



Treatment optimisation in drug development

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Treatment optimisation in drug development

European stakeholder views

The current drug development paradigm is too 'drug-centred' and does not sufficiently take the patients that will receive the new therapy into account. This has led to the emergence of a research gap between the pre-approval development of medicines and their post-approval use in real-world conditions. This gap could potentially be bridged by transitioning towards a patient-focused framework that places strong emphasis on treatment optimisation, which strives to optimise the way health treatments are applied in clinical practice.

Questions remain however regarding the ideal features of treatment optimisation studies and their acceptability among key stakeholders. In this qualitative research study, semi-structured interviews were performed with 26 experts across 5 stakeholder groups and 10 different EU Member States. The results offer an overview of the concept of treatment optimisation. A set of policy options is also presented that could help enable implementation of treatment optimisation.

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Executive summary

1. Introduction

The development of novel health technologies is a complex and costly process that follows an extensive set of regulatory guidelines and legal provisions intended to ensure that the treatments reach the patients that need them in a highly controlled and standardised manner. In the European Union (EU), the first step in the path to market access for a new therapeutic intervention is the marketing authorisation procedure coordinated by the European Medicines Agency (EMA), in which applicants have to provide evidence of the safety, quality and efficacy of their product, which is mainly derived from the conduct of clinical trials. Once approval has been granted, each individual EU Member State will decide on how the drug will be introduced into their healthcare systems based on nationally diverging criteria determining its price setting, reimbursement conditions and clinical application.

However, in recent years, this established paradigm has faced increasing criticism from authors in the field, especially in relation to cancer treatment, who have highlighted its contribution to the existence of a research gap between the pre-approval development of anticancer medicines and their post-approval use in real-life practice. A drug-centred attitude dominates the present framework, leaving important patient-focused aspects relating to the real-world utilisation of antitumor therapies unaddressed, including how to combine them with existing health technologies, how their effectiveness compares to that of therapeutically relevant alternatives, how long they have to be administered to achieve the desired effects, whether a lower dose could produce the same results with potentially fewer toxic side effects and how they perform in terms of patient-relevant outcome measures such as quality of life and overall survival.

This situation has led to calls for a transition towards a new paradigm that puts the patient at the centre of clinical drug development and places a strong emphasis on treatment optimisation. Treatment optimisation, which has also been called applied research, seeks to optimise the way health technologies are used in real-world conditions through the conduct of studies designed to provide an answer to one or more of the above mentioned questions. It is not intended to replace the current clinical research framework; instead, it aims to generate results complementing those of the registrational trials as a way to bridge the research gap. However, a number of crucial questions remain regarding the ideal features of treatment optimisation studies, as well as their acceptability among the actors involved in the development and adoption into practice of novel therapies.

2. Aims and methods of the study

This report describes the findings of a qualitative research study. The objective of this study was to explore the views of key stakeholders in the drug development process with respect to the concept of treatment optimisation and the trials conducted within this context. To this end, semi-structured interviews were organised with academic clinicians in addition to representatives of patient organisations, regulator and payer authorities, pharmaceutical industry, and health technology assessment agencies. The interviewees were selected through a combination of purposive and snowball sampling. In total, 25 participants from 10 different EU Member States and a single participant from the United States were included in the study. Although the majority of them had expertise in oncology, several experts from other medical fields also took part in the research project. The interviews took place between December 2018 and May 2019 and were transcribed *ad verbatim* upon their conclusion. The data collected were analysed in NVivo® using the framework method.

3. Results

The interview questions were categorised into three main themes. Key observations and findings are presented for each theme below.

The **first theme** dealt with the current situation in drug development.

- A majority of interviewees (22 out of 26) thought drug development research is not sufficiently patient-centred, but there was no agreement on whether it is also too drug-centred.
- Most participants (18 out of 26) agreed with the statement that there is a lack of real-world evidence for the use of many drugs on the market today.
- A number of reasons were given for this perceived lack of real-world evidence:
 - Complexity and costs of real-world data collection;
 - Diverging evidentiary demands from regulators, payers and HTA agencies;
 - Perception of poor quality;
 - Lack of regulatory demands and incentives for gathering real-world data.

The **second theme** concerned the ideal features of treatment optimisation studies.

Feature	Findings from interviews
Conduct	Consortia comprised of all relevant stakeholders OR Academia and not-for-profit organisations, with support from industry (drug supply)
Funding	Combinations of public and private funding
Timing	No clear consensus whether pre- or post-approval
Design	<ul style="list-style-type: none"> • Fewer inclusion and exclusion criteria • Standard of care or best available treatment as comparators • Patient-relevant outcome measures • No clear consensus on blinding • No clear consensus on randomisation • Publication of all results
Setting	No particular preference, decided on case-by-case basis OR National, with international coordination and oversight

- There was broad support among the participants for inter-stakeholder collaboration and discussion during the design and conduct of treatment optimisation studies.

The **third theme** focused on the acceptability of treatment optimisation studies.

Advantages and opportunities	Disadvantages and challenges
Benefits for patients: clinically relevant outcomes and increased personalisation	Lack of funding
Cost savings for healthcare systems	Missing methodological framework
Therapies with added clinical value are rewarded	Competition with commercial trials for recruitment
If performed before approval: early assessment of marketability	Reluctance of industry to invest due to associated business risks
Registration of new combinations and additional indications in specific subpopulations	Missing infrastructure for international and/or multi-stakeholder setting
Filling of evidence gaps left by clinical trials	Ethical issues: conflicts of interest
Improvement of HTA and payer decision-making	Legal issues: liability, change in label
Improvement of clinical decision-making	If performed before approval: delay in patient access to new therapies
Faster patient accrual	If performed after approval: recruitment difficulties
Marketing advantage for industry	If performed by industry: increase in drug prices

- There was broad support among the participants for regulatory measures to facilitate treatment optimisation, although there was no agreement on the optimal scale and nature of these initiatives.
- Most interviewees (18 out of 26) believed the evidence strength of well-designed treatment optimisation studies that are performed according to rigorous quality standards is greater than or at least equal to that of classical registrational trials.
- There was a strong consensus among the experts interviewed that the results of treatment optimisation studies should be taken into account during the decision-making of regulators, payers and/or clinicians.

4. Policy options

From the interviews, three different policy options emerged for the implementation of treatment optimisation into the existing drug development paradigm.

Policy option 1. The first option involves making the conduct of treatment optimisation studies part of the requirements that manufacturers have to satisfy in order to obtain a marketing authorisation for their products. If a company does not provide the requested information or if the results indicate that there is insufficient reason to believe the new medicine will be useful in clinical practice, approval would not be granted.

Policy option 2. The second option consists of including treatment optimisation studies as part of the post-authorisation commitments that are imposed on the industry in the context of the EMA's conditional approval procedure. In this scenario, the EMA would grant a marketing authorisation to the applicant based on the data that was acquired from the standard registrational trials, on the condition that additional evidence derived from applied research is presented within a predetermined timeframe. If this condition is not met or if the findings cast doubt upon the clinical utility of the intervention, the approval would be retracted or adapted (e.g. by narrowing down the patient population that can receive the medicine).

Policy option 3. In the third option, conditional reimbursement mechanisms would be employed to compel the manufacturers to carry out treatment optimisation studies. This means that the national payer would temporarily reimburse the treatment while the manufacturer collects supplementary evidence in the form of applied research data. If the information requested is not provided within a predefined number of years or if the results reflect negatively upon the therapy in question, the reimbursement could be halted or the conditions under which it was negotiated may be altered.

These approaches mainly differ in terms of the timing of the treatment optimisation studies as well as the legal mechanism through which they would be requested. Advantages and disadvantages are associated with each of the three identified strategies. To realise these policy options, the applicable European or national legislative frameworks will need to be modified, which in turn will require significant political effort.

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1. Introduction

1.1 The clinical drug development paradigm

The current framework surrounding the clinical development of medicines has provided patients with many innovative therapies whose safety, quality and efficacy have been empirically demonstrated by the manufacturer and thoroughly scrutinised by the regulatory authorities. In the European Union, the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) evaluates registration dossiers submitted by pharmaceutical companies for drugs undergoing the so-called centralised procedure, which, if completed successfully, grants the applicant a marketing authorisation across all Member States (Scholz, 2015). Once a novel treatment has obtained such an approval by the EMA, individual Member States will decide on its real-world use based on country-specific criteria that determine its price setting, reimbursement and clinical indications.

In recent years however, this paradigm has come under increasing pressure, with some authors (Ioannidis, 2016; Lacombe et al., 2019a; Mullins et al., 2014; Wieseler et al., 2019) criticising it for being too drug-centred and not sufficiently focused on the patients that are eventually going to be administered the drug in real-world clinical practice. The clinical development framework as it exists today mostly aims at achieving the regulatory approval milestone, thereby overlooking the real needs of patients and society (Lacombe et al., 2019a). In oncology, the growing importance of the precision medicine model, which strives to provide the right patient with the right treatment at the right time through characterisation of an individual's genotypes and phenotypes (European Council, 2015; Salgado et al., 2017), along with its associated costs and limitations (Tannock and Hickman, 2016), has further highlighted the need for more patient-centred drug development (Lacombe et al., 2019c).

1.2 Dominance of drug-centred development strategies

Nevertheless, clinical cancer research is still too drug-focused at present, as illustrated by the predominance of trials that feature badly chosen comparators which do not reflect the best available therapeutic alternatives (Tao and Prasad, 2018), surrogate endpoints which may not necessarily translate into clinical benefit (e.g. progression-free survival or response rate) (Chen et al., 2019; Kim and Prasad, 2016; Prasad et al., 2015; Svensson et al., 2013) and strictly homogeneous samples of participants representing just 2-4 % of the overall targeted population, thereby generating results with a poor external validity (Kennedy-Martin et al., 2015). As such, these studies are not primarily designed to inform clinical practice and do not answer to patients' needs (Lacombe et al., 2019a), despite serving as the basis for the EMA's decisions to authorise new therapies.

For instance, in a recent retrospective cohort study (Davis et al., 2017), it was concluded that 39 out of the 68 anticancer drugs approved by the EMA between 2009 and 2013 entered the market based solely on improvements in surrogate outcomes and without having been shown to increase the overall survival or quality of life of patients, which are outcome measures that can be considered to be truly patient-centred (Kempf et al., 2017). At a minimum of 3.3 years after their registration, there were either still no data available indicating that they prolonged or improved patients' lives, or the observed gains were more often than not determined to be clinically insignificant. Similar findings were seen in the United States (Kim and Prasad, 2015), where at a median of 4.4 years after their approval, 57 % of the antitumor agents registered by the Food and Drug Administration (FDA) between 2008 and 2012 had no or unknown effects on overall survival. A subsequent analysis of the FDA's oncological medicine approvals between 2006 and 2015 affirmed these observations (Rodríguez et al., 2019). Furthermore, clinical trials providing the evidence needed to underpin the regulatory approval process (hereinafter referred to as 'registrational trials') can be prone to bias,

which often remains inadequately reported (Naci et al., 2019). Moreover, the accelerated and conditional marketing authorisation mechanisms, which were launched by the FDA and the EMA respectively to allow promising new therapies addressing unmet medical needs to enter the market faster, have further solidified the use of surrogate endpoints in clinical trials (Downing et al., 2014; Fleming, 2005; Hoekman et al., 2015), despite recent reviews (Gyawali et al., 2019; Schuster Bruce et al., 2019) underscoring the limited number of confirmatory trials establishing any benefits in overall survival for antineoplastic drugs that underwent the former. These results suggest that the regulatory approval procedure does not sufficiently filter out medicines that are of limited value to patients and their healthcare providers (Prasad, 2017), which in turn contributes towards the issue of medical reversal, i.e. the costly phenomenon where new, more rigorously designed studies disprove the clinical utility of medical interventions that have been adopted into the healthcare system (Prasad and Cifu, 2011). Additionally, regulators show little interest in rescinding the marketing authorisation of ineffective cancer therapies, regardless of their exorbitant prices (Rupp and Zuckerman, 2017). In conclusion, it can be stated that the real-life patient is not at the core of the current registrational trials and procedures (Lacombe et al., 2019a).

1.3 The research gap

Although the drug-driven approach to bring new treatments to the market should ideally be balanced with a more patient-focused strategy, the former tends to dominate treatment development in oncology. As a result, many important aspects relating to the use of novel antitumor therapies in real-world settings are neglected throughout the process (Kempf et al., 2017; Lacombe et al., 2017, 2019b), including:

- how to combine them with other existing treatments (radiotherapy, surgery, chemotherapy);
- in which sequence they have to be applied when combined with additional therapies (e.g. treatment A is best given before, after or at the same time as treatment B);
- how their effectiveness compares to that of therapeutically relevant alternatives;
- how they will perform in populations that were not studied in clinical trials (e.g. patients with comorbidities);
- how long they have to be administered to achieve the desired effects;
- whether a lower dose could produce the same results with potentially fewer toxic side effects;
- how their efficacy, effectiveness and safety evolve over a longer period of time;
- how they perform in terms of patient-relevant outcome measures such as quality of life and overall survival.

Such clinically patient-centred questions are being addressed in a non-systematic and voluntary manner in the post-approval stage by non-commercial entities (Kempf et al., 2017), including academic research teams and not-for-profit organisations. However, given the unsustainable nature of the funding available for studies performed outside of commercial interests, a more systematic approach is needed (Kempf et al., 2017). The industry has no incentive to invest in this type of research as its results can negatively impact the profitability of their products (Lacombe et al., 2019a), for example when it establishes a shorter overall treatment duration or a lower optimal dose.

It is clear that there exists a research gap between the development of anticancer medicines and their use in real-life circumstances (Kempf et al., 2017), resulting in the emergence of two

disconnected stages. The first stage is situated in the pre-approval setting and encompasses most of the clinical studies performed today. The research carried out in this stage focuses on characterising the safety, quality and efficacy of novel medicinal compounds in highly selected samples of participants and its ultimate goal is to obtain a marketing authorisation (Kempf et al., 2017). The second stage, at present comprising a minority of trials conducted, takes place in the post-approval environment and involves the setup of studies that tackle questions intended to accommodate patients' and clinicians' needs in real-world clinical practice. Since different actors coordinate the two stages, with the industry taking the lead in the first stage and academia and non-commercial partners playing a more prominent role in the second, the studies organised in the second stage, if done at all, are usually not pre-planned, marking a discontinuity that can undermine the optimal implementation of research findings in clinical practice guidelines (Kempf et al., 2017). This situation is not only detrimental to patients, whose true needs are left unaddressed, but also to society as a whole, because it presents a major financial burden to healthcare systems which face growing uncertainty as to the real-life effects and benefits of new interventions when deciding whether or not to reimburse them, potentially leading to the coverage of less cost-effective treatment options (Lacombe et al., 2019a).

1.4 Treatment optimisation

This situation has led to calls for a transition towards a patient-centred paradigm that puts a strong emphasis on applied research (Kempf et al., 2017; Lacombe et al., 2019b, 2019a; Lieu and Platt, 2017). Applied research, which has also been described as treatment optimisation (EORTC, 2019; Lacombe et al., 2019c), aims to optimise the way treatments are utilised in real-world conditions through the conduct of studies set up to provide an answer to one or multiple of the abovementioned clinically relevant research questions (Kempf et al., 2017; Lacombe et al., 2019a). It is not intended to replace the current drug development trials; instead, it seeks to deliver results complementing those of the registrational studies as part of a streamlined process that bridges the gap between the first and second stage of research (Kempf et al., 2017; Lacombe et al., 2019b).

While no definitive methodological framework has yet been formulated for such treatment optimisation studies, it is likely that prospective designs capable of producing robust level I evidence will be required to reduce uncertainty and improve the acceptability of research outcomes (Lacombe et al., 2019b, 2019c). Although population-level observational studies such as those based on cancer registries could provide useful data on long-term outcomes of treatments (Brewster et al., 2005), doubts have been raised as to whether these real-world data collection schemes can replace the conduct of randomised controlled trials for the evaluation of therapeutic effects (Giordano et al., 2008; McGale et al., 2016). Nevertheless, an integrated treatment optimisation approach incorporating both interventional and observational research could be a way forward (Kempf et al., 2017; Lacombe et al., 2019a).

1.5 Need for pragmatism

When an interventional setup is employed, treatment optimisation studies should be performed taking into account the principles of pragmatism in order to increase the applicability of findings to real-life practice (Kempf et al., 2017; Lacombe et al., 2019a). The term 'pragmatic trial' was introduced by Schwartz and Lellouch (Schwartz and Lellouch, 1967) to refer to clinical trials that focus on comparing interventions under real-world conditions. It has since become widely used to denote studies which are characterised by their inclusion of a heterogeneous population of participants, their patient-centred outcome measures, their choice of clinically relevant comparators, their real-life setting and their low follow-up intensity of trial subjects (Loudon et al., 2015; Tunis et al., 2003).

