Empirical Investigation of Ethical Challenges Related to the Use of Biological Therapies

Tara Bladt, Thomas Vorup-Jensen, Eva Sædder, and Mette Ebbesen

Many new and expensive treatments are coming onto the market, raising an ethical dilemma of how to prioritise the financial resources available in the health care system. Biological drugs are an especially expensive form of treatment in a field where many new drugs are currently being developed.[1] Decisions about how scarce medical resources ought to be prioritized involve individual and political values. Resources in a health care system are always limited and implementing an expensive treatment in one area leads to fewer resources available in other areas. It is important to investigate this ethical problem since a better understanding of its basis may nuance the discussion and illuminate how different parties weigh various aspects of the issue. The American ethicists Tom Beauchamp and James Childress, warn that: "Countries lacking a comprehensive and coherent system of health care financing and delivery are destined to continue on the trail of higher costs and larger numbers of unprotected citizens. They need to improve both utility (efficiency) and justice (fairness and equality)."[2]

In 2018, the Danish Council on Ethics published a report on the just distribution of resources in the Danish health care system.[3] The Danish Council on Ethics advises the Danish parliament on request and initiates public discussions on ethical subjects. The report clearly identified increases in the cost of medical treatments, access to treatments, and the allocation of resources between different disease indications as ethical problems of justice, distributive justice, and beneficence. Furthermore, the report states that these ethical issues are notoriously complicated and that explicit decision-making instruments are needed in health policy to determine how to set priorities. The report concludes that the decision-making instruments should be based on well-founded ethical principles, here, at least in part, citing Beauchamp and Childress.[4]

Ethics committees in other countries also worked on the subject of prioritising treatments and found no clear answer on how to distribute resources. The Norwegian National Research Ethics Committees published an anthology about research and money, which discusses subjects such as the relationship between the pharmaceutical industry and medical professionals and the price of a human life. No recommendations were given, but the anthology was intended to start a debate about money and health.[5] The Austrian Bioethics Commission has discussed the balance between morality and economics, and it recommends transparent solutions and that limited resources are used as responsibly as possible.[6] The German Ethics Council stated that it is impossible to reach consensus among the parties involved and recommends an open debate involving medical, economic, ethical, and legal expertise to avoid decisions exclusively based on economics, and that rationing decisions should never be made by the individual nurse or physician.[7]

From a utilitarian standpoint, improving utility should be done by maximising health for the resources available. At an American hospital, it was shown that expenses for costly treatments could be markedly

Tara Bladt, M.Sc., *teaches in the Danish College of Pharmacy Technicians, Denmark;* **Thomas Vorup-Jensen, M.Sc., Ph.D., D.M.Sc.**, *is a Professor in the Department of Biomedicine at Aarhus University, Denmark;* **Eva Sædder, M.D., Ph.D.**, *is an Associate Professor in the Departments of Biomedicine and Clinical Pharmacology, Aarhus University and Aarhus University Hospital, Denmark;* **Mette Ebbesen, M.Sc., M.A., Ph.D.**, *is an Associate Professor in the Centre for Science Studies, and Department of Molecular Medicine, Aarhus University, Denmark.*

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reduced by implementing a review process of their effect.[8] After all, what is the point in using expensive treatments without evidence for effect? But a costly treatment might have a small effect. Who should then have the authority to decide whether the effect is worth the cost? Giovanni Maio argues that the treating physician should not be a gatekeeper of resources.[9] Instead, politicians should set overall guidelines, while the physicians should make the medical decisions, deciding whether a treatment is futile or not. Otherwise, the relationship between the physician and the patient will be shaken.[10] Such economic decisions can be made using Quality-Adjusted Life Years (QALYs). However, this method has been widely criticised. One critique is that saving the life of a person in a wheel chair yields fewer QALYs than saving the life of a person not in a wheelchair, which, as it was argued, is not ethically justifiable.[11] Beauchamp and Childress also criticise the use of QALYs. For instance, they do not support that health maximization is the only factor evaluated, as it is in a QALY analysis, because other values, such as the way the care is provided, are also important. They also argue that the QALY calculation implies that it is better to save one person with a life expectancy of 40 QALYS than saving two people with 19 QALYs each, which they do not necessarily support.[12] A strictly utilitarian way of distributing resources focused on health care maximisation by calculating QALY-gains could therefore give rise to ethical concerns.

