reasoning more than the standard requirements. The first question then activates an epistemological discussion of our understanding of evidence and claims for documentation behind recommendations and financing.

Among the clinicians, the industry and the government there is disagreement on the trustworthiness of evidence not provided through a RCT. While there are several RCTs for the various MS-drugs on the market, there is only one, small RCT for rituximab (4). However, rituximab has been studied in non-randomised studies (NRS), e.g. data collected from MS-registries or patients' charts.

Some clinicians and the industry claim that a study without control group through randomisation cannot be trusted as there are too many factors that can influence the results and are not properly controlled. This view refers to the international agreed requirement that RCTs provides the gold standard of evidence, as the study design allows more control on confounding factors (5), and which is the most accepted way to study causality between intervention and outcome.

The clinicians who recommend and prescribe rituximab argue that there is good and trustworthy evidence on effect and safety from the registry studies conducted in Sweden. They highlight the importance of long follow up-time, the notion that there is less drop-out for rituximab users than for other drugs, the fact that more than 10 000 patients in Sweden are on rituximab and that the use has been patient-driven[4]. In addition, they refer to challenges with the RCTs on approved drugs, as short follow-up, lack of treatment alternatives for patients at certain study sites, the bias in industry driven trials, accumulating evidence of serious adverse effects that are not captured by the RCTs, and narrow patient inclusion criteria, questioning if the RCTs represents the crude MS-population in Norway.

Is it possible to conclude on the question on quality of the study design and the level of evidence of effect and safety of rituximab used as treatment for MS-patients? To do so is beyond the scope of this analysis, but in the decision on accepting rituximab as a standard treatment, the decision makers have to consider these diverging views and argue for their decision.

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[3] Disease-modifying treatments for relapsing remitting multiple sclerosis, including rituximab. A health technology assessment. Report from Norwegian Institute of Public Health, Folkehelseinstituttet, Oslo, June 2019

[4] Presented by professor Anders Svenningsson at public meeting October 24th 2018

Will acceptance of an off-label drug like rituximab reduce innovation and decrease the industry´s investment in research and development of new and better drugs?

The pharmaceutical industry has argued that acceptance of rituximab can lead to less innovation since the incentives for developing and testing new medications with the necessary profit may decrease. The argument for this statement is that there will be uncertainty in prospects of future income when developing a new drug, if a competing off-label drug exists and might be accepted. New drugs are rarely more cost-effective than existing off-patent drugs, unless their effectiveness is substantially higher. Our society depends on the willingness of the industry to invest in research and development, and it is potentially very harmful if their ability to innovate new drugs is reduced. Evaluating the evidence of this potential harmful outcome is crucial.

Unfortunately, we could not find any publications on MS-drugs, costs for research and development and possible consequences on: a) distrust in the regulatory body/government; and b) reduced income from sale of other drugs. But there is some available documentation from the cancer-field, which might illuminate the field of interest.

In a recent JAMA publication Tay-Teo *et al* (6) compare sales income and research and development costs for FDA-approved cancer drugs and show that the median cumulative sales income was USD14,5 per dollar invested in research and development. The authors claim that cancer drugs, through high prices, have generated returns to the pharmaceutical companies in far excess of research and development costs. Further, they conclude that lowering prices of cancer drugs and facilitating greater competition is essential for improving patient access, health systems' financial sustainability, and future innovation. Other studies describe how some companies are using what they call a "de-risking strategy" by duplicating and pursuing marginal indications, expecting that the market would continue to bear the high prices irrespective of the magnitude of benefits in the name of innovation (7-9). Tay-Teo *et al* conclude that in the long term "such distortion of incentives and investment may stifle clinically meaningful innovation" (6).

Contrary, for example Moreno and Epstein (9), employed at Novartis Pharma, claim that less income will lead to prize escalation caused by a profitability race between companies. They argue that deviation from value-based pricing principles and less certainty on future profit will distort access by firms to capital and lead to an undesirable level of innovation in the long term.