As such, pragmatic trials may be useful tools to help fill the aforementioned research gap (Kempf et al., 2017; Lacombe et al., 2019a). However, they represent only a fraction of clinical studies carried

out each year, with one estimate (Chalkidou et al., 2012) putting them at fewer than 1.2 % of all randomised controlled trials performed yearly between 1990 and 2010. The true number could be even lower, given that this percentage was obtained through inclusion of studies that self-reported as being pragmatic. Moreover, Buesching and colleagues noted (Buesching et al., 2012) that only 9 industry-sponsored pragmatic trials were conducted globally in the period 1996-2010, illustrating the reluctance of pharmaceutical companies to do them, in part due to their associated business risks.

1.6 Need for inter-stakeholder collaboration

Efforts to implement a more patient-focused drug development paradigm that includes treatment optimisation as an essential step in the path to full adoption of new therapies will likely fall short if it is solely left to the industry to launch and supervise such applied research initiatives. These activities should therefore be coordinated by an independent actor to ensure that commercial interests do not undermine or form a barrier towards their execution (Kempf et al., 2017; Lacombe et al., 2019a). The introduction of treatment optimisation will necessitate interaction and cooperation between all stakeholders involved in the development and market access of medicines, including (but not limited to) (Kempf et al., 2017):

- Patients, who desire improvements in their survival and/or quality of life;
- Clinicians and physicians, who decide whether or not their patients should receive a certain treatment and want to provide them with the best possible care;
- Pharmaceutical industry, which develops new treatments and commercialises them in order to generate profit;
- Academia, which conducts research independently or in collaboration with the industry;
- Regulatory agencies, which evaluate the evidence submitted by the manufacturers in terms of the treatment's safety, quality and efficacy and can subsequently grant a marketing authorisation that is valid across all member states of the European Union;
- Health technology assessment (HTA) agencies, which operate on a national level and review relevant scientific literature and/or perform cost-benefit analyses to support the decision-making of payers;
- Payers, who decide whether or not a given national healthcare system should reimburse the treatment based on an evaluation of its cost-effectiveness;
- Policy makers, who draft the legal framework governing the development of medicines.

Oftentimes, these actors have conflicting goals or motivations, which can contribute to the further increase of the research gap (Kempf et al., 2017). For example, patients and clinicians might want a promising innovative therapy addressing an unmet medical need to be introduced into the European market as fast as possible, which can put pressure on HTA agencies to recommend its uptake by individual member states based on limited available data instead of waiting until more real-world evidence is delivered (Kempf et al., 2017). An interconnected partnership comprised of all relevant stakeholders could help overcome these differences in priorities through collective discussions and early input of each partner in the design and conduct of treatment optimisation studies.

1.7 Outstanding questions to be addressed

The EORTC has composed a manifesto (EORTC, 2019) in which several directions for changes and policy actions are outlined that could help establish treatment optimisation as an essential element within the development pathway of personalised medicine in Europe. This call to action has received support from a multitude of different stakeholders, including scientific societies, patient organisations, industry associations and Members of the European Parliament. However, a number of important questions remain. For instance, it is not yet clear how applied research should be financed: is it the responsibility of the manufacturer to provide the appropriate funding, or should it be fully or partially covered by the EU national healthcare systems? Another aspect that demands further attention relates to the timing of treatment optimisation studies: can they run in parallel with the classical registrational trials, or should they take place only after the marketing authorisation has been granted? Furthermore, the extent to which regulatory agencies or payers should impose applied research and consider its outcomes during their (re-)evaluation of product dossiers requires clarification. These are just a few examples of outstanding issues that still need to be resolved. Given the multi-stakeholder nature of the environment in which drug development takes place, input on these remaining questions should be gathered from all actors involved in the process and considered thoroughly before launching any initiatives to implement treatment optimisation into the existing clinical research paradigm.

1.8 Aims of the research project

The purpose of the research project detailed in this report was to explore the views of key stakeholders in the drug development process across Europe with respect to the concept of treatment optimisation as well as the studies conducted within this context. The findings represent the thoughts and opinions of numerous experts. They offer an indication as to how applied research could be organised and how it would be received and interpreted by different actors.

2. Methodology and resources used

2.1 Interviews

The topic was explored through the conduct of semi-structured interviews with six different groups of stakeholders who are involved in the drug development process, namely patient organisations, academic clinicians, regulators, payers, HTA agencies and pharmaceutical industry.

2.1.1 Recruitment of participants

Table 1 – Inclusion criteria for recruitment of representatives of each stakeholder group

Stakeholder group	Inclusion criteria for recruitment of representatives
Pharmaceutical industry	<ul style="list-style-type: none"> ➤ Is in a senior or upper management position ➤ Has been a member of a clinical drug development team before or has expertise in real-world evidence ➤ Works or has worked in a Member State of the European Union
Patient organisations	<ul style="list-style-type: none"> ➤ Has experience working as a professional patient representative ➤ Has knowledge of clinical drug development ➤ Works or has worked in a Member State of the European Union
HTA agencies	<ul style="list-style-type: none"> ➤ Is in a position of authority at an HTA agency ➤ Is actively involved in decision-making ➤ Works or has worked in a Member State of the European Union
Regulators	<ul style="list-style-type: none"> ➤ Is in a position of authority at a national medicines regulator or at the European Medicines Agency ➤ Is actively involved in decision-making ➤ Works or has worked in a Member State of the European Union
Payers	<ul style="list-style-type: none"> ➤ Is in a position of authority at a government agency responsible for drug reimbursement decisions or at the expert body advising said agency ➤ Is actively involved in decision-making ➤ Works or has worked in a Member State of the European Union
Academic clinicians	<ul style="list-style-type: none"> ➤ Has been involved in phase III trials as a principal investigator ➤ Has a senior position at a university hospital ➤ Is a member of a scientific society in their field (e.g. the European Society for Medical Oncology) ➤ Works or has worked in a Member State of the European Union

Potential participants were selected through a purposive sampling method based on a number of stakeholder-specific inclusion criteria (see table 1). This strategy was complemented by a snowball sampling approach once the first interviews had been performed.

As the study aimed to examine the European landscape, delegates of institutions and organisations that are active on a European level were included wherever possible. Potential interviewees were contacted and invited to participate via e-mail.

In total, 25 participants from ten different EU Member States (namely Belgium, the Netherlands, France, Germany, Italy, Spain, the United Kingdom, Sweden, Austria and Poland) and 1 participant from the United States were included in the study. The participant from the United States was recruited in order to draw a potential parallel with the situation outside of the EU and because they had previously worked in several different Member States. The interviewees were evenly distributed across the targeted stakeholder groups (see table 2). Although the majority had expertise in oncology, there were also experts from other medical fields (namely rheumatology, hematology and respirology) who took part in the research project.

Table 2 – Number of experts interviewed per stakeholder group

Stakeholder group	Number of experts interviewed
Pharmaceutical industry	5
Patient organisations	5
HTA agencies	5
Regulators	3
Payers	3
Academic clinicians	5
TOTAL	26

2.1.2 Interview preparation

Upon showing interest to participate by replying to the invitation that was addressed to them, each potential interviewee was sent an informed consent form by e-mail which informed them that the interview was going to be recorded and transcribed. In addition, it assured them that they would remain anonymous in any reports and publications.

If a participant agreed to take part in the study by returning a signed version of the informed consent form, they received another document with the questions that were asked during the interview. This allowed them to contemplate their responses beforehand, which improved the overall flow of the interview session. The interview questionnaire was designed based on a review of the available literature on the topics of treatment optimisation as well as the aforementioned research gap (EORTC, 2019; Ioannidis, 2016; Kempf et al., 2017; Lacombe et al., 2019b, 2019a; Lieu and Platt, 2017; Mullins et al., 2014).

2.1.3 Timing and logistics of interviews

The interviews were conducted via Skype® between December 2018 and May 2019. To minimise bias as a result of interviewer variance, the same person was responsible for performing all interviews. The sessions were recorded using the software MP3 Skype Recorder. A back-up of the audio file was made and stored on a thumb drive after each interview to ensure no data would be lost. All files were destroyed once the study had been concluded.

2.1.4 Content of interviews

All interviewees were asked the same questions in the same order to allow for inter-group comparisons and to minimise the risk of order effects bias. However, some questions had to be adapted to accommodate each individual stakeholder group. Moreover, depending on the answers that were provided by the participants, some additional questions may have been posed with the intent of further clarifying the interviewees' standpoints.

The interview questions were categorised according to three main themes:

➤ **Theme 1: Current situation in drug development research**

1. *What do you think of the notion that current drug development research is too drug-centred and not sufficiently patient-centred?*

2. *How does the current approach impact patients?*
(for the patient organisation representatives)

How does the current approach impact clinical decision-making?
(for the academic clinicians)

How does the current approach impact HTA decision-making?
(for the HTA agency representatives)

How does the current approach impact reimbursement-related decision-making?
(for the payers)

How does the current approach impact regulator decision-making?
(for the regulators)

How does the industry justify the current approach they are taking?
(for the industry representatives)

3. *What is your opinion regarding the statement that there is a lack of real-world evidence for the use of many drugs on the market today?*

What are some of the reasons, you think, for this lack of real-world evidence?
(if agreement was expressed with the statement)

➤ **Theme 2: Features of treatment optimisation studies**

4. *Who should perform treatment optimisation studies (industry, academia, not-for-profit organisations,...)?*

5. *How should these studies be funded (public funding, private funding, combinations of the two,...)?*

6. *When should these studies best take place in the drug development process?*

7. *What would be some of the most important features that treatment optimisation studies should have (in terms of objectives, recruitment, randomisation, blinding, follow-up, outcomes, reporting, etc.) to be as relevant as possible for clinical practice?*

8. *What would be the best setting for the conduct of these studies (local, national, international)?*

9. *How would members of your stakeholder group react if they were invited to contribute to the planning and conduct of treatment optimisation studies?*

10. *What could members of your stakeholder group bring to the table?*

11. Which other stakeholders should be at the table?

➤ **Theme 3: Acceptability of treatment optimisation studies**

12. What is your opinion on the assertion that regulatory agencies should take measures to facilitate treatment optimisation?

What kind of measures should be taken?

(if agreement was expressed with the assertion)

13. What are some of the advantages/opportunities you can think of as a member of your stakeholder group with respect to the conduct of these treatment optimisation studies?

14. What are some of the disadvantages/challenges you can think of as a member of your stakeholder group with respect to the conduct of these treatment optimisation studies?

15. How would you view the evidence strength of these studies in the context of making treatment decisions for patients?

(for the patient organisation representatives and academic clinicians)

How would you view the evidence strength of these studies in the context of making HTA decisions?

(for the HTA agency representatives)

How would you view the evidence strength of these studies in the context of making reimbursement-related decisions?

(for the payers)

How would you view the evidence strength of these studies in the context of making decisions to approve drugs for use in patients?

(for the regulators)

How would you view the evidence strength of these studies in the context of decision-making by regulators and reimbursement legislators?

(for the industry representatives)

16. Do you have any additional remarks, questions, doubts, concerns regarding the topic of treatment optimisation?

2.1.5 Procedure for analysis

The interviews were analysed according to the framework method for qualitative research (Gale et al., 2013; Smith and Firth, 2011; Spencer et al., 2013). This approach involves going through several different stages in a stepwise fashion.

Stage 1: Transcription of interviews

In view of the protection of the participants' privacy, the interview recordings did not contain the interviewees' names. Instead, a code was employed, the key for which remains with the principal investigators. After the study was completed, all audio recordings were deleted and the coded transcripts were placed in a secure and confidential place where they will be kept until such time as they might be used for future studies. All of this was mentioned in the informed consent form so that the participants were aware of how their data would be handled.

Stage 2: Familiarisation with the interviews

Familiarisation with the interviews was mainly achieved through reading the transcripts and repeatedly listening to the audio recordings. During this stage, the interviewer, who was also

responsible for analysing the data, used the spacing between the transcript lines to write down his thoughts, impressions and remarks (e.g. an apparent contrast between the answers of different interviewees).

Stage 3: Coding

In this stage, the transcripts were analysed sentence by sentence and descriptive labels were added to excerpts discussing a particular topic through the use of the NVivo[®] software, which is specifically designed for qualitative data analysis. This process is referred to as coding.

As the study was primarily deductive in nature, the coding list was pre-defined to a certain extent, since the codes largely overlapped with the question topics. Additionally, open coding was applied for the more inductive aspects of the study (e.g. participants' experiences, views, concerns).

The coding should ideally be done by at least two different researchers working independently from each other, so that the results can be compared afterwards. Although there was no parallel analysis of the transcripts performed due to the limited number of researchers involved in the project, the person responsible for analysing the transcripts discussed any uncertainties they were confronted with during the coding process with one of the principal investigators of the study.

Stage 4: Developing a working analytical framework

In this stage, a working analytical framework was developed by coding a limited number of transcripts and grouping related codes together into categories in NVivo[®]. Again, where any ambiguity emerged in terms of the coding, discussions with one of the principal investigators were held to come to a final decision.

Stage 5: Applying the analytical framework

Once a working analytical framework had been established, it was applied to all transcripts by attaching the appropriate codes to specific sections of text through the use of NVivo[®].

Stage 6: Charting data into the framework matrix

Data from each transcript was summarised and mapped in an Excel[®] spreadsheet, where the rows represented cases (i.e. individual interviewees) and the columns contained the different codes.

Stage 7: Interpreting the data

The final framework matrix was examined to identify connections and patterns within and between the stakeholder groups.

3. Results

The results of the study are presented across the three main themes, which were explored during the interviews. Participants are referred to by their stakeholder group followed by a number, e.g. 'Industry representative 1' or 'Academic clinician 2', to ensure anonymity. The full questions can be found framed and in italics below each subheading.

3.1 Theme 1 – Current situation in drug development research

3.1.1 Question 1

What do you think of the notion that current drug development research is too drug-centred and not sufficiently patient-centred?

Summary

Most interviewees (22 out of 26) agreed with the notion that drug development research is not sufficiently patient-centred. They believed that patients are not being adequately involved at the design stage of clinical studies, when the research questions are defined and the protocols set up. Furthermore, at the time of approval, very little knowledge is available on the tangible benefits of a new therapeutic intervention for the patient, according to these participants.

However, there was no agreement on whether drug development research is also too drug-focused. For instance, some participants highlighted the necessity of the present drug-centred attitude to ensure the treatment is safe, efficacious, and of sufficient quality. Nevertheless, they added that it should be balanced with a more patient-focused strategy which addresses patients' real needs, stressing that the two types of approaches are not incompatible but even complementary with one another. Other interviewees thought that the system is, for a variety of reasons, undergoing a major shift towards implementing a paradigm that puts the patient at the centre of the development process.

Participants who disagreed with the notion that drug development research is too drug-centred and insufficiently patient-centred either believed it is already strongly patient-driven today or were of the opinion that the terms 'drug-centred' and 'patient-centred' were too simplistic to describe the current system and that the perceived dichotomy between the two is false.

Patient organisation representative 1 asserted that the present situation reflects the overall lack of a holistic view on therapeutic interventions in today's drug development strategies, leaving the gaps in the existing care pathways unaddressed.

Academic clinician 2 corroborated this sentiment, stating that drug development is mainly focused on the number of patients that will eventually be treated with a new medicine and not on their actual needs.

Payer representative 2 believed that research intended to develop new therapies does not sufficiently tackle the unmet medical needs because it is mainly being guided by investors and shareholders, whose primary objective is to secure a high return on investment. Patient-oriented notions like quality of life, clinical relevance and added therapeutic value are rarely taken into account when designing pivotal studies. At the moment, it is mostly academia that concerns itself with undertaking patient-centred research, the participant remarked.

HTA agency representative 1 was of the opinion that too much emphasis is being placed on the process of obtaining a marketing authorisation, which does not tend to take into account the real-life effectiveness of medicines. In this regard, the interviewee indicated that they thought the split in competencies between regulatory and HTA agencies has been a historical mistake.

Similarly, **HTA agency representative 5** criticised the current drug approval procedure for concentrating too much on short-term outcomes with no relevance to patients and lamented the fact that the regulatory authorities have allowed many anticancer therapies with no or only a marginal clinical benefit to come to the market.

Payer representative 3 also criticised the regulators for approving expensive new therapies based on increasingly limited evidence, such as improvements in surrogate endpoints instead of patient-relevant outcome measures. The introduction of mechanisms that enable the regulatory decision-making process to be accelerated at the request of manufacturers of supposedly innovative health technologies have only exacerbated the issue, this interviewee claimed.