Beauchamp and Childress present a framework for ethically justified decision-making in their book *Principles of Biomedical Ethics*.[13] This book was first published in 1979 and has been revised over the years with the latest 8th edition published in 2019. In this study, the 7th edition published in 2013 is used, as the edition was the newest available version at the time of the interviews. Beauchamp and Childress present four principles central for biomedical ethics. These principles are beneficence, nonmaleficence, respect for autonomy, and justice. According to Beauchamp and Childress, one should consider what is at stake for each of the principles, and then weigh and specify the principles in dialogue with the parties involved.[14] This approach has been widely used in the field of biomedical ethics.

In the field of healthcare, the four principles of biomedical ethics can be used to identify the issues at stake in an ethical dilemma. An example is given in a paper on the use of biological therapies for dermatological diseases in the US.[15] Based on the principles of beneficence and nonmaleficence, the authors argue that the most optimal treatment option for the patient should be found based on effect of the treatments available and the physician's experience from previous patients. According to the principle of respect for autonomy, the decision should be made jointly by the physician and the patient based on the patient being informed about risks and side effects. With regard to the principle of justice, these authors concluded that the patient should receive the biological treatment if it is considered medically necessary even though the price is high. If the patient's insurance cannot cover the cost, a biosimilar option could be considered.[16] In consequence, the result of the justice discussion varies depending on the organisation of the health care system and the fact that the patient might have to pay for some of the drugs herself. These costs might be high and, therefore, it was suggested that economic barriers for effective cancer treatments in the US should be removed.[17] Some patients may be forced to end an effective treatment because of costs, and drug prices can suddenly rise without a clear reason. Furthermore, the US federal health insurance program Medicare has been criticised for not having the possibility of negotiating drug prices.[18]

As just outlined above, this ethical dilemma is different, depending on the organisation of the health care system. Beauchamp and Childress advocate a two-tiered health care system with a right to a decent minimum of health care. This model is built on egalitarian and utilitarian theories of justice.[19] This way of organising a health care system is in line with the Scandinavian model of health care, including the Danish system, which is also the context of the study presented below.

Mette Ebbesen and Birthe D. Pedersen showed that the ethical principles by Beauchamp and Childress are applicable to the daily work of Danish molecular biologists and oncologists.[20] They investigated how molecular biologists and physicians in Denmark perceived the four principles and found that all four principles were reflected in their daily work, although these two groups of respondents had different perceptions of nonmaleficence and respect for autonomy.[21]

In the present study, the four ethical principles of Beauchamp and Childress were used as an open framework to structure the data analysis. This study investigated whether these principles are at stake in the process of decision-making involved in prioritising access to expensive biological treatments in Denmark. The chronic disease multiple sclerosis was used as an example. The following three themes were investigated:

1. Whether the four principles of biomedical ethics are at stake in the discussion about prioritising resources for biological treatments.

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Table 1

Example of a disease field with expensive treatment options.

MS: an example of a disease with biological treatment options

MS is an autoimmune disease with biological treatment options. It is a neurological disease of unknown origin that leads to physical impairments. This disease develops gradually over many years, and there are no recognised prognostic biomarkers for predicting whether the disease will have an aggressive or a mild progression. Typically, the impairments build up during the course of the disease and 50% of patients are in need of a wheel chair after 25 years of disease.[31] Early in the course of the disease, therapeutics can be effective. Later on, only symptom-modifying treatments are available.

The treatment of MS therefore raises at least two central ethical dilemmas: 1) since the disease progression is unpredictable, what risks of adverse events should be accepted when choosing a treatment? and 2) since the disease is chronic and patients may receive the treatments for several years, what expensive treatments should be used? Other options could be prioritized, such as nursing help, assistive technology, and indirect costs, which could potentially be reduced, if the patient receives appropriate treatment.

2. What specific content of each principle is at stake, and whether some related issues not covered by the principle or the interviewer are at stake.
3. How the principles are weighted and specified in this ethical dilemma.

Background

The Danish Health Care System

The Danish health care system provides mostly free medical treatment to all citizens and is financed by taxpayers. Around 30% of the population have private insurance, providing them access to faster treatment and around 40% have insurance that gives subsidies for prescription medicine, dentist bills, spectacles, etc.[22]

The Danish Medicines Council evaluates drugs and establishes guidelines for the use of drugs for the various therapeutic fields. The price of each drug and the evidence for its effect are analysed by the Council in the process of recommending drugs. This is done to ensure the quality of treatments, homogenous treatments across the regions of Denmark, and a reasonable correlation between the price and the effect of drugs.[23]