Is it possible to conclude on the question if the use of an off-label drug like rituximab reduces innovation and decreases the industry´s investment in research and development of new and better drugs? Due to the lack of evidence it is not. More information is needed to clarify the outcomes for innovation strategies and effect of accepting off-label drugs when other drugs have market authorization for the indication.

Step III: What laws, rules or guidelines regulate the decision?

In the chapter "Legal aspects" in the NIPH-report, relevant laws and legal regulations are presented and discussed.[5] Adherence to established laws and regulations are fundamental in a

[5] Disease-modifying treatments for relapsing remitting multiple sclerosis, including rituximab. A health technology assessment. Report from Norwegian Institute of Public Health, Folkehelseinstituttet, Oslo, June 2019

democratic society and if the government does not follow these regulations, it leads to challenges that are discussed more in detail in that report. Violations of established regulations also imply other difficulties in this particular case: overriding marketing regulations may lead to anger and distrust by the pharmaceutical companies, also among clinicians, patients and the public.

National priority setting regulations in general are actualized in this particular case. Increasing health care budgets are driven by factors like patient needs, patient demands, and new drugs and technologies. In Norway, priority setting in health care is regulated by law (Prioriteringsforskriften) (10). The current set of priority setting criteria are the health-benefit criterion, the resource criterion, and the severity criterion (11). Innovation as a separate priority criterion was discussed in the revision process of the criteria, but was excluded (12). The rationale was that the innovation criterion could potentially lead to fewer healthy life years in the population; "…interventions with low degree of severity or low expected benefit could be prioritized before interventions with high degrees of severity or high expected benefit, based on assumptions on potential for innovation" (13). Both in the report "Open and Fair - priority setting in the health service" and the white paper other incentives for innovations were suggested (12, 13).

Step IV: Who are the involved stakeholders?

There are a number of stakeholders in this case: current and future MS-patients in Norway, the pharmaceutical industry, health care providers, the hospitals, other patients (with other indications/conditions), the regulatory bodies and the society (including people with interests that they may forego due to introduction of MS drugs, e.g. investments in education, infrastructure etc.).

Step V: What are the stakeholders' potential burdens and benefits?

Consequences for the various stakeholders should be made explicit, and concerns must be weighed against each other. The table below is not comprehensive, but indicates various trade-offs for various stakeholder groups if rituximab is accepted.

Stakeholder	Potential benefit	Potential burden/harm
The MS-patients in Norway:	Access to an effective and safe drug for new patients and for those who are already on rituximab and will not change to other drugs. Due to the low prize, it is more likely that all patients will be provided with early start of "highly active" medication.[6]	Evidence is not from RCTs: can it be trusted? Perhaps difficult to argue to use more expensive drugs which may also be needed. If treatment for MS will be cheaper, the authorities´ willingness to pay for MS drugs may decrease. Potential serious adverse effects of an off-label drug will not be followed up or covered by the pharmaceutical company.
MS-patients in the future	Access to an effective and safe drug. The recommendation by the clinicians is based on experience and register data. Results from the Swedish and Norwegian RCT comparing rituximab with other treatments will be available.	The incentive for the industry to invest in the innovation of new drugs may be reduced (evidence for this concern is not well documented). Willingness to pay for future high costs drugs for MS treatment may be reduced by the society/Beslutningsforum?
The industry	Acceptance by the authorities for other documentation for marketing authorisation by re-indication of drugs, for example evidence supported by other study types than RCTs. The companies that produce or start to produce rituximab get income from selling it.	Lack of immediate and future income from similar but newer drugs. Less predictability on what the government might decide.
The clinicians	Autonomy to choose what they find best for their patients.	Clinicians may feel obliged to prescribe a drug they don't trust, and knowing there is a competing registered drug available in other countries, may further influence their feeling of autonomy. The industry might be less interested in funding remuneration, research and travels.

[6] A strategy with early «aggressive» start will require an accepted cost-effectiveness, which may not be met by the more expensive drugs with marketing authorisation.