Meanwhile, **academic clinician 4** underscored the importance of considering the context in which the treatment is ultimately going to be applied, especially in the field of oncology, as a multitude of different antineoplastic agents have been developed in recent years and it is not so obvious anymore to determine what the best treatment option for a given cancer patient might be.

Academic clinician 1 and **HTA agency representative 2** approached the question more from a clinical drug development perspective. They mentioned that there are several key differences between how drugs are studied in clinical trials and how they are subsequently being used in a real-world environment, specifically pointing out a number of important discrepancies, namely:

- Short duration of studies versus potential long-term use of the drug in clinical practice
- Inappropriate comparators in clinical trials (placebo or not the best available treatment)
- Differences between trial participants and real-life patients (lack of comorbidities, lack of polypharmacy, milder symptoms, younger of age, only non-smokers, no pregnant women, no children)
- Expertise of investigators versus inexperience and broad scope of primary care physicians
- Differences between adherence to treatment in clinical trial settings and in real-life practice
- Application of investigational drug as monotherapy or in very specific combinations versus more diverse combinations in real-world conditions

However, **academic clinician 1** also noted that the characterisation of drug-centredness or patient-centredness as a binary choice was not valid: both are necessary, and placing more importance on either one could have detrimental effects on drug development in general. This opinion was shared by **payer representative 1**, who saw drug-centred research as a crucial part of the development process, while simultaneously emphasising the need for the adoption of more patient-focused approaches.

Academic clinician 3 equated patient-centricity with the current trend towards developing and applying personalised therapies. In this respect, the interviewee saw drug-centred clinical research as laying the foundation for further therapeutic personalisation. Once multiple drugs have entered the market for the same indication, the patient has to be put at the centre and matched to the correct treatment instead of the other way around. The participant claimed however that the regulatory framework needed for such patient-centred research is not yet available.

Patient organisation representative 3 distinguished between trials conducted by big pharmaceutical companies and those performed by smaller start-ups. The former are primarily conceived with the drug in mind, whereas the latter tend to be designed in a more patient-focused manner. Although patient engagement is becoming more frequent across the entire industry, it is

not yet being implemented regularly into the earlier stages of treatment development, when many different parameters can still be changed. Methodologies for the involvement of patients early on in the research process are severely lacking, the interviewee declared.

Similarly, **patient organisation representative 2** advocated consulting patients more during the writing of study protocols.

As **patient organisation representative 5** put it, the involvement of patients in the drug development process at present amounts to nothing more than a window-dressing exercise. Their contribution is usually limited to reviewing informed consent forms or providing feedback on methods to recruit participants for a study, but their input comes too late to actually make meaningful changes to the way the trial is set up. That is why they already want to be included in the initial stages of drug development research, when the studies are still being designed, to make sure that the questions that are being raised address their needs and are relevant from a patient's point of view.

Besides the planning of trials, patients should also be involved more in the acquisition of data, as **HTA agency representative 4** argued. For example, although it has been established that patient-reported outcome measures can provide investigators with an additional source of valuable information on the performance of experimental treatments, they have not been utilised in many trials so far. Furthermore, even when they are employed as endpoints in studies, patients' experiences with the investigational therapy are often recorded on a population level, making it difficult to assess the relevance of mean or median scores for individual patients, **academic clinician 5** added.

Regulator representative 1 thought that the terms 'drug-centred' and 'patient-centred' were overly simplistic and did not express their agreement with the statement, arguing that the perceived dichotomy between the two is false. **HTA agency representative 3** stated that the problem is not so much that drug development research is too drug-focused, but rather that regulatory decision-making occurs almost exclusively on the basis of such research, thereby creating a gap in the evidence required to inform treatment decisions in clinical practice.

Industry representative 2 associated drug-centredness with being innovative and stressed that innovation can also be patient-centred. According to this interviewee, the notion that the industry is not putting the patient at the core of their drug development strategies stems from a general ignorance of the industry's activities and motivations, as a lot is for example already being done to incorporate outcome measures favoured by patients. However, they did acknowledge that a better job could be done in this respect, mainly by involving more patient advocacy groups in the study design.

Industry representative 4 disagreed strongly with the assertion that the industry is not patient-centred and gave a number of specific examples of patient engagement initiatives undertaken by their employer. For instance, the company in question incorporates patient insights into their trial protocols and has developed outcome measures in partnership with patients.

Although **industry representative 5** agreed in principle with the statement, they considered the drug-focused mentality of the industry to be a necessary evil, explaining that if companies would be less restrictive when recruiting patients for their clinical development programmes, this would make it impossible to determine the efficacy of their products. Nevertheless, phase IIIb and phase IV research could be developed more, for example by setting up registries or organising additional observational studies, the interviewee declared.

Similarly, **regulator representative 3** felt that the registrational clinical trials can only be fit for purpose from a regulatory perspective if the manufacturer puts the drug at the core of their design. To address patient-centred research questions, a different type of study will be needed.

Industry representative 1, while admitting pharmaceutical companies are very drug-focused, also underscored that they have understood the importance of patient centricity and are taking active measures to implement this concept more into their development plans, as the pressure from payers and patients to be more patient-centred is increasing. In the current climate, if the industry remained too drug-centred, they would encounter major issues when marketing their products.

A similar view was voiced by many other participants, including **industry representative 3**, **academic clinician 5** and **patient organisation representatives 2, 3 and 4**. While the drug-centred approach had until recently been the standard method for developing new treatments, the industry has been stepping away from this paradigm, realising that such a transition is crucial in the contemporary age of personalised medicine. In addition, the patient voice is becoming stronger, with advocacy groups not afraid to demand that the positions of the therapy's end users are taken into account. The industry is also aware of the added value that patient-centric research can bring to their products, as their efforts to prioritise the needs of patients would eventually be recognised by the payers and rewarded with more favourable reimbursement modalities. All of these factors spur the evolution towards a framework that puts patients at the heart of clinical research.

Additionally, according to **regulator representative 2**, it is not only the industry that is approaching drug development from an increasingly patient-focused perspective: the regulatory authorities have adopted this strategy as well and employ it when assessing clinical dossiers and giving scientific advice to pharmaceutical companies. In the European setting, they have been inviting patients to come to the table and provide their input on aspects related to the design of proposed studies. The importance of patient-reported outcomes is also being recognised more and more by the EMA. On the national level, several medicines agencies of EU Member States have been convening ad hoc working groups which feature patients and have been involving them in the discussions concerning the benefit-risk profile of novel therapies.

3.1.2 Question 2

For patient organisation representatives:

How does the current approach impact patients?

For academic clinicians:

How does the current approach impact clinical decision-making?

For HTA agency representatives:

How does the current approach impact HTA decision-making?

For payer representatives:

How does the current approach impact reimbursement-related decision-making?

For regulator representatives:

How does the current approach impact regulator decision-making?

For industry representatives:

How does the industry justify the current approach they are taking?

Summary

The interviewees who believed that the current drug development paradigm is too drug-centred were convinced that the present approach severely complicates the decision-making of HTA bodies, payers and clinicians. As reimbursement assessments are based on the available results from clinical trials, a costly new drug may be reimbursed either only for a very specific patient population that adheres to the inclusion criteria applied in the studies, thereby limiting patient access to the treatment, or for a group of patients that is more heterogeneous than the sample of trial participants, thus introducing uncertainties with respect to the clinical utility of the therapeutic intervention. In the latter case, a lower price may be negotiated or a managed entry agreement can be set up to mediate further data collection. An overly strong focus on the drug may therefore result in missed opportunities for patients and impact the way physicians operate in clinical practice, since their treatment decisions are influenced by evidence-based guidelines and financial considerations.

As for the impact the current approach in drug development has on their respective fields, the answers varied widely for each stakeholder group, as could be expected beforehand.

Patient organisation representatives

Patient organisation representative 1 again repeated the view that only a small portion of the patients' lives is being explored in clinical trials and that this leads to an incomplete characterisation of the available care pathways, which in addition to the administration of the drug often also include social and psychological interventions as well as physical therapy. In this interviewee's opinion, these and other crucial aspects are being neglected, which ultimately negatively impacts the patient.

Patient organisation representative 4 tackled the question from a much broader perspective, stating that the profit-driven attitude of the pharmaceutical industry has led companies to mainly invest in therapeutic areas that are capable of making them as much money as possible. The argument that the high costs of drug development are the main reason why novel treatments are so expensive does not hold true according to this interviewee. Society needs to question the dogmatic belief that research and policy are two distinct domains which should not to be mixed, seeing as one cannot separate the way research is funded from decisions related to the pricing of and access to innovative therapies. The current situation harms public health in general, the participant asserted.

Patient organisation representative 2 confirmed many of these points, adding that the profit-oriented mindset of pharma companies is also why we do not see combination or comparison studies being performed. Such trials would after all require them to collaborate with competitors, thereby potentially undermining themselves and inadvertently helping their rivals. The drive to corner the market results in missed opportunities and distorts the available therapeutic armamentarium by allowing some medicines to be granted a marketing authorisation in spite of their limited clinical utility.

Patient organisation representative 5 corroborated these sentiments as well, explaining that a lot of resources are being wasted on clinical trials that address either the wrong questions or questions we already know the answer to. For instance, there are many so-called me-too drugs (i.e. medicines with an active substance whose chemical structure differs slightly from that of a first-in-class compound and whose mechanism of action is identical) being developed and marketed whose clinical utility is or will be extremely limited. This in turn slows down research in other therapeutic areas, where patients do not have the luxury of choosing between a multitude of different treatment options. Furthermore, because research expenses are factored into drug prices, it also needlessly drives up the costs of new therapies, which undercuts patients' access to them.

Patient organisation representative 3, who argued that the industry is slowly abandoning the drug-centred research paradigm in favour of a more patient-focused framework, claimed that this transition would allow patients to be involved more in the drug development process, which would benefit them directly.

Academic clinicians

Academic clinicians 1, 2 and 3 expressed how the scarcity of data on optimal durations and combinations of treatments complicates their clinical decision-making, as they often cannot rely on evidence-based guidelines to determine which patients should be treated with a particular drug. This is especially problematic when the first-line treatment for a particular disease has failed and an alternative therapeutic approach needs to be taken, academic clinician 3 said. Moreover, academic clinician 1 declared that the industry sometimes pushes drugs onto the market which have no real clinical value and are therefore of very limited use to physicians.

Academic clinician 4 believed sufficient evidence can be derived from the drug-focused registrational trials for the immediate and short-term administration of treatments to patients, but not enough to support their long-term application.

Academic clinician 5 mainly decried the lack of available clinical trial data on the effects of new therapies on specific patient subpopulations, which severely limits clinicians' options to treat many of the patients they encounter in daily practice. Since the regulators do not typically recommend the use of health technologies in groups of people for whom no evidence of efficacy or safety has been provided by the manufacturer, the payers will not reimburse their application for this particular purpose. Even if a physician might be convinced that a patient with a certain comorbidity could also benefit from being given the intervention in question, there is often no way to initiate the treatment due to its associated costs. In short, the current drug development approach has a significant impact on the decision-making of clinicians.

Regulator representatives

Regulator representative 1 emphasised that it is the regulator who influences drug development and not the other way around, since the industry has to work within the existing legal framework which revolves around the acquisition of data on the quality, safety and efficacy of novel drugs. The interviewee saw little reason to change this framework.

Similarly, although regulator representative 3 acknowledged that clinical trials do not properly inform real-world practice, they considered the evidence obtained from such studies to be of sufficient value to underpin regulatory decision-making.

Regulator representative 2 was convinced that the increasingly patient-focused decision-making methods adopted by the regulatory authorities would make the conclusions of their assessments more valid and acceptable. However, the interviewee also saw challenges with respect to documenting the experiences and opinions of individual patients or specific advocacy groups as a means to investigate the general patient view.

Payer representatives

Payer representative 1 stated that the current clinical trials, which only include homogeneous populations of patients fitting a multitude of selection criteria, have a very limited scope that complicates reimbursement-related decision-making. When the treatment is administered in a real-life setting, the outcomes will not be the same as those observed in the studies that were performed to obtain the marketing authorisation. The participant also added that payers can react to this by negotiating managed entry agreements with the manufacturers in order to ensure that the necessary additional data are collected in the future.

Payer representative 2 thought that the reimbursement procedure at present is mainly being steered by the development of commercial pipelines and not, as it ideally should be, by the unmet medical needs. Taking into account the finite nature of healthcare budgets, the payers should give priority to medicines for which no therapeutic alternatives are available instead of, for example, reimbursing yet another product to treat hepatitis C, for which effective treatments already exist. The current drug-centred approach to developing new health technologies does not sufficiently generate medical interventions that fill the existing treatment gaps.

According to payer representative 3, the regulatory mechanisms to accelerate the drug approval process have aggravated the existing uncertainties that complicate the decision to reimburse therapies. The payers have reacted to this by negotiating more managed entry agreements and restricting the reimbursement to patient groups that will profit the most from receiving the treatment.

HTA agency representatives

The HTA agency representatives all mentioned that they struggle with producing assessments of new treatments based on the information which they currently have at their disposal. HTA agency representative 1 explained that the data are not fit for purpose, mostly because the results of the drug-centred clinical trials cannot be extrapolated to clinical practice. Very limited data on the real-world effectiveness of therapies are available at the time the reimbursement decision has to be made, the participant remarked.

HTA agency representative 3 shared this view, claiming that the present drug development framework introduces a lot of uncertainty which the HTA agencies are confronted with when determining the cost-effectiveness of novel therapies and formulating reimbursement recommendations. This uncertainty also translates to real-life clinical practice, where clinicians and patients will ultimately face the same questions asked by the HTA agencies. As it stands today, the system does not accommodate the stakeholders involved in the post-authorisation decision-making, leading to negative HTA assessments as well as missed opportunities for patients, the interviewee asserted.

HTA agency representative 4 believed that the industry's current modus operandi is to have their drugs approved as early as possible, using the mechanisms launched by the regulators to accelerate the marketing authorisation procedure of innovative treatments addressing an unmet medical

need. As a result of this strategy, only response data derived from single arm trials are available when the HTA bodies have to perform their assessments of the drug, making it difficult to determine its clinical utility. This has a major impact on the decision-making of not just the HTA agencies, but also the payers and the clinicians, the participant stressed.

HTA agency representative 5 claimed that the EMA's approval procedure is poorly designed because it does not require the manufacturer to implement patient-relevant endpoints into their studies, which often means that companies refrain altogether from gathering useful data on overall survival, for example. According to the interviewee, this has made the HTA agencies more powerful and influential, since they are chronologically speaking the first stakeholder that examines how well the drug performed in terms of outcome measures that patients find valuable.

Industry representatives

Industry representative 1 justified the predominantly drug-centred approach the industry is taking by saying that pharmaceutical companies operate within the commercial sphere and therefore need to deliver products that make enough profit to satisfy their shareholders. However, as stated before, the interviewee recognised that patient-centricity is becoming more and more important as payers are increasingly demanding evidence that shows a drug is actually bringing value to patients. Industry representative 2 interpreted patient-centricity mainly in terms of ensuring that the patients have access to innovative treatments, and mentioned the fear of off-label marketing lawsuits as a barrier to providing access outside of clinical trials, especially in the United States. This participant believed that the industry is already undertaking patient-centred initiatives within the context of clinical drug development, and felt these actions were not being adequately recognised.

Industry representative 3, who explained in their answer to question 1 that the industry is in the process of implementing a more patient-centred drug development approach, justified this paradigm shift by framing it in the context of the evolution towards a value-based healthcare system. Payers will recognise the added value that a patient-focused research strategy will bring to real-world clinical practice by negotiating more favourable reimbursement conditions for the resulting health technologies.

Industry representative 4 said that the reason why the industry has become so patient-driven and has launched so many patient engagement initiatives in recent years is to make sure their research really delivers what the patients need, taking into account the fact that they are the end users of the product. Additionally, the regulatory authorities, HTA bodies and payers are increasingly demanding the patient perspective to be included in the drug development process.

According to industry representative 5, the industry's drug-centred mentality is being driven by the guidelines and requirements composed by the regulatory authorities. While the manufacturers are willing to be innovative and implement new types of outcome measures that could be valuable for patients, the regulators are often not very accepting of such deviations from the standard endpoints, which complicates the introduction of changes to the established research framework.

3.1.3 Question 3

What is your opinion regarding the statement that there is a lack of real-world evidence for the use of many drugs on the market today?

If agreement is expressed:

What are some of the reasons, you think, for this lack of real-world evidence?