Biological Treatments

Biological therapies are often offered to patients in the Danish health care system as part of the treatment of common diseases such as cancer, arthritis, and MS. These biological therapies are more expensive than other kinds of treatments offered[24] with typical costs of DKK 45,000–250,000 a year per patient [USD 7,200-40,000 (exchange rate, September 2020)].[25] The prices were obtained February 2020 and the price movements per unit, since the conduction of the interviews November 2017 – January 2018, are inserted in the note number 25. At least in part, the costs of the drugs relate to the complex manufacture of proteins expressed in living cells.[26] These drugs are typically large molecules, e.g. the so-called antibodies. Antibodies are produced as part of normal physiology in the body during the immune response to challenges with "non-self" molecules, notably proteins, as would happen when infectious agents intrude in the body. Typically, antibodies bind very specifically to their targets, in this way avoiding reactivity with "self" molecules. At the end of the 19th century, it was discovered that antibodies raised against specific targets can work efficiently as a treatment.[27] It is not possible to make generic copies of biological treatments due to the natural complexity of the molecules, which involves small variations in the molecules, mainly in attached carbohydrate structures or chemical modifications of the amino acid residues through oxidation or deamination.[28] These variations arise in the production and storage of the drugs. Therefore, copies of biological drugs are referred to as biosimilars, since these are not *identical*, but *similar* to the original product. Consequently, biosimilars must undergo stricter pharmaceutical and clinical testing than simpler generic drugs.[29] This is an expense for the manufacturer, which reduces competition in the field. Less competition and an expensive manufacturing process are two parameters that contribute to the high price of biologicals and their biosimilars, although price setting is a complex subject and prices might not correspond to development costs. An indication that prices do not necessarily correspond to development costs, is found from how much money the hospitals can save by switching all patients from the original drug to a biosimilar drug, when the original drug no longer is the only drug on the marked.[30]

Table 1 shows how an effective but expensive form of treatment raises ethical questions about choosing a treatment and prioritising resources.

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Many different players and interests are at stake for the use of biological treatments. Researchers perform the basic research to find new biological treatments. These findings are further developed by the pharmaceutical industry to make it into medicine. Physicians use the medicine to treat the patients in the Danish health care system, which is led by politicians. Politicians have chosen to form the Danish Medicines Council to make treatment guidelines. All these different players have different opinions on the use of biological treatments, which make their perspectives relevant to investigate.

Method

Ethical Theory

This study used the principles of Beauchamp and Childress as an open framework for the overall design of the study, the interview guide, and structuring the data analysis. According to Beauchamp and Childress, in an ethical dilemma, these principles must be specified and weighed against each other to make an ethically justified decision. The four principles are briefly presented in Table 2, below.

Beauchamp and Childress propose that there is a common morality for morally serious persons. Furthermore, they specify that the four ethical principles are a part of this common morality. According to Beauchamp and Childress, therefore, all morally serious persons find the principles relevant and important.[33] Beauchamp writes: "The common morality is not merely *a* morality that differs from *other* moralities. It is applicable to all persons in all places, and all human conduct is rightly judged by its standards."[34] The common morality contains basic principles, virtues, and obligations for instance the principle of respect for autonomy — and, as specified in contexts of medicine and research — the obligation of informed consent. These principles and the obligations that descend from them have prima facie standing and are part of the common morality on the same normative level as the principles of beneficence, nonmaleficence, and justice. These principles and the obligations they generate are universal and not culture sensitive. Therefore, the right of informed consent is a universal right to give "*an autonomous authorization* by individual patients or subjects" when an intervention is proposed.[35] It is not a culturally relative principle or right.

However, specifications of these basic principles and overall obligations into more specific rules, procedures, etc. may in some contexts be culturally sensitive, especially when these norms are component parts of particular moralities that are nonuniversal such as codes of ethics for medical societies.[36] While the obligation of a health professional to obtain an informed consent that authorizes an intervention may be essentially universal, by contrast, the elements of *the specific process* of authorization of informed consent as part of particular morality can be culture guided. The specific process of authorization also may be deeply rooted in cultural practice. For example, families may play a much larger role in the process of authorizing than health professionals even though basically a true informed consent for a competent patient or subject is a first-party consent.

By "culture," we here refer to culture as multidimensional and including knowledge, beliefs, arts, specific rules, laws, customs, and any other capabilities and habits acquired by a human as a member of society. In addition, national, ethnic, religious, regional, and generational considerations can have some role in creating a wide range of cultures with many differences.[37]

Table 2

The principles of biomedical ethics by Beauchamp and Childress.