Stakeholder	Potential benefit	Potential burden/harm
The hospital / regional health authorities	Can provide and afford to provide what many of the clinicians find as the best treatment for the MS-patients, and also meet MS-patients requests for it. Their drug budget will be less tight.	Disagreement between clinicians may lead to conflicts both internally at hospitals and between hospitals. This may in turn lead to violation of the equal treatment principle. Clinicians and patients may accuse that the hospitals' overarching goal is to save money, not to provide best care. Uncertainties about liability, both ethically and economically, if adverse effects occur.
The regulatory bodies	Acceptance of off-label use may support the availability of such treatments outside the common marketing authorization procedure.	Their regulatory function may be questioned and their recommendations may be of less value/significance. Distrust to the system.
The government	Substantial resources can be reallocated without well documented reduction in heath benefit for the MS-patients; the authorities don't have to compromise health for the MS-patients in order to use resources elsewhere.	If the juridical evaluation shows that the government are breaking their own rules in order to implement rituximab, they get a reputation problem and a problematic relation to the industry.
The society	More resources to other public funded health interventions. Tax-payers trust that decisions are made according to the priority criteria.	Reduced cooperation with the industry might harm other areas in health.

Table 1. *Potential benefits and burdens for the stakeholders affected by the decision to accept rituximab or not.*

Step VII: What and who´s interests are in conflict?

In this step, we have identified several conflicting interests of the different stakeholders if rituximab is accepted for the treatment of MS. We find the most important ones to be:

- The industry´s interest in not accepting rituximab *versus* the patients´ who want rituximab as their treatment, the clinicians who want to prescribe it and the authorities who want to redistribute the resources that can be saved if accepting rituximab as MS-treatment.
- The diverging interests of MS-patients today *versus* future MS-patients: Allowing for off-label use of rituximab can provide current patients with a drug many patients and clinicians find beneficial and even better than other drugs, and at the same time more funds will be available for other health interventions due to reduced costs on MS-drugs. But, due to the argument by some clinicians and the industry, this will reduce innovation due to less income and certainty of future income and thereby potential patients in the future might lose health

benefits. In the literature on priority setting the identified lives versus statistical lives trade-off is discussed (14), and several ethicists hold that there is no normative difference between the two. Others hold that there is, and refer to the "rule of rescue" (15), i.e. that we as human beings are morally obliged to act in order to save a person we see is in need, and for many this obligation is stronger the closer relation you have to that person (16).

- The clinicians´ integrity and autonomy in treatment decisions *versus* the regulatory body/authorities. The clinicians have diverging opinions and have an interest in not being forced to recommend a drug they do not find sufficiently documented.

Step VII: What are the values and principles at stake?

In our assessment, all the four ethical principles are at stake or in conflict with each other (17). The weight given to *the principle of doing good (beneficence)* or *the principle of avoiding harm (non-maleficence)* lie behind the discussion about efficiency and safety of rituximab, the acceptance of method and uncertainty and the possible innovation. The *principle of respect for autonomy* is actualized in two ways: First, the patients' self-determination in decisions about themselves: Patients have right to take part in decisions about their own health and treatment. In order to have a true informed consent when starting treatment, patients should understand why the physician finds this treatment option best for them (18). However, it is important to be aware of which sources the patient is influenced by; the physicians recommendation and the information provided, which would build on trust; input from social media; information from patient organizations; previous experiences; information from the industry; and available research information (19). The weight of these sources may differ between patients.

Shared decision making is a goal in patient care, though the understanding of the decision-making strategy varies both in theory and practice (20). One important dilemma that may arise, is that the respect for patients´ autonomy might conflict with the clinicians´ evaluation of what is best practice, causing less harm and the fairest use of resources. Shared decision making can be particularly challenging when the disease is as complex as MS, especially as it is a condition where some patients also are cognitively affected (21). In this case, if rituximab is accepted, and there are no clinical reasons why another drug should be given to the patient instead, can a patient then claim to get another drug? This would lead to higher costs. A conflict between respecting patient autonomy and the principle of justice might then arise. Also *respect for clinical professional autonomy* is at stake. Both in meetings and in the media, the leading clinicians on MS-treatment at the different hospitals in Norway have fronted different opinions about rituximab. This is also reflected in which treatments are used at the different institutions. If rituximab is not allowed for common use, the physician following his or her best practice integrity as well as the patients requesting it, will be limited in their autonomy. Similarly, if rituximab is allowed, physicians that are reluctant to use the drug might feel obliged to prescribe it, either because patients demand it, or that the government enforce it.