Summary

The majority of interviewees (18 out of 26) agreed with the assertion that there is insufficient real-world evidence underlying the use of many drugs on the market today. When asked to explain the sparse availability of such evidence, these participants listed a number of different reasons:

- Real-world data collection is complex and costly;
- Evidentiary demands from regulators, payers and HTA agencies diverge;
- Real-world data are perceived to be of poor quality;
- There is a lack of regulatory demands and incentives for gathering real-world data.

Most of the interviewees who did not feel it was accurate to say that there is a lack of real-world evidence for the use of many therapies available on the market today argued that large quantities of real-world data are already being captured and stored by pharmaceutical companies, as illustrated by some of the projects launched with support from the industry in the context of the Innovative Medicines Initiative (IMI). Nevertheless, these participants underscored that there was a strong need for gathering such data in a more well-structured, standardised and transparent manner so that regulatory authorities would be increasingly willing to take this type of evidence into account for their assessments.

The majority of participants (18 out of 26) agreed with the statement that there is a lack of real-world evidence for the use of many drugs on the market today. However, several interviewees noted that the concept of real-world evidence has no clear definition. For example, **HTA agency representative 1** did not believe observational studies could generate sufficiently strong evidence for the real-world effectiveness of a drug.

Conversely, **academic clinician 1** made a distinction between two types of real-world evidence studies, namely the observational studies and the pragmatic trials. The former are performed on data that have already been collected and which are for example contained in registries, health records and insurance files. The latter are interventional in nature, investigating the use of medicines in settings that more closely resemble real-life clinical practice.

A number of different reasons were cited by the interviewees for this perceived lack of real-world evidence.

First of all, the collection of fit-for-purpose real-world data is complex, often requiring the application of advanced data acquisition systems. This makes it difficult and costly for pharmaceutical companies to routinely gather such information. Privacy and data protection laws present additional hurdles to performing real-world effectiveness studies, especially in Europe, where the recently introduced General Data Protection Regulation (GDPR) could undermine data access and sharing according to some interviewees. Moreover, there are significant differences between individual countries in what exactly constitutes clinical practice, which further complicates the gathering of real-world data.

Secondly, the European regulatory landscape is extremely fragmented, with the marketing authorisation being granted at the European level and the decision to reimburse the drug taking

place at the national level. Both processes involve the review of available data but focus on different aspects. The lack of systematic communication between the regulators on the one hand and the payers and HTA agencies on the other leads to the industry prioritising the requirements for regulatory approval by the EMA, which only examines information on the quality, safety and efficacy of the drug and leaves its effectiveness out of consideration. For their subsequent assessments, HTA agencies and payers therefore often cannot rely on the availability of real-world evidence showing that manufacturers' products are actually effective in clinical practice.

Thirdly, even if real-world data are available, they are usually deemed of inadequate quality to inform the decision-making by decision-makers. **Industry representative 3** even used the term 'dirty data' when describing the limited utility of the information derived from most real-world evidence studies today.

Industry representative 2 claimed that the lack of therapeutic standardisation in real-life conditions is a major contributing factor to this issue: if there is no standardised way to prescribe a new treatment, it is not immediately clear whether an apparent lack of effect seen in clinical practice is caused by the drug not being effective, or the result of it not being administered in the optimal way.

HTA agency representative 2 made a similar comment: new medicines are often first given to the patients with the worst prognoses, so if no effects are observed, this lack of response should not necessarily be attributed to the interventions themselves. Moreover, if there is no comparison between the investigational therapy and a particular control treatment and/or no randomisation, the data obtained will be considered less reliable.

HTA agency representative 4 underscored the difficulty of including a control group in studies taking place in a real-life environment, since most patients would want to try the novel drug instead of receiving the old standard of care or placebo. Historical controls may be employed, but these could differ significantly from prospectively collected data.

Industry representative 3 added that a lot of uncertainty remains regarding the use of real-world evidence to inform the decision-making by regulators and clinicians, which is a complicating factor that these stakeholders will eventually have to get used to. For instance, the FDA is now accepting the inclusion of virtual control groups in clinical trials for certain indications, based on earlier recorded information acquired from registries.

Lastly, the manufacturer is usually not obligated to conduct studies designed to assess the effectiveness of new treatments, so there is no pressure on the industry to actually undertake them. As there is no overarching regulatory framework in place, no one is responsible for collecting real-world data at present. There are also no real incentives for any of the actors in the drug development process to take the lead and launch spontaneous efforts to gather such data. For instance, most clinicians would likely not be prepared to perform any supplementary administrative work without being paid an honorarium for doing so, and the industry might refrain from setting up any initiatives in this area because they could uncover additional drug complications that were not detected during the preceding clinical trials. Companies are eager to get their products on the market as soon as possible, supported by regulatory mechanisms to accelerate the approval process and demands of patients and patient organisations for faster access to innovative treatments, while not always sufficiently delivering on their commitments to collect fit-for-purpose real-world data in the post-authorisation real-life environment. European policymakers should incentivise the collection of real-world data and invest in the proper infrastructure to enable the exchange of information across borders.

Despite the fact that both **patient organisation representative 3** and **academic clinician 4** agreed with the initial statement, these interviewees had opposing views on which medicines were affected the most by a lack of effectiveness data supporting their use in clinical practice. While the former

believed that newer drugs had the least amount of real-world evidence underpinning their application in real-life conditions, the latter thought the same of older treatments, which may not have been subjected to the strict evidentiary requirements that are employed by decision-makers today.

Academic clinician 4 also complained about the hypocritical attitude that regulatory authorities are displaying in this respect by solely being concerned about real-world effectiveness when the price of the therapeutic intervention is very high. To this participant, it was clear that the payers only care about the healthcare budget and not about whether the treatment actually works, regardless of how expensive it is.

Industry representative 3, payer representatives 1 and 3 and **patient organisation representative 4** were among the eight interviewees who did not feel it was accurate to say that there is a lack of real-world evidence for the use of many therapies available on the market today. They argued that large quantities of data are already being captured and stored by companies, as illustrated by some of the projects launched with support from the industry in the context of the Innovative Medicines Initiative (IMI). Nevertheless, the participants emphasised that there was a strong need for gathering real-world data in a more well-structured and standardised manner, so that regulatory authorities would be increasingly willing to take this type of evidence into account during their assessments.

In this regard, a set of minimum standards for the collection of such data should be defined to counter the fragmentation seen across European countries, **payer representative 3** proposed. **Patient organisation representative 4** decried the underlying inertia present in the system, with many of the stakeholders involved being too slow in stepping away from established procedures and guidelines. It took a long time for the methodology surrounding the classical randomised controlled trials to become widely accepted, so the same can be expected for studies performed in real-life settings, **payer representative 1** added. According to this participant, the extent and nature of the evidence required for the decision-making by payers should be defined prospectively.

Industry representative 4 strongly disagreed with the assertion that the industry is not providing enough real-world evidence to support the use of their products in clinical practice. On the contrary, the interviewee claimed that there has been an explosion in the creation of such evidence in recent years, which is being driven by a number of different factors, including the growing demand of HTA bodies and regulatory authorities for additional information to facilitate their decision-making, an increased variety of available data sources and advancements in the field of computational health informatics.

Regulator representative 3 also thought that the initial statement was incorrect and explained that there is a wealth of real-world data being gathered by companies to complement the information derived from clinical trials. However, the interviewee did not believe that real-world evidence was capable of bridging the gap between the development of drugs and their application in clinical practice, given the associated lack of comparison with any control data.

Meanwhile, **HTA agency representative 5** argued that such evidence is usually not publicly accessible, undermining its use for the evaluation of the real-life effectiveness of treatments.

Regulator representative 1 did not agree with the original statement as they were not convinced that the regulatory authorities should ask for more real-world evidence than they are demanding right now. The interviewee mentioned that it has never been clearly established that after a drug is approved based on the results of highly selective clinical trials, its toxicity will increase and its effects will decrease in size once it is applied in clinical practice. The participant defended the current clinical development framework, in which real-world evidence is already routinely being collected to complement the information obtained from the phase I, II and III studies. This expert also added

that the inclusion of a heterogeneous patient population to make trials more pragmatic in nature would require them to have a larger sample size in order to detect a statistically significant difference in therapeutic response between the experimental and control treatment, which could overexpose certain subpopulations to unnecessary toxicities, possibly without any health benefits at all.

3.2 Theme 2 – Features of treatment optimisation studies

3.2.1 Question 4

Who should perform treatment optimisation studies (industry, academia, not-for-profit organisations,...)?

Summary

When asked which stakeholder(s) should be responsible for the conduct of treatment optimisation studies, the interviewees gave divergent answers. Nevertheless, two main options emerged from their responses.

The first option consisted of having treatment optimisation studies be performed by academic groups and not-for-profit organisations in the form of independent research institutions, not only because these actors have no ulterior commercial motives, but also due to their prior experience and expertise in this area. Moreover, compared to the industry, they are more pragmatically inclined and more aware of what exactly constitutes real-world clinical practice. However, while manufacturers might have no incentive to engage in applied clinical research, they could still be involved in this process, for example by supplying the coordinating investigators with the study drug at a reduced price or even free of charge.

In the second option, treatment optimisation studies would be undertaken by consortia or collaborative groups comprised of all relevant stakeholders. Proponents of this scenario were convinced that these trials should not be carried out by any single particular actor, as their results are useful for everyone involved in medicines development.

The interviewees gave various different answers to the question of who should perform treatment optimisation studies.

HTA agency representatives

HTA agency representative 1 thought that treatment optimisation studies would ideally be conducted by academia organised in a similar fashion as the EORTC or other independent clinical research institutions, since these actors know the rules of the game and already have the expertise and experience needed to set up such trials. According to this participant, the industry has no incentive to engage in applied research.

HTA agency representative 2 believed that groups of physicians would be the most suitable stakeholders for performing treatment optimisation studies, given the fact that such groups have been responsible for coordinating large pragmatic trials in the past. The interviewee also brought up the possibility of collaboration with the industry and underscored the importance of involving other stakeholders early on.

HTA agency representative 4 was of the opinion that it is the duty of the industry to make sure that data derived from treatment optimisation studies are available for their products. However, the interviewee mentioned one exception: in the case of comparative effectiveness research, one cannot expect the manufacturers to directly compare their novel therapeutic intervention with that of a competitor's, in light of the risk that these trials could indicate that their drug is the inferior one. Here, academia could play a leading role.

HTA agency representative 5 also saw the conduct of treatment optimisation studies as one of the responsibilities of the industry. According to this interviewee, there should be calls from public

institutions and policy makers for trials addressing a specific issue or question that is of particular clinical relevance, to which companies can then respond.

Academic clinicians

Academic clinicians 1 and 2 both argued that it should be academia and non-profit organisations who should carry out these studies independently from any commercial interests, with support from the industry for the supply of the drug under investigation.

Academic clinician 3 thought that the industry would avoid doing dose reduction studies out of fear of losing revenue and that academic groups are therefore best placed to bring treatment optimisation trials to fruition.

Academic clinician 4 voiced their preference for an academic research setting, although they would not necessarily be opposed to the industry aiming their efforts at conducting treatment optimisation studies. Academic groups are typically more pragmatically inclined, more efficient at using resources and more aware of what exactly constitutes the real-life environment, they explained.

Academic clinician 5 made a distinction depending on when in the drug development process applied research would be performed. In the pre-approval setting, it could originate from a collaboration between academic clinicians and industry, in which the former could help the latter with integrating certain questions that are relevant for clinical practice already early into the research protocols, based on the problems they encounter on a day-to-day basis and their knowledge of the unmet medical needs. In the post-approval environment, treatment optimisation studies could emerge from a cooperation between academia and governmental agencies such as HTA bodies. The manufacturer is less likely to contribute to their conduct in this situation, given that they carry significant financial risks.

Patient organisation representatives

Patient organisation representative 1 asserted that at the moment, there is no incentive for any of the suggested actors to perform treatment optimisation studies. In ideal circumstances, the responsibility should fall on academia and not-for-profit organisations, but they do not typically have the financial means to support those activities. The participant also claimed that the industry could be mandated by the regulatory agencies to undertake treatment optimisation studies as part of the post-approval commitments, and then outsource them to academia if necessary.

Patient organisation representative 4 saw academia as the best option for managing these studies, mostly due to the scientific rigor academic institutions could bring to this type of research.

Patient organisation representative 5 felt that the industry has no incentive to be at the forefront of a transition towards a paradigm in which such studies play a prominent role in the generation of evidence, especially considering they might feature head-to-head comparisons between competing products of different manufacturers. Not-for-profit organisations spearheading applied research would be a dream scenario for this interviewee, although they saw funding as major barrier to actualising this approach. Hence, the participant concluded that academic centres are optimally positioned to take the initiative in conducting treatment optimisation studies, not only because they have no ulterior commercial motives, but also due to their prior experience with this kind of research. So-called investigator-initiated trials have for years been tackling the issues that are driving the growing need for treatment optimisation, but are not able to effectively contend with industry-coordinated studies which offer larger compensations to clinicians for the recruitment of patients, the interviewee clarified.

Industry representatives

Industry representative 1 admitted that the industry tries to avoid doing studies that directly compare a new drug with that of a competitor's, as the results could undermine the approval process. The interviewee did not feel confident enough to name a specific actor who should be responsible for treatment optimisation and said that this is something that has to be organised by the health authorities.

Industry representative 2 was convinced that the industry can play and is already playing a major role in the conduct of these studies, and believed that certain aspects of treatment optimisation can be realised by academia (dose de-escalation and head-to-head comparison studies) and others by pharmaceutical companies (combination and duration studies).

Industry representative 5 did not have an explicit preference for any of the suggested stakeholders, as long as they would be able to fulfil the general requirements (e.g. data monitoring, follow-up of subjects, reporting responsibilities) imposed on anyone that is performing clinical research, such as the Good Clinical Practice (GCP) regulations. This interviewee also did not exclude the possibility of cooperation between industry, academia and/or not-for-profit organisations in the context of treatment optimisation.

Regulator representatives

Regulator representative 1 did not want to comment on who in particular should perform treatment optimisation studies, but stressed that it is not up to the regulator to place additional obligations on the industry to implement them, since they fall outside the scope of the current democratically established legal framework.

Regulator representative 2 said that the goals and objectives of these studies will determine who is best suited for conducting them. While academia might play a role, the regulators and HTA agencies could also push the industry to ramp up their efforts through imposing additional post-authorisation requirements on manufacturers or negotiating managed entry agreements with them.

Ideally, according to regulator representative 3, both academia and industry would be involved in the conduct of treatment optimisation studies. The former can formulate interesting and clinically important research hypotheses and questions, whereas the latter has a lot of experience in setting up and coordinating clinical trials. However, the participant added that realistically, funding would present a significant hurdle to the participation of academic institutions. Therefore, the manufacturers would be the only actors for whom it would be financially and organisationally feasible to partake in applied research.

Payer representatives

Payer representative 2 emphasised that the inclusion of not-for-profit organisations and academia in the conduct of treatment optimisation studies is required to improve the legitimacy of the results and to prevent marketing issues from corrupting the design of such trials. Nevertheless, the interviewee also underscored that the industry cannot be excluded either, and that they should be present together with patient representatives during study-related discussions to be able to give feedback and learn from the findings.

Payer representative 3, who shared a similar view as regulator representative 2, explained that various different stakeholders could undertake applied research and that the questions it strives to address and the circumstances under which it takes place will decide who should take the initiative. For example, if treatment optimisation activities are in any way linked to obtaining or maintaining

the marketing authorisation, then the manufacturers should bear the responsibility of organising them, otherwise the burden of evidence generation would be shifted to the public.

Remaining interviewees

A recurring answer was that these trials should not be carried out by any single particular actor, as their results are useful for everyone involved in medicines development. Instead, consortia or collaborative groups composed of all the relevant stakeholders should take up the responsibility of coordinating treatment optimisation research. A response of this kind was given by industry representatives 3 and 4, HTA agency representative 3, patient organisation representatives 3 and 4, and payer representative 1.

Patient organisation representative 4 argued that it does not matter who would take the lead in such a consortium, as long as the desired output is achieved. However, this participant warned against engaging the regulators in any parts of the process beyond the design of the studies, since this would make a later objective evaluation of the data collected impossible.

Industry representative 3 strongly expressed that the industry must always be included as a partner, no matter who is steering the treatment optimisation activities. The marketing authorisation holder is after all ultimately liable for any adverse effects occurring as a result of their product being administered in non-approved combinations or doses. Additionally, the conclusions of applied research would nurture the further development programme of the medicine and could allow the companies to request a change in the label.