Principle	Content of principle
Beneficence	One is obliged to benefit others by doing good, preventing, and reducing harm.
Nonmaleficence	One ought not to inflict either physical or psychological harm. Unlike the principle of beneficence, this principle is passive, since it can be followed by not interacting with other people.
Respect for autonomy	One ought to further autonomous decision-making. Autonomous choices and actions should not be controlled by others. Informed consent is central for this principle, which consists of an information component and an authorisation component. Authorisation is defined as a first-person agreement (personal communication with Beauchamp).
Justice	Beauchamp and Childress propose a framework for the allocation of health care resources based on the right to a decent minimum of health care that integrates both utilitarian (cost-effective rationing) and egalitarian (justice) aspects, a so-called two-tiered system.[32]

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Table 3
First column: description of the respondent. Second column: background of the respondent.

Respondent	Background information
Patient	A woman suffering from MS. Disease has progressed to secondary MS.
Respondent from the MS Association	A representative from the patient organisation for Danish MS patients.
Treating physician	A physician treating MS patients in everyday work in a clinic.
Physician involved in drug regulation	A physician employed at a university and a university hospital who is also involved in the work of regulating drugs in a Danish region.
Respondent from the Danish Medicines Council	A representative from the Danish Medicines Council where guidelines on the use of treatments in Denmark are drawn up.
Researcher	A researcher employed at a university working on antibody therapy who has been involved in the development of antibody drugs.
Respondent from the drug industry	A representative from the Danish Association of the Pharmaceutical Industry.
Politician	A politician particularly involved in the health care system.

In order to achieve a valid informed consent as "*an autonomous authorization* by individual patients or subjects,"[38] health researchers should discuss with patients and subjects any known cultural consideration that might affect the decision to authorize or refuse an intervention. This obligation of health researchers reflects the positive (active) obligation of respect for autonomy, which refers to "respectful treatment in disclosing information and actions that foster autonomous decision making."[39] In that sense, health researchers are obligated "to disclose information, to probe for, and ensure understanding and voluntariness, and to foster adequate decision making."[40] Beauchamp and Childress describe the content of the concept of authorization in medical contexts as follows: "Patients and subjects usually should understand, at a minimum, what an attentive health care professional or researcher believes a reasonable patient or subject needs to understand to authorize an intervention. Diagnoses, prognoses, the nature and purpose of the intervention, alternatives, risks and benefits, and recommendations typically are essential. Patients or subjects also need to share an understanding with professionals about the terms of authorization before proceeding. Unless agreement exists about the essential features of what is authorized, there can be no assurance that a patient or subject has made an autonomous decision and provided a valid consent."[41]

The theory of Beauchamp and Childress has been criticised over the years. In the preface to the 7th edition of their book, the authors write that many critics argue that the theory has an American individualist orientation and that the principle of respect for autonomy overrides the other principles.[42] Beauchamp and Childress argue that this is a misinterpretation and emphasise that no principle is overriding. Søren Holm says that the theory is based on an American common morality, which is not always transferable to other societies.[43] However, Holm misinterprets Beauchamp and Childress' account. Beauchamp and Childress clearly differentiate between two normative levels, the one of the common morality as universal and the other of particular moralities as nonuniversal. Beauchamp writes: "Universality is located in the common morality and nonuniversality in other parts of the moral life, called 'particular moralities.'"[44] The four principles of biomedical ethics and the obligations that descend from them are part of the common morality and are hence universal. These principles are then specified and balanced in particular moralities, and these specifications and the specific process of balancing are culture sensitive and hence, nonuniversal. Holm does not consider this differentiation between two normative levels and he does not recognise that Beauchamp and Childress consider the basic principles and basic obligations as universal and the specific process of specification and balancing as nonuniversal.

Sample and Sampling Procedure

This study was based on eight semi-structured interviews with Danish respondents who are familiar with and have experience in the field of antibody therapy, MS, or prioritising resources for expensive treatments. These respondents include important stakeholder

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positions, e.g. patient, physician, and politician. This allows various different perspectives on the ethical problems in decision-making and the allocation of expensive biological treatments to be explored. The description and background of the eight respondents are presented in Table 3.

The type of sampling used is purposive sampling,[45] based on the everyday work of the respondents. The respondents were specifically selected to make it possible to explore multiple aspects of the issue of expensive treatments and MS in Denmark. The respondents have been anonymised.

Interviews and Interview Guide

The eight qualitative interviews were conducted using a semi-structured interview guide. This interview format was chosen to let the respondents reflect on the questions and to clarify their considerations. Each interview lasted 40–62 minutes and was recorded and transcribed word-for-word. The interviews were conducted in the period November 2017 – January 2018.

The questions in the interview guide were divided into 6 groups as shown in Table 4.