Is deviating views among clinicians an ethical problem? Clinicians are supposed to follow best practice, and as the views deviate, it is challenging to implement "*the principle of equal treatment*" (likebehandlingsprinsippet), which should be followed in Norway. The different practices in Norwegian hospitals of prescribing rituximab, is in itself a violation of this principle. An important question would therefore be to which extent clinicians are free to execute their

autonomy in the choice of treatment, or if they feel pressured to follow the decisions from the authorities. Clinicians are also influenced by the industry, although conflicts of interest are constantly monitored (22). It can therefore also be a challenge for clinicians to execute neutral autonomy in their prescription, as well as in the information given to their patients (23).

The fourth ethical principle is about *just distribution of resources*. This principle might conflict with the principles of doing good and the principle of autonomy. The question being raised is if cost-savings for MS-drugs is a legitimate argument for accepting the use of rituximab. A common method in ethics is to turn the question the opposite way: Is it ethically acceptable *not to* save substantial resources that can be used for other purposes in the health care system, if possible? The legitimacy of such a question is clear, and arguments for not saving substantial resources if this doable without decreasing health for MS-patients, would have to be strong. Responding to this question will be one of the main tasks for the decision makers in the decision of whether it is ethical legitimate to accept rituximab in MS-treatment or not.

Last, but not least, the important value *trust* is at stake in this case. The concept of trust means confidence or in reliance on a person or system's quality. It can also entail that we are confident that something will happen in the future, or that we are sure that we will get something in the future (24). Can we trust results from non-randomized studies? Can we trust physicians´ opinions and recommendations when they are receiving research grants and remuneration from the industry? Can we trust that the industry will use their income on innovation and development of better drugs? Can we trust that the health authorities will keep their own regulations and not gradually shift to unpredictable decisions? Can we trust that money saved will be used in a way to gain more health in the population? And who can trust who?

Discussion

In this chapter the ethical implications of accepting common use of rituximab as an off-label MS-treatment are presented. The given assignment was not to conclude on what is the ethical right solution, or to provide clear recommendations for the decision makers. Though, by going through the seven step ethical analysis, the decision makers should be in a better position to respond to diverging arguments, interests, values and ethical principles that we have identified, and to deliberate on what should be given most weight.

There are several limitations in this ethical analysis. Collection of evidence to support the different issues were not performed in a systematic way; the available information may be incomplete and could have been misunderstood or reported incorrectly. Hopefully the transparency and impartiality in the analysis can compensate for that, and that further discussions can make the analysis more accurate.

By focusing on the ethical challenges of providing rituximab, light has been shed on several underlying problems of the ethical problematic and potentially unjust system of clinical evidence and financing of drugs. While the off-label use of rituximab in MS-treatment is unique in many ways, the discussion of documentation of research evidence, prizing of medications, role of the industry in research and development, and binding between clinicians and industry are general and relevant ethical challenges in the health system. A broader discussion and

exploration of these challenges should be prioritized, as we probably will see many similar cases in the years to come.

Concluding remarks

As the process has evolved (up to June 20th 2019), there seems to be a decreasing trust among the stakeholders, both between the industry and the health authorities, but also among clinicians, and the tone in the argumentation is harsher. Are we moving away from a discussion on what is best for the patients and for our society, to a discussion on how we can interpret the paragraphs in different laws and who are entitled to define what is right? The loss of a common agenda and trust in the process of decision-making can be damaging and might prohibit transparency and mutual agreement on procedural conditions.