While industry representative 4 stated that they preferred to see as much collaboration as possible, this interviewee also believed that all stakeholders should be able to organise treatment optimisation trials independently, as long as the necessary scientific rigor is assured.

3.2.2 Question 5

How should these studies be funded (public funding, private funding, combinations of the two,...)?

Summary

A combination of public and private funding was considered to be either a feasible or the most feasible mechanism for financing treatment optimisation research by a majority of the interview participants (16 out of 26). This was mainly because they believed that the conduct of such studies should be as independent from the commercial interests of the industry as possible, while also recognising that academia or not-for-profit organisations cannot fund them fully themselves. Additionally, both the public and the private sector could potentially benefit from the findings of these trials, and a financial partnership reduces the risk of bias from either side.

Regardless of the eventual funding mechanism of treatment optimisation research, there will always be limited resources available for these studies, which implies that choices will need to be made regarding which topics and treatments to prioritise.

Most interviewees (16 out of 26) saw a combination of public and private funding as either a viable or the most viable mechanism for financing treatment optimisation research. One of the main arguments given in support of this position was that the conduct of these studies should be independent from the commercial pressure of the pharmaceutical industry in order to prevent bias, but that at the same time, academia or not-for-profit organisations do not have the means to fund them fully on a sufficiently large scale. The industry can then contribute by supplying their treatments free of charge. Another reason why many interviewees preferred joint funding partnerships was that both the public and commercial sectors would potentially stand to benefit from the conclusions of treatment optimisation studies. Healthcare systems could realise major savings and improve patient outcomes, while pharmaceutical companies could increase their revenues and negotiate more favourable reimbursement conditions.

Furthermore, a good mix between public and private sponsorship of applied research ensures a balanced protocol and prevents the introduction of bias from either side, as **industry representative 5** explained. In addition, according to **patient organisation representative 4**, financial cooperation can be used as leverage to drive down the costs of innovative therapies.

HTA agency representative 1 saw it differently: this interviewee thought that the healthcare payers should be the main sponsors of these studies, since they are actively asking for more treatment optimisation research to be performed in order to inform their decision-making.

Similarly, **patient organisation representative 5** favoured public over private funding because they considered the payers and society overall to be the main beneficiaries of treatment optimisation, which could help avoid the ineffective use of expensive therapies and thereby lead to reduced healthcare spending. Moreover, if the industry supported applied research financially, they could justify increasing the prices of their products based on these additional expenses. However, while the participant felt that the government should sponsor the conduct of treatment optimisation studies, they also added that there are currently no budgets available for such activities.

Patient organisation representative 2 on the other hand was more cautious about the option of using public resources, keeping in mind that pharma companies could capitalise on positive trial results by expanding the label, thereby boosting their profits. It would also be difficult to allocate a budget for this kind of research if it were to be financed by tax payers, especially when the studies

are carried out on an international level. Decisions on which topics to prioritise would be hard to make in such a scenario, the participant thought.

Industry representative 2 noted that the industry is already financing treatment optimisation, but would welcome more investments from public sources.

Industry representative 4 did not want any restrictions to be imposed with respect to who should be able to finance applied research. All sources of funding should be taken into consideration, including combinations of public and private sponsorship. As the demand for treatment optimisation studies will rapidly increase, any actor capable of providing the financial means to set up such trials should be allowed to do so.

Academic clinician 4 argued that if the marketing authorisation holders alone were tasked with doing treatment optimisation research, they should also be the ones to pay for it fully. If academia were to manage the conduct however, then they should receive financial support from the industry, which will need to be regulated by the health authorities.

Academic clinician 5 believed that in order to ensure the independence of applied research in the post-approval setting, structural funding from governmental agencies would be necessary. Sponsoring by the manufacturer would be sensitive at this point given the potential loss of revenue that would accompany the findings. Nevertheless, one cannot expect the public to invest in individual companies' development programmes, so if certain facets of treatment optimisation would already be integrated into the pre-approval registrational trials, then the industry should not be able to count on tax payer money to finance these studies, especially considering there is still a chance that the drug will fail and never reach the market at this stage.

HTA representative 4 was of the opinion that the manufacturer should pay for treatment optimisation studies involving their own products, except in the case of trials that compare different new treatments with each other under real-world conditions. Since the payers have an active interest in knowing which therapeutic intervention is the most cost-effective one, they can benefit from funding comparative effectiveness research.

HTA representative 5 advocated a transition towards a new system in which health technologies would be publicly owned and the regulatory authorities would launch calls for specific studies as needed, including treatment optimisation trials. Pharmaceutical companies could then answer these calls and conduct the requested studies in exchange for financial compensation. In such a framework, applied research would therefore be funded with public means.

Regulator representative 1 did not want to comment on who should fund treatment optimisation, since they felt it could be perceived as criticism of current funding mechanisms which differ from country to country and are primarily a national competence. However, the participant did mention that insurance organisations should consider investments in this type of research as it could eventually save them a lot of money.

Although **regulator representative 3** was not against the idea of a joint public-private sponsorship, they were not convinced of the feasibility of public funding, explaining that clinical trials are seldom organised without financial support from the industry. In fact, most of the studies that regulators use for their decision-making are fully funded by the manufacturers. This does not take away from their power to demonstrate certain treatment effects, so it should not be an issue for applied research either, the interviewee claimed.

While **payer representative 3** expressed their preference for a combined public-private funding mechanism, they also stressed that healthcare systems should not be expected to pay for further evidence generation in addition to reimbursing the therapeutic intervention for patients, unless the research in question would result in substantial cost savings. The interviewee also mentioned

studies that investigate whether a reduced treatment duration would achieve the same outcomes as examples of trials that could be partially financed by the payers.

An important point that some interviewees brought up was that no matter how treatment optimisation is going to be financed, choices will have to be made regarding which topics and medicines to focus on as there will not be infinite resources to spend on these studies. Therapies can be optimised endlessly and there are countless amounts of treatment combinations that can be investigated. The therapeutic areas and products that are affected the most by the current lack of applied clinical research need to be identified and given priority.

3.2.3 Question 6

When should these studies best take place in the drug development process?

Summary

There was no clear consensus among the people interviewed concerning the optimal timing of treatment optimisation. Some participants were convinced that the studies in question could already be initiated before the therapy has been approved by the regulatory authorities, while others considered the post-authorisation conduct of these trials to be the most realistic option. Nevertheless, several of the interviewees that saw treatment optimisation taking place exclusively in the post-approval stage of the drug development process emphasised that the questions to address and the type of information to collect should preferably be defined as early as possible, for example during phase three, so that applied research can start immediately after the therapy has received marketing authorisation.

Multiple interviewees thought that treatment optimisation could commence prior to the EMA's evaluation of the marketing authorisation application and should not be confined to the post-approval setting.

For instance, **HTA agency representative 1** argued that these studies could already be implemented during phase III of the drug development process and defended their view by asserting that the evidence obtained through treatment optimisation research is needed as early as possible to ensure informed decision-making by regulators, payers and the HTA bodies advising them. However, the participant did note that this would necessitate a strong collaboration between the EMA and the payers.

HTA agency representative 2 also advocated the pre-approval approach, but mainly for treatments that will be applied in large populations, since it would reduce the uncertainty clouding the subsequent reimbursement decision. For other therapies, a more suitable strategy could perhaps be to register them based on the findings of smaller randomised controlled trials, which would then be followed by post-approval treatment optimisation studies.

Patient organisation representative 1 said they would ideally like to see treatment optimisation being introduced early on to ensure that the data will be available on time to inform the decision-making of payers, but that this would require a complete overhaul of the current framework as well as more advanced stakeholder engagement, which is currently not yet possible in their opinion. The present system only allows for post-approval applied research.

Patient organisation representative 2 believed that the objective of dose reduction could be tackled in phase II of the drug development paradigm, while combination and comparison studies can be carried out in parallel with the classical registrational trials in phase III. For this participant, it was important that treatment optimisation already takes place before the treatment is on the market, because some compounds might not be approved as single agents, but could possibly be authorised for use in patients as part of combination therapies with other products. If applied research were solely undertaken in the post-approval environment, such potentially effective treatment strategies might never be investigated in the first place.

Patient organisation representative 3 and **payer representative 2** thought that this type of research could start in phase III and continue on for many years after the marketing authorisation has been granted.

Patient organisation representative 4 described how treatment optimisation should be a thread running through the entire development process, from the initial stages to the post-authorisation setting, and that it should therefore be partially integrated into the pre-approval research.

A similar answer was given by **industry representative 4**, according to whom applied research could be organised in parallel with the registrational phase I-IV studies, in order to fill any evidence gaps that might not be covered by the conventional trials. For example, while pharmacovigilance activities in the post-marketing setting mainly focus on safety issues encountered in real-world clinical practice, treatment optimisation studies could concurrently investigate the long-term efficacy of the therapy, which would produce useful information for HTA agencies as well as clinicians.

Academic clinician 3 explained how academia-led treatment optimisation studies are currently always performed after the treatment is available on the market and that this should change since pharmaceutical companies prioritise their own commercial interests, to the detriment of patients and society. For example, the industry will likely collect data on what the effects of a dose reduction are on the activity of a particular drug, but then subsequently never publish this information to avoid losing revenue. If academia undertook applied research early on, substantial savings could be realised and patients could be spared of unnecessary side effects resulting from the needlessly high dosage given. However, the interviewee added that they did not believe this was possible at present as the business world would not want to relinquish control over the therapy's development programme at this point in time.

HTA agency representative 4 was of the opinion that treatment optimisation studies investigating the effects of a therapeutic intervention on a diverse set of subjects that closely resembles the real-world population could already take place during phase III. Today, there are often no outcome data available for patients that were not included in the highly selected and uniform groups of participants studied in clinical trials, such as elderly or comorbid people. This should change according to the interviewee, since it is very difficult to collect such information once the drug is on the market. After all, nobody would want to take part in a study in which there is a chance that they could be assigned to the control group if the novel medicine can also be accessed outside of a research setting. Moreover, ethics committees will likely not approve the trial protocol in this scenario. Other aspects of treatment optimisation, including dose reduction, optimal treatment duration and comparative effectiveness, could be addressed in the post-approval environment, so as not to delay manufacturers' development programmes or increase their expenses.

HTA agency representative 5 was convinced that a therapy cannot be approved if it is not known how long it should be administered to achieve the desired effects or in which subpopulations of patients it would be most effective. Hence, this participant thought that applied research must be organised in the pre-authorisation stage.

Industry representative 3 asserted that treatment optimisation could begin as soon as the first patients receive the investigational medicine, so quite some time before the marketing authorisation application is submitted. The participant expressed their belief that this could be achieved by incorporating applied research within the adaptive pathways framework introduced by the EMA. This approach would expand in a step-wise fashion the patient population in which the therapy is authorised for use, based on additional evidence collected along the way, such as the findings of treatment optimisation trials. The conventional drug development paradigm only allows such studies to be performed after the EMA has approved the health technology, the interviewee claimed.

Ideally, treatment optimisation should take place before the marketing authorisation procedure has been finalised, **regulator representative 3** asserted. This would allow the evidence it generates to be taken into account during regulatory assessments of product dossiers, which would resolve the

uncertainties complicating the decision-making process. However, to realise this strategy, the regulators would have to take action and coerce the industry into conducting applied research, since the latter has no interest in collecting these data without being forced to do so. Such additional obligations could cause the market launch to occur later than normal. The post-authorisation approach could therefore present a pragmatic compromise, the interviewee concluded.

In **payer representative 1's** opinion, treatment optimisation should be done as early as possible, but only once there is a reasonable indication that the drug will successfully complete the different research phases. Otherwise, more money could be wasted on medicines that will never reach the market.

Payer representative 3 insisted that certain elements of treatment optimisation could already be addressed in the pre-authorisation setting (e.g. identification of subpopulations in which the medicine is or is not effective, elicitation of patient preferences), while others may be tackled in the post-approval stage (e.g. comparative effectiveness, dose reduction, optimal duration, therapy adherence).

The interviewees who claimed treatment optimisation studies would best be set up and carried out only after the drug has been approved by the regulatory authorities explained their reasoning using various different arguments.

Academic clinician 1 was wary of the pre-approval approach, since they feared that this would give the industry too much power to influence the design and conduct of these studies. Furthermore, they predicted that it would drive up the prices of new medicines, as the development stage could be significantly prolonged due to the additional time it takes to organise supplementary studies.

Regulator representative 1 and **industry representative 1** stated that a treatment can only be fully optimised once it has entered the market, and that a drug's efficacy has to be fully characterised before its effectiveness can be determined. Similarly, **patient organisation representative 5** said that the results of the registrational clinical trials have to be known before treatment optimisation can commence. Like industry representative 3, this interviewee also brought up the possibility of implementing applied research into the adaptive pathways framework, but not before the initial approval of the therapy in a narrow patient population. That way, its findings would be available to inform the reimbursement-related decision-making as the product is gradually authorised for use in more and more patients. However, the participant stressed that the process should be streamlined to ensure the pre- and post-approval studies follow each other in rapid succession. This can only be achieved by planning ahead and anticipating the design and conduct of treatment optimisation trials while the drug is still being developed.

Academic clinician 2 did not believe that the industry would be interested in supporting or allowing the conduct of pre-approval treatment optimisation studies involving their products. Instead, these studies could potentially be done in the timeframe between the granting of the marketing authorisation and the decision to reimburse the drug, this participant suggested.

Academic clinician 5 argued that by involving clinicians in a company's plans to develop a new health technology, certain facets of treatment optimisation could be incorporated into the design of the registrational clinical trials early on. Based on their knowledge of the unmet medical needs and the problems they encounter in daily practice, physicians can formulate patient-relevant research questions and help determine how study participants differ from real-world patients. However, applied research itself would only be undertaken once the drug has been launched onto the market, at the initiative of academia.

Industry representative 2 warned that if treatment optimisation studies are performed too early, this could delay or even prevent access of patients to innovative treatments. They gave as an example the drug Perjeta[®], which is widely recognised today as a major advance in the treatment of

metastatic and early breast cancer, but almost never made it to the market because of this exact type of trials being done before approval of the drug, according to them. A lag in patient access to novel therapies was also anticipated by **academic clinician 4** and **HTA representative 3**, who for that reason favoured the post-approval strategy.

Although **industry representative 5** acknowledged that applied research could perhaps be organised after phase II in the pre-authorisation setting, they added that this would necessitate a well thought-out plan and that companies would be reluctant to invest additional resources into the development of their products. According to this interviewee, a more realistic approach for involving the industry in the conduct of treatment optimisation studies would be to include such trials as part of the post-authorisation commitments imposed on the manufacturer in the context of the EMA's conditional approval mechanism. Hence, the participant preferred post-approval applied research.

3.2.4 Question 7

What would be some of the most important features that treatment optimisation studies should have (in terms of objectives, recruitment, randomisation, blinding, follow-up, outcomes, reporting, etc.) to be as relevant as possible for clinical practice?

Summary

When asked which features treatment optimisation should ideally have, the interviewees listed the following elements:

- They should have fewer inclusion and exclusion criteria than the classical clinical trials;
- They should employ the standard of care or the best available alternative treatments as comparators;
- They should implement outcome measures that are relevant for patients;
- Some participants believed randomisation would be necessary to reduce bias and ensure the robustness of the results, while others saw it as a barrier to simulating real-world conditions;
- Some interviewees thought blinding would be needed to increase the validity of the outcomes, while others preferred an open-label design because it more closely approaches real-life clinical practice;
- All results should be published, regardless of whether they reflect well upon the therapy or not.

Not all interviewees felt that they had enough knowledge of treatment optimisation studies to answer this question, but those who did respond brought up the following features, which are mainly applicable to interventional trials. For observational studies, many of these aspects cannot be controlled.

Patient selection

With respect to the recruitment, fewer exclusion criteria should be applied, and the effects of the drug should be examined in more diverse subpopulations, e.g. patients with comorbidities, elderly patients, smokers, patients taking multiple additional medications, cancer patients with a poor performance status, etc. Moreover, trial subjects should not solely be recruited by academic clinicians in university hospitals, but also by primary care physicians or specialists working in smaller or private hospitals. A more pragmatic and less stringent selection procedure will generate a sample of participants that is reflective of the true patient population. The focus should lie on the real patient, rather than the ideal one.

Current recruitment strategies, while useful for demonstrating the efficacy of therapeutic interventions, slow down the clinical development process and have made pharmaceutical companies look to less developed countries in order to find patients that satisfy all the inclusion criteria and who do not have access to effective alternative treatments. However, this raises questions about the applicability of the eventual findings to patient populations in Western countries. Nevertheless, these conventional methods for selecting participants should not be abandoned, but simply applied in the right context, namely that of the classical registrational trials. Treatment optimisation studies should adopt a broader perspective.