Data Analysis

The data from this study were analysed using a phenomenological hermeneutical method for interpreting interview texts inspired by the philosopher Paul Ricoeur's theory of interpretation.[46] The interviews were transcribed word-for-word in text form. To enter the hermeneutical circle, the data analysis has three stages: 1) naïve reading, 2) structural analysis, and 3) critical interpretation:

1. *Naïve reading*: the transcribed text was read several times with an open mind, in an attempt to understand the whole text without bias.
2. *Structural analysis*: the text was divided into units, which might be a sentence or part of a sentence. The meaning of these text units was condensed to cover only the most relevant points. These were further condensed by making themes

Table 4

Structure of interview guide.

Warm up	Questions asked to warm up the respondent and get him/her to speak freely. The respondent was asked about his/her everyday work.
Work related to this project	The respondent was asked about his/her work and its relation to the specific ethical discussion. As a result, the respondent explained why his/her perspective is important to the debate.
Economic and social considerations	The interviewer asked the respondent about social considerations, medicine pricing, and his/her opinion regarding the price of specific drugs for treating MS. The questions were formulated to be as open-ended as possible to let the respondent come with his/her own thoughts.
Questions related to the four principles of biomedical ethics	Questions related to beneficence, nonmaleficence, respect for autonomy, and justice without asking directly about these principles. This threw light upon the respondent's thinking about each principle and the weight it should be given.
Questions about ethical considerations	The respondent was asked whether he/she was aware of ethical dimensions for the topic not covered by the interviewer and was then introduced to the principles of biomedical ethics. The respondent was asked whether the ethical challenges discussed were considered in his/her everyday work or with regard to the use of expensive medicines.
Round-off	The respondent was asked if he/she had anything else to add.

Table 5

Example of structural analysis from the present study.

Respondent	Quote	Meaning condensation	Subtheme	Theme
Researcher	"There is a need for antibodies that specifically target cancer stem cells, so an antibody that kills all cells is not given."	There is a need for more specific cancer antibodies	• Quality of life • New medicine • Minimising side effects	Beneficence

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and subthemes for the units. The structural analysis was compared to the naïve reading. An example of the structural analysis is shown in Table 5.

3. *Critical interpretation*: the themes and subthemes were compared to the research questions, previous studies, and the literature.[47] The bioethical principles of Beauchamp and Childress were used in this last stage of the data analysis to structure and inspire the data interpretation.

Results

Various themes emerged during the analysis for each of the principles. Some of these themes are discussed in the following data analysis.

The Principle of Beneficence

Beneficence is a central theme since all the respondents had an urge to benefit patients, but although they agreed on this, they had very different views on how beneficence can be achieved.

ACCESS TO MEDICINE

One way of being beneficent to patients is to give them the best treatment available on the market. The interviews explored whether it is acceptable that a good treatment is not available in Denmark because the price is too high:

> … no, I do not think it is acceptable, well because, it gives, it gives us all hope, every time something is mentioned in newspapers, magazines, or on Facebook (Patient).

This patient did not find it acceptable that efficient treatments are rejected by the Medicines Council, because of her strong hope for better treatments. The treating physician agreed with the patient and emphasised that effective treatments should be made available.

The respondent from the Medicines Council had a different opinion on this question:

> If we imagine a significantly more effective drug for treating multiple sclerosis became available, which could really make a difference for the patients, then I think one would really try to make it possible for the patients to get this treatment. One could say, it is the [Medicines] Council that makes this decision, and the economic conditions can be so compelling that a treatment, well [..] it is a decision that has been made (Respondent from the Medicines Council).

The respondent from the Medicines Council, the physician involved in drug regulation, and the politician, all wanted to implement effective treatments in Denmark, but were aware that limited finances might mean that this is not possible. In particular, the physician involved in drug regulation thought it was important that only treatments that have been scientifically proven to have significant effect are implemented.

NEW MEDICINE

Another way of helping patients is to develop new and more effective drugs than those currently available. This was especially important for the respondent from the pharmaceutical industry and the researcher:

> (Talking about pressing down the price on drugs) "We need more medicine, but it would mean that fewer new treatments will be developed, because the risk of failure is always big. Only a few treatments actually get to the market (Researcher).

According to the researcher and the respondent from the pharmaceutical industry, new treatments will only be produced if there is an economic incentive to develop new drugs. Since new drugs are needed, a favourable market for the pharmaceutical industry must be present, according to these two respondents.

The Principle of Nonmaleficence

Adverse events and side effects are specific subjects of the principle of nonmaleficence. Adverse events and side effects for biological treatments range from mild to severe.