References

1. Moe L. Biogen trekker forskningsstøtte. Dagens Medisin. 2018.
2. Miljeteig I, Johansson KA, Sayeed SA, Norheim OF. End-of-life decisions as bedside rationing. An ethical analysis of life support restrictions in an Indian neonatal unit. Journal of Medical Ethics. 2010;36(8):473-8.
3. Statens legemiddelverk fagområde klinisk utprøving. Faser i legemiddelutvikling. In: Statens legemiddelverk, editor. https://legemiddelverket.no/godkjenning/klinisk-utproving/faser-i-legemiddelutvikling2016.
4. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676-88.
5. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. BJOG. 2018;125(13):1716.
6. Tay-Teo K, Ilbawi A, Hill SR. Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies. JAMA Netw Open. 2019;2(1):e186875.
7. Workman P, Draetta GF, Schellens JHM, Bernards R. How Much Longer Will We Put Up With $100,000 Cancer Drugs? Cell. 2017;168(4):579-83.
8. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the

John Conley Lecture. JAMA Otolaryngol Head Neck Surg 2014;140(12):1225-36.

9. Prasad V, McCabe C, Mailankody S. Low-value approvals and high prices might incentivize ineffective drug

development. Nat Rev Clin Oncol 2018;15(7):399-400.

10. Helse- og omsorgs departementet. Forskrift om prioritering av helsetjenester, rett til nødvendig helsehjelp fra spesialisthelsetjenesten, rett til behandling i utlandet og om klagenemnd (prioriteringsforskriften). https://lovdata.no/dokument/SF/forskrift/2000-12-01-12082016.
11. Norwegian Ministry of Health and Care Services. Principles for priority setting in health care

Summary of a white paper on priority setting in the Norwegian health care sector. Oslo: https://www.regjeringen.no/contentassets/439a420e01914a18b21f351143ccc6af/en-gb/pdfs/stm201520160034000engpdfs.pdf; 2017.

12. Helse- og omsorgsdepartementet. Official Norwegian Report 2014:12 Åpent og rettferdig – prioriteringer i helsetjenesten [Open and fair – priority setting in the health care services]. https://www.regjeringen.no/no/dokumenter/NOU-2014-12/id2076730/2014.
13. Helse- og omsorgsdepartement. Meld. St. 34 (2015–2016) Verdier i pasientens helsetjeneste Melding om prioritering. https://www.regjeringen.no/no/dokumenter/meld.-st.-34-20152016/id2502758/sec9#KAP8-42016.
14. Cohen G, Daniels N, Eyal N. Identified versus Statistical Lives. An Interdisciplinary Perspective. Press OU, editor. Oxford2015.
15. McKie J, Richardson J. The rule of rescue. Soc Sci Med. 2003;56(12):2407-19.
16. Carlsen B, Norheim OF. "Saying no is no easy matter" A qualitative study of competing concerns in rationing decisions in general practice. BMC Health Services Research. 2005;5(1):70.

17. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. Fifth ed. New York: Oxford University Press; 2001.
18. Colligan E, Metzler A, Tiryaki E. Shared decision-making in multiple sclerosis. Multiple Sclerosis Journal. 2017;23(2):185–90.
19. Synnot AJ, Hill SJ, Garner KA, Summers MP, Filippini G, Osborne RH, et al. Online health information seeking: how people with multiple sclerosis find, assess and integrate treatment information to manage their health. Health Expect. 2014;19:727-37.
20. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. N Engl J Med. 2012;366(9):780-1.
21. Reuber M, Chappell PJ, Jackson C. Evaluating nuanced practices for initiating decision-making in neurology clinics : a mixed-methods study
https://doi.org/10.3310/hsdr06340. Health Services and Delivery Research. 2018;ISSN 2050-4357.
22. Robbins NM. Ethical Issues Pertaining to Conflicts of Interest Between Neurologists and the Pharmaceutical and Medical Device Industries. Seminars in Neurology. 2018;38(05):589-98.
23. Klein E, Solomon AJ, Corboy J, Bernat J. Physician compensation for industry-sponsored clinical trials in multiple sclerosis influences patient trust,. Multiple Sclerosis and Related Disorders. 2016;8:4-8.
24. Gambetta D. Can We Trust Trust? In: Gambetta D, editor. Trust: Making and Breaking Cooperative Relations, electronic edition. Oxford 2000. p. 213-37.