Randomisation

Some participants believed that randomisation would still be necessary to reduce bias. Without randomisation, the results of these studies will likely not be considered robust enough by regulatory agencies or clinicians to inform their decision-making, according to them. However, they also acknowledged that it is not always feasible to randomise patients to parallel treatment arms. In rare diseases for example, the extremely limited number of potential participants and the lack of therapeutic alternatives does not realistically allow for the presence of control groups. Other interviewees saw randomisation as a barrier to simulating real-world conditions, since patients and doctors outside of trial settings can actively choose which treatments they will undergo or administer. Industry representative 5 added that if the study is large enough, randomisation would not be needed, as long as its omission does not undermine the statistical analysis of the trial data.

Blinding

Similarly, there was disagreement among the interviewees on whether blinding would be required in treatment optimisation research. Several participants thought that the act of blinding the trial subjects and investigators to the intervention they were allocated to receive or assigned to administer would be necessary to increase the validity of the results. Conversely, others believed that it would ultimately diminish the value of the conclusions, as patients and physicians in real-life clinical practice are actually aware of which treatment they are receiving or prescribing.

Perceptions they have about the medicine can influence its effectiveness but are ignored in blinded studies, which is why an open-label setting would be preferred by these interviewees. In addition, blinding is not always feasible, and patients today may be technologically adept enough to figure out which treatment arm they were assigned to by looking up information on the internet and communicating with each other via social media.

Comparator treatment

Active comparators should be used, and they should constitute the standard of care or the best available alternative treatments. Since what is considered standard of care varies widely between different regions, the comparator will differ from country to country as well. However, HTA agency representative 2 warned that this could introduce a bias in the sense that new treatments will typically be first adopted by university hospitals, so if you then compare the new drug with an existing, widely applied therapy, any differences in effect you observe could also be attributed to the disparity in settings (academic versus general hospital). Academic clinician 5 stressed that the comparator should not be chosen out of opportunism, as is often the case today. The comparison in question is only valid if the way the control treatment is administered reflects how it is utilised in real-world clinical practice.

Patient organisation representative 2 and industry representative 4 offered a different take on the nature of the comparator treatment as well as the necessity of randomisation and blinding. According to these interviewees, synthetic control arms could be implemented, based on aggregated data collected from earlier performed trials. If such virtual comparators were introduced, there would be no need for randomisation or blinding, as every study subject would just be given the novel therapy of interest. Patient organisation representative 5 and HTA agency representative 4 shared a similar view and brought up the possibility of using historical control data as a way to avoid having patients randomised to treatment arms in which they will not receive the investigational medicine.

Outcome measures and endpoints

The outcomes must be relevant for patients and should be able to objectively express the drug's effects in real-world conditions. Some of the examples of useful outcomes quoted by the

participants were quality of life, overall survival, time to treatment failure, treatment duration, long-term effectiveness and toxicity, and patient-reported outcomes. Regulator representative 3 on the other hand believed treatment optimisation studies should employ the same outcome measures as the ones used in the registrational trials that preceded them, thereby allowing them to be validated.

Reporting of results

Concerning the reporting of the results, all data should be published, regardless of whether they reflect well upon the drug. New journals should be established for this purpose, since the current high-impact ones favour classical phase II or III studies with positive results. Transparency is key because the findings of treatment optimisation research need to inform regulatory and clinical decision-making.

3.2.5 Question 8

What would be the best setting for the conduct of these studies (local, national, international)?

Summary

The majority of the interviewees did not have a preference for a specific setting and argued that this particular aspect should be determined on a case-by-case basis. However, some interviewees explicitly favoured a national setting, arguing that differences in standard of care and population characteristics between countries render country-level data extremely valuable for HTA and payer decision-making. Nevertheless, they did not exclude the possibility of international coordination and cooperation in the setup and conduct of treatment optimisation studies.

Most participants did not express a preference for a particular setting, stating that this is something that should be decided on a case-by-case basis, since it depends on the type of disease and intervention that are being investigated in the study. Rare disorders and orphan drugs would for instance benefit from an international approach, whereas infectious diseases are often restricted to specific geographic areas, making a locally or nationally conducted trial the most obvious choice. Additionally, there are merits as well as limitations associated with each possible setting, which underscores the need of having prior knowledge of the context in which a treatment optimisation study will be organised before singling out a specific setting as the optimal one.

However, for those interviewees who did explicitly favour one of the options over the other two, a national setting was seen as the most appropriate alternative for carrying out treatment optimisation studies. Only four participants believed that applied research should ideally be undertaken internationally.

Patient organisation representative 4 argued that the international approach would enable as many patients as possible to have access to innovative therapies. **HTA agency representative 1** stressed that high-level treatment optimisation evidence can only be produced by trials with a sufficiently large sample size, for which international collaboration will be required. **HTA agency representative 4** was convinced of the added value that a multicentre, multinational setup could bring to the conduct of treatment optimisation studies. Not only would it improve the quality of the research by preventing one country or site from dominating the collection of data, it would also allow the recruitment of subjects with a distinct genetic makeup to proceed faster for trials in oncology due to the larger pool of available patients.

HTA agency representative 5 was adamant that any differences in the way patients with a given disease are treated between countries are minimal and should not interfere with initiatives to set up treatment optimisation studies across national borders. If needed, subgroups reflecting such inter-country discrepancies can nonetheless be introduced during the trial design. Other advantages of an international applied research setting that were mentioned by the interviewees include its relevance for the EMA's regulatory assessments, its efficiency (one protocol and one methodological framework for multiple countries) and its potential for comparisons of the outcomes between EU Member States.

Patient organisation representative 2 on the other hand argued that this was the wrong question to ask: for the patient, the only setting that counts is their hospital. Whether a treatment optimisation trial is best performed locally, nationally or internationally is mainly determined by whose criteria it is designed to satisfy. HTA bodies and payers might demand more locally or nationally collected data, while EMA or FDA requirements could necessitate internationally organised initiatives.

All other interviewees gave a similar argument to justify their support for a national setting: standards of care can vary widely between different countries, making it difficult to design studies with overarching objectives that are relevant for most nations. Even on just the European level, the treatment landscape for many diseases can be very fragmented. In addition, the effectiveness of drugs can be influenced by ethnicity and genetic diversity, further complicating international treatment optimisation efforts. Hence, since it is important for clinicians to have access to information that is applicable to the patients they see in daily clinical practice, the conduct of applied research would have to be limited to environments in which there is a certain degree of homogeneity in the availability of different therapeutic options as well as the genetic profile of potential participants. Furthermore, as mentioned above, HTA agencies and reimbursement authorities typically operate on a national level and therefore place great value on country-level data, so if treatment optimisation strives to influence payer decision-making, a national setting could generate more convincing and impactful evidence. In the case of combination studies, it would likely also be more efficient to distribute the large number of possible combinations to be tested over multiple countries, instead of setting up a single large, centralised, comprehensive international trial. Moreover, an international setting would necessitate intense collaboration between countries with possibly very dissimilar healthcare systems and economies, and coming to agreements regarding funding and data ownership could pose a major challenge. This would likely mean that a national approach would deliver results considerably faster than a multinational strategy if recruitment is not an issue.

Regulator representative 3 added that applied research should be able to show that the findings of earlier performed registrational trials can be extrapolated to the national context by replicating their outcomes in a country-specific environment.

Nevertheless, the majority of the participants favouring a national setting indicated that international coordination and oversight of nationally organised treatment optimisation studies still remains possible. Protocols could be exchanged and data shared between countries to ensure learnings are implemented and results can be compared. Furthermore, efforts to introduce more standardisation into the conduct of applied research are best undertaken through the creation of international guidelines.

3.2.6 Question 9

How would members of your stakeholder group react if they were invited to contribute to the planning and conduct of treatment optimisation studies?

Summary

Although all interviewees believed that members of their stakeholder group would want to contribute to the design and conduct of treatment optimisation studies, they listed several challenges that could undermine their commitment to such activities.

All participants thought that the members of their stakeholder group would be interested in contributing to the design and conduct of treatment optimisation studies. However, several challenges were cited by some of the interviewees that could jeopardise their willingness to devote themselves to such activities.

Academic clinicians

The academic clinicians worried that they would be compensated less than for classical randomised controlled trials, given the limited funding that is currently being made available for treatment optimisation research. Additionally, the results of pivotal phase II or III trials are typically published in high-impact scientific journals, thereby furthering the academic careers of the clinicians involved. The interviewees did not anticipate the same kind of recognition emerging from their involvement in treatment optimisation studies. Both of these aspects would be especially problematic when investigators have to choose between recruiting patients for industry-sponsored trials, which offer them a multitude of perks in exchange for their time and efforts, or for treatment optimisation studies, which likely cannot match those benefits.

HTA agency and regulator representatives

The HTA representatives warned that their agencies are already under-resourced and under-staffed for their present responsibilities. Furthermore, if these treatment optimisation studies took place in an international setting as some participants advocated, then this would create additional issues due to the national framework in which HTA agencies operate. Moreover, HTA agency representatives 2 and 3 feared that their involvement could introduce a bias, since HTA agencies are probably more inclined to produce favourable assessments for medicines whose development they were actively involved in. A similar argument was given by regulator representative 1, who did not think the regulator should have a say in how trials are designed out of concern that the risk for conflicts of interest to arise would be too great. Their contribution must be limited to giving scientific advice to the organising parties, as is currently done when a company explicitly requests such guidance.

Payer representatives

Payer representatives 2 and 3 noted that payers do not have the resources to join discussions surrounding the design and conduct of treatment optimisation studies every time a new trial is planned. Instead, they would only participate occasionally, mostly when the impact of these studies is expected to be large, such as in therapeutic areas where there is an urgent need for more applied research. If the payers do not derive any concrete gains in terms of their own goals and objectives from their participation in these dialogues, they will halt their support and refuse to attend future meetings.

Patient organisation representatives

Although the patient organisation representatives showed great enthusiasm about the prospect of being invited to discuss the design of treatment optimisation studies, they also openly admitted that most patients and patient organisations are not ready yet to commit themselves to such an advisory role in a meaningful way. It would require a complete overhaul of the current system, with the creation of new methodologies and strategies to find patients and patient advocacy groups and subsequently recruit, train, mentor, involve and support them. Without the implementation of such changes, it would be too difficult to generate useful results from the incorporation of the patient perspective.

3.2.7 Question 10

What could members of your stakeholder group bring to the table?

Summary

The interviewees had a clear view of what the members of their stakeholder group could contribute to the planning and conduct of treatment optimisation studies.

Each interviewee answered this question from the perspective of their own field of expertise.

HTA representatives

The HTA representatives thought the input of their agencies would reflect the activities they are currently already doing, such as performing systematic literature reviews and making sure that the results of the studies can be interpreted by health economists for the purpose of producing cost-effectiveness assessments. Moreover, these inter-stakeholder dialogues would present them with the opportunity to express which type of data they need for their decision-making and to voice their concerns about the selected outcome measures or comparators that might not be appropriate for predicting clinical utility. In this regard, the PICO (Population, Intervention, Control, Outcomes) process can offer a structured method to address trial aspects that are of relevance to the HTA side.

HTA bodies also typically have prior experience in collaborating with patients and patient organisation representatives and could therefore facilitate the involvement of these actors in the discussions. HTA agency representative 5 added that the parallel advice framework, which allows manufacturers to request early feedback on their development plans from both the EMA and multiple national HTA agencies simultaneously, could serve as a platform to launch more extensive inter-stakeholder initiatives.

Industry representatives

The industry representatives underscored the industry's experience with conducting clinical trials, as demonstrated by the complex systems they have in place and the networks they have built up over the years with clinicians around the world. For the collection of real-world data, their partnerships with big technology companies could prove to be useful. Pharmaceutical companies also have a wealth of expertise at their disposal, which would facilitate the design and conduct of treatment optimisation studies. Instead of disregarding the supplementary information the manufacturers have collected about their products in the past but which often goes unpublished, it makes more sense to engage them directly and offer them a seat at the table to provide input.

Academic clinicians

The academic clinicians highlighted their knowledge of the underlying pathophysiology of the disease as well as the present treatment landscape. Their awareness of the unmet medical needs would help identify the therapeutic areas in which treatment optimisation is needed the most. Additionally, their direct contact with patients allows them to better understand what can be done to optimise therapies from a patient-centred point of view. Many academic clinicians are also experienced investigators and are familiar with clinical trial design. Furthermore, they could have some suggestions for research topics to investigate, including promising combinations, lower dosage strengths or reduced treatment durations, based on their observations regarding off-label use of registered medicines in real-life clinical practice.

Patient organisation representatives

The patient organisation representatives thought that patient organisations could defend the interests of patients, giving them a platform to convey what they expect of treatment optimisation studies and to ensure that the conclusions of these trials are of value to them. Both disease-specific and more general overarching patient organisations could be involved according to the interviewees. These advocacy groups or even the patients themselves could bring to the table what it is to live with the disease, all the while making sure that the patient remains at the forefront of the debate.

In addition, they have a much more end-to-end mindset than most other stakeholders, meaning that they will approach the research topics backwards and first ask themselves what the real-world application of the product will be. Lastly, they can help ensure that the benefit-risk balance of taking part in the trial remains positive by assessing whether the burden imposed on the participants does not outweigh the therapeutic effects they are expected to experience.

Regulator and payer representatives

Regulator representative 1 believed that the regulators should not press too hard for the inclusion of any particular design features which they would like to see being implemented into treatment optimisation studies, citing the risk of bias (see also question 9). They could however give feedback on the methodological setup of such studies in the form of scientific advice, as they currently do for the conventional registrational trials at the manufacturer's request.

Regulator representative 2 and the payer representatives on the other hand saw a multi-stakeholder platform as the ideal environment to provide further clarification on the type of evidence they require for their decision-making, just like the HTA agency representatives did. Moreover, they asserted that they would utilise such an opportunity to accentuate potential gaps in the available data and to recommend potential research topics that could be addressed in treatment optimisation trials.

Payer representative 3 noted that most payers independently collect considerable amounts of data on the real-world utilisation of registered medicines, which could generate valuable insights for the design of these studies.

Regulator representative 3 was of the opinion that the regulatory authorities could assist in assessing the methodology of applied research and facilitating the dialogue between academia and the industry. Their expertise in evaluating the results of clinical trials could also prove to be beneficial.

3.2.8 Question 11

Which other stakeholders should be at the table?

Summary

The majority of interviewees believed that discussions surrounding the planning and conduct of treatment optimisation studies should take place in the presence of (1) patients and/or patient organisations, (2) physicians and clinicians from both academic and community hospitals, (3) academic groups and independent research organisations, (4) the pharmaceutical industry, (5) payers, (6) HTA agencies and (7) regulators.

Most participants named the same group of stakeholders when asked who else should be present at the table during the planning of treatment optimisation studies, namely:

- Patients and/or patient organisations
- Physicians and clinicians (from both academic and community hospitals)
- Academia and independent research organisations such as the EORTC
- Pharmaceutical industry
- Payers
- HTA agencies
- Regulators

The reasoning behind these particular answers largely overlapped with the explanations given in the replies to question 10, in which each interviewee described what their own stakeholder group could bring to the table. This suggests that the participants have a good view of the potential contributions of each other's stakeholder groups.

Nevertheless, there were several participants who objected to the inclusion of some of the actors listed above. For instance, **patient organisation representative 2** warned that the cautious attitude of regulators could hold back progress and discourage other stakeholders from supporting innovative strategies aimed at addressing the issues of the current drug development paradigm.

HTA agency representative 5 on the other hand did not want organised patient groups or professional patient advocates to be present during the discussions and would prefer it if their seat at the table were instead given to actual patients.

Lastly, **industry representative 5** felt that the demands of the payers and HTA agencies would conflict with those of the regulatory authorities, which could undermine the efforts to organise inter-stakeholder dialogues and result in lost opportunities. The former two actors could easily be replaced by market access experts, the interviewee claimed.

Some interviewees mentioned that lawmakers (i.e. the European Commission), contract research organisations (if their services are needed) and scientific societies like the European Society for Medical Oncology (ESMO) could also be invited to take part. **Patient organisation representative 2** believed that other healthcare professionals such as nurses and pharmacists should be included as well, the former due to their day-to-day care of the patient and their awareness of what exactly comprises real-world clinical practice, the latter because of their knowledge of the treatment's potential for interactions with any concomitant therapies.

3.3 Theme 3 – Acceptability of treatment optimisation studies

3.3.1 Question 12

What is your opinion on the assertion that regulatory agencies should take measures to facilitate treatment optimisation?