ACCEPTANCE OF SIDE EFFECTS

All the respondents emphasised that some side effects may be acceptable if a treatment is effective.

> … as a medical doctor you have to choose the optimal. Optimal does not mean there are no side effects or adverse events. Optimal means that there is a balance between the efficacy and the adverse events and that you take the risk because, for example, you don't have other treatments with the efficacy that the patient needs (Treating physician).

The treating physician considered that a balance between side effects and efficacy must be achieved. All other respondents agreed that some side effects could be tolerated.

The two physicians considered how, whether, or not side effects and adverse events are acceptable could be evaluated. The treating physician, who has patient

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contact, focused on the individual patient. For less severe side effects, he stated that the individual patient should decide whether the side effects are acceptable or not. For more serious side effects, he thought that the physician should evaluate how much the patient needs the treatment and how big the risk of getting the side effect is. The physician involved in drug regulation thought less severe side effects are acceptable and she considered the frequency of side effects when evaluating whether they are acceptable or not. This view contrasts with the focus on the individual patient by the treating physician.

MINIMISING ADVERSE EVENTS AND SIDE EFFECTS

All the respondents thought it is important to try and minimise side effects and adverse events as much as possible and they had various views on how to do this. The researcher wanted to make cancer antibodies more specific, with less side effects. The treating physician was reluctant to use biosimilars and preferred the original drugs, because he was unsure how biosimilars work. Gene sequencing and not offering treatment to terminal patients were also suggested.

The Principle of Respect for Autonomy

Because of the above-mentioned risks of adverse events and side effects, informing patients, and informed consent were important themes for the respondents.

Informing the Patient

All the respondents emphasised that it is important that patients are informed about side effects or adverse events from a treatment and only choose a treatment that he/she is well-informed about.

> … it has to be based on information to the patient, that a treatment is given, yes, it always has to, the patient must be consulted and of course have the side effect/adverse events explained as well as possible (Respondent from the MS Association).

As shown in the quote above, the respondent from the MS association thought it important to inform the patient. The treating physician stated that he spends a lot of time discussing possible side effects and adverse events with patients and he thought it very important that patients know about these effects. Several respondents mentioned the importance of physician and patient discussing treatments and reaching a mutual decision.

Although all the respondents thought it important to include the patients in the decision process about a treatment, the politician, the patient, the respondent from the MS association, and the treating physician all agreed that there may be specific situations where respect for autonomy of the patient should be limited. This could be a situation where a patient wants a drug without scientifically proved effect or a drug with very high risks of serious side effects. According to these respondents, in such a situation the physician should decide that the treatment is not available for the patient and the patient should accept this decision.

PHYSICIAN AUTONOMY

Not only the autonomy of the patients, but also the autonomy of the physician was explored in the interviews:

> In Denmark, there are already very strict guidelines which we [physicians] have to follow [..] we always talk, also in Denmark, maybe especially in Denmark, about precision medicine, but at the same time, precision medicine is limited by the guidelines that are implemented by the national health insurance (Treating physician).

The treating physician argued that because he must follow the guidelines set by the Medicines Council, he is not able to personalise medicine for patients. He would like to be able to personalise medicine by having multiple treatment options and being able to give each patient the treatment that fits this specific patient individually. The politician, who was a co-initiator for the foundation of the Medicines Council, also supported use of precision medicine. But he focused on personalised medicine as medicine for a specific genotype, and not as choosing medicine with the most tolerable side effects for the individual patient, as the treating physician did.

The Principle of Justice

The interviews illuminated several aspects of the principle of justice.

MEDICINE PRICING

All the respondents thought that it is reasonable that the price of medicine is high. The respondents focused on what effect medicine has for patients and how long it takes to develop a new medicine. Furthermore, the respondents argued that expensive treatments might be cost-effective.

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> ... the person might be able to work, and then there will be lost earnings, there might be days off work because of illness, there will be all kinds of expenses for assistive technology that the person will not need anymore. Yes, I think that even though it sounds like a lot of money, one must think in a broad sense what you get for this money (Respondent from MS Association).

The above argument was put forward by the respondent from the MS Association, the respondent from the pharmaceutical industry, the patient, and the politician. They argued that all the expenses of a patient should be considered together when analysing whether a drug is worth the price because society also spends money on care, equipment, and early retirement benefit.

Despite these considerations about high prices, all the respondents except the treating physician (who made no comment on prices) thought the prices of medicine might sometimes be too high. They suggested that the pharmaceutical industry sometimes set the prices of medicine too high, and the respondent from the pharmaceutical industry thought that pharmaceutical companies always go after the highest possible price.