If agreement is expressed:

What kind of measures should be taken?

Summary

There was broad support among the participants for regulatory measures to facilitate and support treatment optimisation, although there was no agreement on the optimal size, scale and nature of these initiatives.

Some interviewees favoured strong action and wanted to make it mandatory for the industry to undertake applied research. This could be achieved by implementing treatment optimisation studies into the regular marketing authorisation procedure, the conditional marketing authorisation procedure or the conditional reimbursement procedure.

Other participants feared that making treatment optimisation compulsory would ultimately prolong the time to approval and/or reimbursement, thereby increasing the costs of drug development and preventing timely access of patients to novel therapies. Instead, they expressed their preference for an approach in which applied research would be incentivised rather than mandated, for example by offering companies which undertake treatment optimisation studies extended periods of market or data exclusivity.

Moreover, according to these interviewees, the regulatory authorities could take measures to promote applied clinical research by coordinating workshops, debates and discussions on this topic, setting new assessment criteria for trials of this type and giving early scientific advice to stakeholders involved in their conduct.

While the interviewees supported the introduction of regulatory measures to facilitate treatment optimisation, they did not agree on the optimal size, scale and nature of such initiatives.

Patient organisation representatives

Patient organisation representative 1 advocated the creation of consortia of public health bodies to stimulate mutual cooperation for the purpose of agreeing on a strategy to facilitate applied research and take its findings into account during their assessments. Moreover, this interviewee wanted the conduct of treatment optimisation studies to be mandatory.

Patient organisation representatives 2 and 4 were very supportive of this idea as well. Nevertheless, they disagreed on the regulatory mechanism through which such trials could be enforced, mostly depending on when they thought these studies should take place (see also question 6).

Patient organisation representative 3 however feared that making treatment optimisation compulsory would ultimately prolong the time to approval, thereby preventing timely access of patients to novel therapies. This participant was only willing to accept applied research as a supplementary requirement if it were guaranteed that the drug would be approved.

Similarly, patient organisation representative 5 did not believe that the availability of data derived from treatment optimisation trials should be a prerequisite for market access. Furthermore, this interviewee was of the opinion that while the regulators should coerce the industry into taking up patient-centred outcome measures such as quality of life as standard endpoints in the conventional clinical trials, they must also provide incentives to companies for engaging in applied research. Additionally, the involvement of patient organisations in the early dialogues between the EMA and the manufacturer should be obligatory according to this participant.

Academic clinicians

Academic clinician 1 argued that the HTA agencies should ask the manufacturer to deliver evidence on the real-world effectiveness of their products within a certain timeframe. Moreover, all European HTA bodies should collaborate with each other and with the EMA to ensure treatment optimisation is undertaken in the post-approval environment. Applied research programmes could also be launched within the frameworks of IMI and Horizon Europe.

Academic clinician 2 proposed that the regulators would look at the number needed to treat (NNT) and the number needed to harm (NNH) during their review of the available data in the context of the marketing authorisation procedure. If the NNT is too high and/or the NNH too low, they should demand to see the findings obtained from additional trials that take place in real-world settings, including treatment optimisation studies.

Academic clinician 3, who saw academic groups as the most appropriate stakeholders for performing treatment optimisation studies, asserted that the regulatory authorities need to facilitate the funding of such research, for example by forcing pharmaceutical companies to finance the work of academia. Furthermore, this participant did not think that the same regulatory requirements that govern the conduct of industry-sponsored clinical trials should be applied to studies carried out in an academic environment. The rigorous quality demands and the associated costs can cripple non-commercial clinical research, so a different set of standards should be employed for evaluating its setup.

According to academic clinician 4, a milestone system should be implemented, in which treatments are initially approved for a set amount of years and additional evidence has to be collected within that timeframe. The consequences of not doing so would then depend on whom is tasked with conducting treatment optimisation studies. If the industry is responsible for performing them and the relevant milestone is not reached in time, the therapy should not be made available or reimbursed anymore. If the payers or academic groups are supposed to undertake applied research but refrain from launching any significant efforts, access to the medicine should not be restricted in any way and the reimbursement should be continued until the drug is proven to be ineffective.

Academic clinician 5 said that the EMA should be able to obligate the manufacturer to already integrate certain features of treatment optimisation studies into the design of the registrational trials. The inclusion of patients and/or patient organisations in the exploratory inter-stakeholder discussions could also be imposed by the regulatory authorities.

HTA agency representatives

HTA agency representative 1 thought that the regulators could permit the actors responsible for organising treatment optimisation studies to opt out of certain legal requirements surrounding the conduct of clinical trials. The participant gave as an example the dispensing of the investigational drug, which, in order to simulate a real-world clinical environment, could be done by a regular pharmacist instead of a hospital pharmacist working at the trial site. In addition, the interviewee repeated that a more intense collaboration between the regulators and the HTA agencies would be most helpful.

HTA agency representative 2 was convinced that the regulators would not be very interested in facilitating applied research and claimed that HTA agencies and physicians would be better suited to ask for treatment optimisation studies to be undertaken. Nevertheless, this interviewee believed that the regulatory authorities and/or payers could set up conditional approval and/or reimbursement schemes which force the manufacturer to collect additional treatment optimisation data within a certain timeframe. If the requested evidence is not provided before the agreed deadline or if the results reflect poorly upon the product, earlier made decisions to approve and/or reimburse the therapy may be revised. Such revisions are to be prevented since they could lead to obligatory price reductions, less favourable reimbursement conditions, or even marketing authorisation retractions.

HTA agency representative 3 mainly spoke about how the current legislation surrounding the regulatory approval of medicines will need to be adapted to include the conduct of treatment optimisation studies as part of the post-authorisation requirements imposed on the marketing authorisation holders. The interviewee also mentioned risk-sharing schemes organised by the payers as a model to coerce the industry into carrying out more of these trials.

HTA agency representative 4 would obligate the manufacturer to perform certain types of treatment optimisation studies already in the pre-approval setting (see also question 6), as a compulsory step in the path to regulatory approval. This participant would also allow the GCP rules to be relaxed for comparative effectiveness trials done by academia, so that these international regulations would no longer form a barrier to the conduct of academic applied research.

According to HTA agency representative 5, the regulators should wait until applicants have presented them with the findings of treatment optimisation trials before granting a marketing authorisation for their products. Furthermore, in such a scenario, the EMA should compose a set of guidelines to clarify which type of evidence they require to approve medicines and how it can be generated.

Industry representatives

Industry representative 1 stated that the regulatory authorities could make it mandatory for the industry to document what they are planning and actually doing in terms of treatment optimisation. If no concrete results or plans are presented, then this should negatively influence the outcome of the regulatory decision-making process, the interviewee insisted.

Industry representative 2 was less enthusiastic about the prospect of a shift towards more extensive regulatory intervention, warning that it could limit the access of patients to innovative therapies. Europe is already much more stringent than the US in its review of marketing authorisation applications, so the bar should not be raised further, as this participant put it. They did however welcome any other actions by regulatory agencies to advance the objective of optimising treatments.

Industry representative 3 shared a similar view, arguing that supplementary regulatory requirements to facilitate applied research would likely fall flat and result in delayed market access and increased development costs. Nevertheless, this participant considered the regulatory authorities to be great enablers of innovation and protectors of public health, and approved of their taking softer measures to promote treatment optimisation, such as coordinating discussions on this topic, setting new assessment criteria for trials of this type and giving early scientific advice to stakeholders involved in their conduct. In addition, the right incentives to engage in such research activities need to be provided.

Like HTA agency representative 2, industry representative 4 believed that treatment optimisation studies could be integrated into the existing conditional approval and/or reimbursement frameworks. As long as there are no additional hurdles put in place by the regulators to secure the

initial marketing authorisation, any supplementary post-approval obligations are acceptable. Moreover, the EMA could help formulate quality standards for applied research.

Industry representative 5 also saw the conditional approval mechanism as a viable tool to implement treatment optimisation into the drug development paradigm.

Regulator representatives

Regulator representative 1 opposed the notion that regulators should enforce the conduct of treatment optimisation studies. Their contribution should be restricted to giving the actors responsible for setting up such trials recommendations on which research questions to address and how to tackle them appropriately.

For regulator representative 2, regulatory initiatives to promote treatment optimisation research should comprise not only soft measures, which includes the organisation of workshops, meetings and debates, but also stronger actions, such as making the conduct of these trials part of the post-authorisation requirements imposed on manufacturers.

Regulator representative 3 expressed their preference for an approach in which applied research would be incentivised rather than mandated, for example by offering companies which undertake treatment optimisation studies extended periods of market or data exclusivity. In this regard, the interviewee drew a parallel with the policy that is currently in place to foster the development of orphan drugs in Europe.

Payer representatives

Payer representative 1 would make it mandatory for the industry to incorporate treatment optimisation studies early on in the clinical development process. Additionally, this interviewee lamented the fact that at present, only the marketing authorisation holders can request changes to the label of one of their products. As they are not likely to voluntarily do this when the results of applied research indicate that their medicine is effective in just a small subpopulation of patients, the procedure has to be revised so that other stakeholders can also ask for the label to be modified.

Payer representative 2 thought that managed entry agreements could serve as a vehicle for incorporating treatment optimisation studies into the follow-up research activities that are organised in the post-approval setting.

Payer representative 3 on the other hand was of the opinion that the regulators should ensure that evidence derived from applied research is provided by the manufacturer, whether as part of the pre-approval obligations or the post-authorisation commitments.

3.3.2 Question 13

What are some of the advantages/opportunities you can think of as a member of your stakeholder group with respect to the conduct of these treatment optimisation studies?

Summary

Some of the advantages and opportunities of treatment optimisation studies that were mentioned by the interviewees include:

- They could employ clinically relevant outcome measures and generate more personalised treatments, both of which would benefit patients directly;
- They could achieve major cost savings for healthcare systems;
- They could allow therapies with an added clinical value to be rewarded;
- If they are performed early on in the drug development process, they could enable companies to better evaluate the marketability of their products and already anticipate the outcomes of the HTA assessments;
- They could lead to the registration of additional drug indications in specific subpopulations and produce new combinations of active substances;
- They could more accurately predict the occurrence of unacceptable side effects in the real-world patient population which were not observed in the strictly homogeneous sample of subjects included in the conventional clinical trials;
- Their findings could improve clinical decision-making;
- Their findings could improve HTA and payer decision-making;
- Patient accrual rates could be faster due to the lack of selection criteria;
- They could give a company's products a major marketing advantage over those of their competitors;
- They could fill the evidence gaps that are left by the conventional clinical trials.

The interviewees listed a multitude of different advantages and opportunities which they associated with the conduct of treatment optimisation studies.

A recurring answer was that patients benefit directly from the results of applied research, since its objectives and outcome measures have been selected based on their relevance for clinical practice. It is useful to investigate how a medicine should be applied in real-life settings to optimise its therapeutic effects and to avoid any harmful adverse events stemming from its suboptimal application and unintended misuse. A shorter treatment duration or reduced dosage strength could for example delay or avert the onset of drug resistance.

Anything that can lead towards meaningful improvements in public health is worth pursuing, as **patient organisation representative 1** put it. Treatment optimisation studies are ultimately beneficial for the patient because they produce increasingly personalised therapeutic strategies, **academic clinician 3** added. **Patient organisation representative 2** thought that these trials could also solidify the use of patient-reported outcomes as legitimate endpoints in the clinical development of health technologies.

Another advantage mentioned by some of the participants related to HTA and payer decision-making. By comparing the effectiveness of different treatments in head-to-head trials, the therapeutic option with the best cost-effectiveness ratio can be determined more directly, which makes it easier to decide whether or not society should pay for a particular drug. Applied research

could prevent or identify inappropriate reimbursement decisions, thereby saving the healthcare system a lot of tax payer money. Additionally, it could filter out subpopulations of patients that are likely to be non-responders sooner, as well as establish lower optimal dosage strengths and shorter treatment durations, thus further decreasing costs and increasing healthcare spending efficiency. Moreover, the multi-stakeholder setting in which the studies will be designed gives HTA agencies and regulators the opportunity to voice their needs and concerns early on. If the regulators are actively involved in this process as well, the discrepancies between their evidentiary demands and those of the HTA bodies could be partially resolved.

HTA agency representative 3 was convinced that a research framework which incorporates treatment optimisation would reward those medicines that have an added clinical value compared to existing alternatives, rather than approve any and all new therapies whose efficacy is only marginally better or not worse than that of an arbitrary comparator.

Patient organisation representative 4 added that they hoped such a system would discourage the development of me-too drugs in particular, as they usually bring little additional benefit despite being reimbursed by the payers.

The academic clinicians mainly underscored the value of such studies in the context of making treatment decisions for patients. Currently, they are lacking guidelines that can tell them how to best treat a patient with a specific clinical presentation. Treatment optimisation can help by providing these physicians with evidence that a therapy works when it is applied in real-world conditions, as well as with information on how it should be administered to achieve the best results.

Furthermore, **academic clinician 4** thought that these studies could be performed cheaper and faster than the classical registrational trials, mostly due to the reduced need for maintaining a strictly controlled research environment and the rapid patient accrual rates resulting from the limited number of exclusion criteria.

Industry representatives 1 and 2 believed that if pharmaceutical companies carried out more treatment optimisation studies, this could give their products a major marketing advantage over those of their competitors. Not only would payers accept higher prices and offer more favourable reimbursement conditions, clinicians would also prefer to prescribe these companies' medicines over the available alternatives since they have been studied more thoroughly and characterised more extensively. Another commercial benefit associated with applied research is that it could lead to the registration of additional indications in specific subpopulations and generate new combinations of active substances, some of which might never have been approved as single agents, resulting in the broader application of drugs in clinical practice and boosting revenues in the process. In addition, if such trials were undertaken early on by the manufacturers, they could better evaluate the marketability of their products and already anticipate the conclusions of HTA assessments.

It would also allow them to more accurately predict the occurrence of unacceptable side effects in the real-world patient population which were not observed in the strictly homogeneous sample of subjects included in the conventional clinical trials, **academic clinician 5** claimed. Nevertheless, to increase the perceived legitimacy of the conclusions, these trials could be conducted independently from pharmaceutical companies.

Industry representative 3 viewed treatment optimisation as an important step towards implementing the industry-approved adaptive pathways model, in which new evidence is continuously gathered and fed back into the system to inform regulatory decision-making throughout the drug development process.

Industry representatives 4 and 5 were of the opinion that applied research could fill the evidence gaps that are left by the conventional registrational trials at the end of the clinical development

programme. This would reassure the HTA agencies and payers of the real-world utility of the manufacturer's product and could therefore have a positive impact on their decision-making.

3.3.3 Question 14

What are some of the disadvantages/challenges you can think of as a member of your stakeholder group with respect to the conduct of these treatment optimisation studies?

Summary

Some of the disadvantages and challenges of treatment optimisation studies that were mentioned by the interviewees include:

- There is a lack of funding for applied research;
- There is no methodological framework available yet for these trials;
- Clinicians might be reluctant to recruit patients due to competition with commercial trials;
- The industry might be reluctant to invest in such research due to the associated business risks;
- The infrastructure needed for a multi-stakeholder, international setting is missing for now;
- They could raise ethical issues due to the potential for conflicts of interest to arise;
- They could raise legal issues concerning who would be liable for any side effects occurring during the study as well as who should be able to request changes to the drug label based on the results of these trials;
- If they are performed before approval, they could delay patients' access to innovative treatments;
- If they are performed after approval, patients would not want to participate due to the risk of being assigned to the control group when the therapy can also be accessed outside of a research environment at that point;
- If they are performed by the industry, this could result in increased drug prices.

The participants were also asked what they considered to be the most apparent disadvantages or challenges that would accompany the conduct of treatment optimisation studies.

The most frequently named hurdle related to the question of how these trials will be funded, especially considering they will likely have to run over a relatively long period of time and include a large number of participants to demonstrate any differences in treatment effects between the control group and the experimental group. Many of the interviewees did not foresee the industry sponsoring such studies without regulatory pressure, and even if they allocated parts of their drug development budgets to treatment optimisation, this could allow them to influence the trial setup, thereby raising questions about the legitimacy of the results.

Companies could then also invoke the extra costs associated with this kind of research as an argument to increase the prices of their products, which would negatively impact not just the patients, but society as a whole. Public funding could offer a solution, but it is not yet clear how this can be realistically organised across the fragmented European healthcare landscape. For instance, the payers, whose limited resources could already restrict their involvement in the inter-stakeholder discussions, would object to financing treatment optimisation in addition to reimbursing the health technology for patients, since they would interpret this double payment as an unacceptable shift of the financial burden linked with developing new medicines towards the public. The general reluctance of most stakeholders to pay for applied research implies that priorities will need to be set and choices will have to be made regarding which topics and therapeutic interventions to focus our efforts on.