ALLOCATION IN DENMARK

Several respondents said that they could not evaluate whether resources in Denmark are distributed in a fair manner. The physician involved in drug regulation, the patient, the politician, and the researcher all proposed that the big focus on cancer means that more money is allocated to cancer than to other therapeutic fields. According to the patient and the politician, it makes sense that many resources are allocated to cancer, and they both thought that the resources in the Danish health care system are allocated in a fair way. The physician involved in drug regulation and the researcher thought the current allocation is unfair.

VULNERABLE PATIENTS

The respondent from the MS association and the respondent from the Medicines Council emphasised that vulnerable patients must be evaluated in an economically different manner than other patients:

> ... because, for example, with this ocrelizumab [antibody] treatment that is on the way to primary progressive MS patients, which is a group that does not have anything yet, there I think that one should be able to accept a higher price for such a group than one normally would (Respondent from the MS Association).

The respondent from the MS association proposed that it is all right to accept more expensive treatments than normal in therapy fields where no treatments are currently available. The respondent from the Medicines Council agreed that patient groups should be evaluated differently.

MEDICINE EVALUATION

The politician, the respondent from the pharmaceutical industry, and the respondent from the MS association considered using a fixed price per QALY when evaluating medicine:

> ... it would make a lot of things easier, one could say, because you would have the opportunity to make some evaluations in these situations where you have no frame of reference (Respondent from the pharmaceutical industry).

> ... we must not have a Danish QALY like they have in the UK, where, a little caricatured, you can look it up in a table, yes or no, but have a Danish model that is based on the fact that we have a different health care system than in e.g. the UK, with free and equal access, publicly financed (Politician).

The respondent from the MS association and the politician agreed that a fixed price for a QALY should not be used in the decision-making process about which medicine should be available in Denmark.

Discussion

Common Morality

This study has shown that the four principles of biomedical ethics are applicable to the ethical dilemma of prioritising scarce resources to biological therapies for the treatment of MS in Denmark. All four principles were at stake and all of them were important for all the respondents. No respondent clearly valued only one or two principles. Based on this, the theory of Beauchamp and Childress seems applicable to this ethical dilemma in a Danish setting.

Beneficence

The principle of beneficence was central to the discussion of expensive, biological treatments and often weighed heavier than the other principles. This makes sense because the whole discussion focuses on being beneficent to the patient and improving the patient's quality of life. Beneficence weighed heavier than non-

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maleficence when it was proposed that it is acceptable to use a treatment that has side effects and adverse events. Some respondents argued that in specific situations the physician's opinion about a treatment is more important than the opinion of the patient, which weighs beneficence heavier than respect for autonomy. It can be argued that the view that evaluation of treatments for vulnerable patients should be different than to other patients weighs beneficence heavier than justice, though it could also illustrate the respondents' perception of justice.

Correlation Between Job and Opinion

In some cases, the respondents' opinions correlated with their job. This was the case when the respondents close to the patients (patient and treating physician) viewed the scenario of good treatments not being implemented in Denmark as unacceptable. The respondents further distanced from the patients (physician involved in drug regulation, politician, and respondent from the Medicines Council) emphasised that it might be necessary to reject a treatment because of the price. This illustrates how the respondents close to the patient focus on the individual patient, whereas the respondents distanced from the patients focus on overall utility.

A correlation between job and opinion was also shown in the respondents' views on how to benefit the patients. The researcher thought it important to develop new treatments, the treating physician thought it important to give the best treatments available, and the physician involved in drug regulation thought it important to spend the limited amount of money most effectively.

Nonmaleficence

The principle of nonmaleficence was important for side effects and adverse events from biological drugs. Depending on the severity of the side effect or adverse event, the respondents could often accept them if the treatment could otherwise help the patient. If no other treatments were available, the risk of serious side effects could generally be accepted, if the patient was informed about it and accepted it. This is important for biological drugs that can be very effective but also have unexpected side effects. Again, the respondents had different views on how to minimise or evaluate side effects and adverse events depending on their professional background and profession.

Respect for Autonomy

All the respondents thought that respect for autonomy is important and all focused on informing the patient and letting the patient be part of the decision-making process about a treatment. The respondent from the MS Association and the treating physician were especially concerned about this topic. This principle is central, because patients can vary greatly in how they perceive risks and which side effects they find acceptable. In the situations where some respondents thought the physician's opinion about a treatment could weigh heavier than the patients' opinion, beneficence and nonmaleficence weighed heavier than respect for autonomy.

Informed Consent

Beauchamp and Childress argue that informed consent can be divided into an information component and a consent component.[48] The respondents in this study had great focus on informing the patients and letting the patients be a part of the decision making, which is focusing on the information component. Authorising an intervention, the consent component, was only briefly or implicitly touched by the respondents. This could be because the specific process of obtaining authorisation is part of particular morality. In Denmark, depending on the procedure, an authorisation might not always be explicitly announced, but can be based on actions by the patient, showing a first-person agreement, which is also a valid authorisation (personal communication with Beauchamp). In a country where health care is free, it is possible that authorisation of a consent becomes more implicit than in other health care systems, because the patient is not the one directly paying for the medical procedure. This of course depends on the specific intervention, and it is debatable if a bigger focus on explicit authorisation would lead to fewer misconceptions between medical professional and patient and therefore more well-treated patients.

Beauchamp and Childress advocate a health care system organised in much the same way as the Danish system, but this system also brings ethical considerations, e.g. on allocation of resources to different areas, personalised medicine, and physician autonomy in the use of medical guidelines.

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Personalised Medicine and Physician Autonomy
The treating physician thought his autonomy is limited by regional medical guidelines. For him, these guidelines lead to less personalised medicine to the patients because he has to follow the guidelines as rules. If more personalised medicine is desired in the Danish health care system, politicians should consider whether the current guidelines limit this. The politician was an advocate for both the use of guidelines and personalised medicine. Here, one must be aware, that different perceptions of the concept of "personalised/precision medicine" exist. The politician views the concept of "personalised medicine" as medicine fitting a specific genotype. The treating physician understands the concept of "personalised medicine" as prescribing medicine to a specific patient in light of the patient's preferences and tolerability of side effects.

Justice
Justice is particularly at stake in the distribution of resources and many different themes evolved in the interviews about justice. One central theme was the price of drugs, where all the respondents found it reasonable that the price of drugs is high, but also considered that it could be too high. This might indicate that it is reasonable to negotiate prices with the medicine industry.

Allocation in Denmark
Some respondents found the allocation of resources in Denmark to be fair whereas others found it to be unfair. The respondents' statements about vulnerable patients and putting a price on a QALY might reveal a specific theory of justice. The opinion that a price per QALY is a reasonable tool in evaluating medicine, as proposed by the respondent from the pharmaceutical industry, indicates a utilitarian perception of justice since it focuses on maximising utility. The politician's reason for not using a price per QALY is that the Danish health care system differs from the British system. He argues that the Danish system offers free health care, and everybody has equal access to treatments which are publicly financed. This free and equal access indicates an egalitarian way of thinking about justice because it focuses on equal access for all citizens. The statements from the respondent from the MS association and the respondent from the Medicines Council about evaluating medicine for vulnerable patients in a different way than to other patients might reflect a belief in the Well-Being or Capabilities theories, since it focuses on getting the patients to a reasonable level of capability or well-being.[49]

Conclusion
The principles of biomedical ethics presented by Beauchamp and Childress are applicable to the ethical discussion about use of biological treatments in Denmark. All four principles are at stake, and especially the principle of beneficence often weighs heavier than the other principles. For the principle of beneficence and nonmaleficence, a correlation between how to be beneficent/nonmaleficent and the respondents' work was sometimes seen. Regarding the principle of respect for autonomy, the patients agreed that it is very important to inform the patients, but some respondents emphasised that sometimes patients should rely on the decision of the physician. The respondents had great focus on the information component of informed consent whereas authorisation of informed consent was often implicit, which could relate to the structure of the Danish health care system. Beauchamp and Childress advocate a health care system organised in much the same way as the Danish system, but this system also brings ethical considerations, e.g. on allocation of resources to different areas, personalised medicine, and physician autonomy in the use of medical guidelines.

Future Perspectives
This study brings new perspectives to the discussion about the use of expensive biological treatments when resources are limited. It shows that the principles of Beauchamp and Childress are applicable to this dilemma. This study introduces ethical considerations encountered in a health care system that is in line with Beauchamp and Childress' perception of a just health care system.

Many topics addressed in this study are important for further investigation. It is important to study the proposed focus on treatment of cancer, mentioned by several respondents, and the limited focus on the authorisation part of an informed consent. Also, whether the use of guidelines leads to less personalised medicine and therefore less efficient treatment and the different perceptions of personalised medicine would be relevant for further studies.

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Note
Dr. Vorup-Jensen reports a patent US 10,166,253 B2 licensed to Cycle Pharma, UK. The other authors have no conflicts to disclose.

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