Although the industry representatives saw major benefits to the conduct of treatment optimisation studies by pharmaceutical companies (see also question 13), they feared that the sector might not be willing to invest if the probability of a favourable outcome for their drugs is too low. No business wants to work against its own interests, and the conclusions of a prior benefit-risk assessment will probably determine whether or not they will actually decide to do the trial, regardless of its clinical value to patients and physicians.

As long as the findings of applied research can result in restrictions in the registered indications or revisions of the pricing and reimbursement conditions, there are no incentives for the manufacturers to optimise their treatments of their own accord, given the loss of revenue such initiatives could cause. In addition, there was some doubt about whether the industry could actually carry out clinical trials outside of the heavily controlled environment they are used to. A real-world setting is characterised by numerous additional uncertainties that cannot easily be managed by pharmaceutical companies due to their lack of experience in operating within this field.

Another obstacle mentioned by one of the interviewees was the additional burden such studies would impose on the healthcare professionals involved. This type of research is not intended to replace the classical phase II and phase III clinical trials, so investigators would be invited to oversee these studies on top of the ones they are currently leading. If they have to then choose which trials to prioritise, they will likely be persuaded by the higher participation and recruitment fees that the industry can afford to pay them for their involvement in commercial clinical studies.

Furthermore, seeing as treatment optimisation is still quite uncommon today, the physicians and nurses coordinating the trials might not be familiar with the intricacies of collecting data in settings that more closely resemble real-life clinical practice. Moreover, academic clinicians could be discouraged to participate by the lack of interest on the part of high-impact scientific journals to publish the results of such trials. All three of these factors could render doctors reluctant to recruit patients for these studies.

At present, no general framework surrounding the optimal design and methodological features of treatment optimisation studies has yet been created. Given the uncertainties that accompany research taking place under real-world conditions, it can be assumed that it will be relatively difficult to carry out these trials. For instance, if no or only a few exclusion criteria are applied, the heterogeneous nature of the included population will necessitate a much larger sample size than that of a classical phase III study to detect statistically significant therapeutic effects. Until quality standards are agreed upon and clear guidelines on the methodology of treatment optimisation are available, most stakeholders will be hesitant to launch any initiatives within this field.

Several participants warned that the infrastructure needed to perform these studies in a multi-stakeholder and potentially international manner is currently not yet available. It will take considerable time to establish collaborations and partnerships between the different stakeholder groups suggested in the replies to question 11, both on the national and, if applicable, international level. Such efforts to increase cooperation in this area also raise questions about the potential emergence of conflicts of interest, most notably concerning the contribution of the regulators, payers and HTA agencies, who will eventually make decisions based on the data that were gathered during the trials.

Besides the ethical concerns associated with the conduct of treatment optimisation studies, there could be legal issues as well: the manufacturer is ultimately liable for any side effects occurring as a result of the use of their product, so if academic groups perform trials in which they administer the therapy in ways that have not been previously approved (e.g. different dosage strength, shorter treatment duration, new combination), it could put the industry at risk of lawsuits. Additionally, only the marketing authorisation holder can ask for changes to be made to the label, so if the conclusions

of these studies warrant such modifications, the company might not be willing to request them, particularly when they would introduce restrictions on certain applications of the medicine.

Lastly, the optimal timing of applied research still remains unclear. Some interviewees feared that if treatment optimisation studies were implemented in the pre-approval stage of the drug development process, this would delay the marketing authorisation of innovative therapies, to the detriment of many patients for whom there are no available alternatives. According to these participants, the need for additional evidence should always be balanced with patients' and clinicians' demand for access to novel medicines.

Another challenging aspect of the pre-authorisation approach is that it could lead to a reduction in the number of regulatory approvals, which would limit the amount of available treatment options and curtail competition. Moreover, the use of a less homogeneous sample of participants could result in a more extensive characterisation of the potential side effects of a drug, which in turn could undermine its chances of receiving a marketing authorisation. Conversely, in the post-approval environment, the findings of treatment optimisation may come too late to influence regulatory or payer decision-making. In addition, it can be challenging to recruit patients for clinical trials in which there is a chance that they could be assigned to the control group when the novel medicine can also be accessed outside of the research setting.

3.3.4 Question 15

For patient organisation representatives and academic clinicians:

How would you view the evidence strength of these studies in the context of making treatment decisions for patients?

For HTA agency representatives:

How would you view the evidence strength of these studies in the context of making HTA decisions?

For payer representatives:

How would you view the evidence strength of these studies in the context of making reimbursement-related decisions?

For regulator representatives:

How would you view the evidence strength of these studies in the context of making decisions to approve drugs for use in patients?

For industry representatives:

How would you view the evidence strength of these studies in the context of decision-making by regulators and reimbursement legislators?

Summary

The majority of the interviewees (18 out of 26) believed that the evidence strength of well-designed treatment optimisation studies that are performed according to rigorous quality standards is greater than or at least equal to that of classical registrational trials.

All participants were of the opinion that the findings of treatment optimisation studies should be taken into account in the decision-making procedures utilised by regulators, HTA agencies, payers and/or clinicians.

Most participants (18 out of 26) believed that treatment optimisation studies would generate results whose evidence strength would be greater than (9 out of 26) or at least equal to (9 out of 26) that of the findings obtained from conventional registrational trials. However, they also noted that the superiority or parity in evidence strength is only valid if the optimal design features (see also question 7) are integrated into these studies and if they are performed according to rigorous quality standards. The latter condition can be achieved through implementation of data quality checks, routine monitoring of patient information, verification of source data, standardised measuring of clinical parameters, education and training of investigators, and other efforts of a similar nature.

The majority of the eight remaining interviewees refrained from directly comparing treatment optimisation studies to classical randomised controlled trials. Three of them stated that both are necessary and can contribute to the totality of evidence that will eventually be reviewed or assessed, so it would not make sense to claim one produces more convincing conclusions than the other. Other participants either did not feel knowledgeable enough to draw a comparison between applied and classical clinical research, or wanted to wait until guidelines have been developed on the methodology of the former.

The interviewees who considered the evidence strength of the conventional registrational trials to be greater than that of treatment optimisation studies noted that they still saw value in optimising therapies, for instance because it could help elucidate the underlying mechanisms that determine why some patients will and other patients won't respond well to a particular medical intervention. Furthermore, while they currently deemed the findings of the classical randomised controlled trials to be of a higher evidentiary standard than those of applied research studies, they also acknowledged that their opinion could change in the future, as more advanced methods to collect and analyse real-world data become available.

There was a strong consensus among the experts interviewed that the results of treatment optimisation studies should have an impact on regulatory, HTA, payer and/or clinical decision-making. Depending on when they thought applied research is best carried out (see also question 6), the participants argued that the assessments performed during the licensing and/or reimbursement application procedures should take into account data derived from such trials, or that a revision of the decision to reimburse the medicine would be warranted if these procedures had already been concluded and the treatment optimisation outcomes reflected negatively upon the drug.

Such an amendment of the reimbursement modalities can be anticipated through the negotiation of managed entry agreements between the payers and the manufacturers. There was less support among the interviewees for reconsidering the marketing authorisation itself, mainly because many participants did not want to restrict the access of patients to innovative therapies if there are no immediate safety-related reasons for doing so, regardless of what is observed during applied research. A withdrawal of the marketing authorisation is not required as clinicians would look at reports and publications following from these studies and decide for themselves whether a specific patient should be given a certain treatment, several interviewees remarked.

3.3.5 Question 16

Do you have any additional remarks, questions, doubts, concerns regarding the topic of treatment optimisation?

Summary

While some participants mentioned that they found the terms 'treatment optimisation' and 'applied research' to be used too broadly, most interviewees did not have any additional comments.

Most interviewees either did not have any additional remarks, questions, doubts or concerns about the topic of treatment optimisation trials, or used this opportunity to repeat some of their key points. Nevertheless, several participants remarked that they found the terms 'treatment optimisation' and 'applied research' to be confusing, explaining that they refer to a concept that is so broad that it cannot be meaningfully denoted by a single overarching label, since it encompasses too wide a variety of studies to make general statements about how it should be funded or when it should take place in the drug development process. The vast majority of experts interviewed however did not raise any objections to the use of these particular terms.

4. Policy options

4.1 Direction for changes

Three potential policy options for the implementation of applied research as an essential step in the path to full adoption of novel medicines into the healthcare system have emerged from the interviews. In light of the broad support that the interviewees expressed for regulatory measures facilitating the conduct of treatment optimisation studies, all three of the identified strategies involve utilising the ability of regulators to demand additional evidence from manufacturers to strengthen their decision-making. They mainly differ in terms of the timing of the trials in question as well as the regulatory mechanism through which such studies would be solicited. The advantages and disadvantages of each alternative approach will be discussed.

4.1.1 Policy option 1. Treatment optimisation as part of the regular approval procedure

Data obtained from treatment optimisation studies could be integrated into the regular approval procedure (Scholz, 2015) and become part of the collection of evidence that the pharmaceutical industry has to submit to the EMA in order to obtain a marketing authorisation for their products. If a company does not provide the requested information or if the results indicate that there is insufficient reason to believe the new medicine will be useful in clinical practice, approval would not be granted. In this scenario, applied research would therefore be performed in the pre-approval setting, in parallel with the classical registrational trials.

Advantages

The main advantage of this policy option is that it forces the manufacturers to engage in treatment optimisation early on, before crucial milestones on the road to market access are achieved. This would allow the findings to be taken into account during the decision-making process of both the EMA and the national payer authorities. Consequently, by raising the evidentiary bar, there would be a lower risk of taking up ineffective or inadequately characterised therapies into clinical practice (Prasad and Cifu, 2011).

Disadvantages

However, there are also disadvantages associated with this approach. Firstly, the industry would have to invest additional time and costs to meet the increased burden of proof placed upon them (Naci et al., 2012), which could lower their overall productivity (Paul et al., 2010; Ruffolo, 2006) and R&D efficiency (Scannell et al., 2012), and may be used as an argument to increase the prices of their products when they eventually enter the market (Barton and Emanuel, 2005; Moors et al., 2014). Secondly, it could extend the duration of the medicines development process, thereby delaying patient and clinician access to innovative treatments (Eichler et al., 2008). Many interviewees perceived this as an undesirable outcome that should be avoided as much as possible. Thirdly, as the pre-approval research setting is largely coordinated by the manufacturer, it would be difficult to maintain and safeguard the independent conduct of such treatment optimisation studies, potentially giving rise to the introduction of bias into their design (Lexchin, 2012; Sismondo, 2008), especially when commercial interests are at stake (e.g. in case of decreased therapeutic duration or lower optimal dosing). Neither the interviewees nor authors in the field (Angell, 2004; Ioannidis, 2013; Kempf et al., 2017; Lacombe et al., 2019b; Lewis et al., 2007) advocate such an industry-centric approach, instead preferring that academic institutions, not-for-profit organisations and/or governmental bodies would be given a more prominent role in clinical research in general or treatment optimisation in particular.

4.1.2 Policy option 2. Treatment optimisation as part of the conditional approval procedure

Treatment optimisation studies could also be performed in the context of the EMA's conditional approval procedure (EMA, 2016b, 2017a). In such a scenario, the EMA would grant a marketing authorisation to the applicant based on the data that was acquired from the standard registrational trials, on the condition that additional evidence derived from applied research is presented within a predetermined timeframe. If this condition is not met or if the findings cast doubt upon the clinical utility of the intervention, the approval would be re-evaluated and if necessary retracted or adapted (e.g. by narrowing down the patient population that can receive the medicine). Here, treatment optimisation would thus be organised in the post-approval setting.

Advantages

A major advantage of this approach, if properly organised, is that it does not impede patient and clinician access to new therapies. Once the initial marketing authorisation has been awarded and the national reimbursement process has been successfully completed, the treatment will be available for use in clinical practice in that particular country. In the meantime, the manufacturer can set up partnerships with independent research institutions for the conduct of treatment optimisation studies. Additionally, to counter the argument of increased development costs, the revenue generated by the company from the sale of their product during this period could be partially used to finance these trials, possibly in combination with public funding. Moreover, since the original approval will be revisited after a certain amount of time, the results of these studies would have a direct impact on regulatory decision-making. This policy option is also in line with the adaptive pathways model (Eichler et al., 2015; EMA, 2016a) designed by the EMA.

Disadvantages

Nevertheless, some disadvantages can also be listed. For instance, while the utilisation of the conditional approval mechanism is currently restricted to treatments addressing an unmet medical need (EMA, 2016b, 2017a), applied research will likely also be necessary in areas where alternative therapeutic strategies already exist, such as in the context of trials investigating combinations or comparisons of different therapies. In addition, the conditional approval procedure as it is applied today allows the industry to introduce new medicines into the market based on incomplete datasets (e.g. data from phase II trials) (EMA, 2016b, 2017a), thereby possibly contributing to the widening the research gap (Gellad and Kesselheim, 2017; Gyawali et al., 2019; Schuster Bruce et al., 2019). Care should be taken that in our efforts to implement the treatment optimisation concept, we do not inadvertently magnify the underlying problem.

4.1.3 Policy option 3. Treatment optimisation as part of the conditional reimbursement procedure

A third potential policy option involves having the national payer authorities temporarily reimburse the treatment while the manufacturer collects supplementary evidence in the form of applied research data. If the information requested is not provided within a predefined number of years or if the results reflect negatively upon the therapy in question, the reimbursement could be halted or the conditions under which it was negotiated may be altered. In this case, treatment optimisation studies would be conducted in the post-approval environment.

The appropriate legal tools to effectuate such an approach already exist and are typically referred to as managed entry agreements (MEAs) (Ferrario and Kanavos, 2013; Gerkens et al., 2017). These are contractual arrangements between a pharmaceutical company that has been granted a marketing authorisation for a specific health technology and the healthcare payers of a particular country. Discussions concerning these conventions are usually only initiated when a formal decision

to reimburse the intervention could not be reached due to uncertainties regarding its cost-effectiveness, budget impact or eventual adoption into clinical practice (Ferrario and Kanavos, 2013; Gerkens et al., 2017). Furthermore, the treatment in question should preferably represent a promising therapeutic strategy addressing an unmet medical need. If these conditions are met, the payers can decide to partially cover the costs of the therapy for a predetermined amount of time. At the end of that period, the request for reimbursement is re-evaluated based on new information that has since become available and if appropriate, a more permanent coverage plan can be set up. However, depending on the results of this assessment, the agreement can also be prolonged or voided (Ferrario and Kanavos, 2013; Gerkens et al., 2017).

Multiple different types of MEAs can be distinguished. For the purpose of this policy option, the outcome-based MEAs, which establish a link between the reimbursement of a drug and its effects on outcomes in real-world clinical practice (Ferrario and Kanavos, 2013; Gerkens et al., 2017), are especially relevant. More specifically, coverage with evidence development (CED) schemes could be used as a vehicle to implement treatment optimisation. In this subtype of outcome-based MEA, the manufacturer commits to gathering the necessary supplementary evidence to convince the payers that their product should receive permanent reimbursement (Carlson et al., 2010; Ferrario and Kanavos, 2013; Gerkens et al., 2017). Applied research could potentially be integrated into CED schemes and produce this additional proof demanded by the payers.

Advantages

Advantages of this strategy include that it does not impair patients and clinicians' access to promising new therapies (Brugger et al., 2015; Gerkens et al., 2017; Russo et al., 2010; Towse, 2010) and that it allows the results of applied research to be taken into consideration in the decision-making of payers. Moreover, instead of depending on the EMA to scrutinise the data obtained from treatment optimisation studies, this responsibility is transferred to the payers, who traditionally review information on the effectiveness of health technologies in real-life patients and can rely on the expert advice of HTA agencies to support them in their assessments. Additionally, for the same reason as policy option 2, the issue of increased development costs is less pertinent here, although finding a sustainable funding mechanism for applied research remains a challenge. A post-approval setting also offers more opportunity for collaboration with independent research institutions.

Disadvantages

As with the other two policy options, several disadvantages accompany this approach. For example, the laws governing the use of MEAs are encoded in national legislation (Gerkens et al., 2017), meaning that there will be differences between European countries with respect to the circumstances under which these schemes may be applied (de Pouvourville, 2006; Towse and Garrison, 2010). Therefore, it would be much more challenging to perform and coordinate treatment optimisation studies in an international setting, since each EU Member State has different priorities and thus could ask for diverging research questions or topics to be incorporated. In addition, only a small minority of MEAs currently in place are outcome-based (Carlson et al., 2014; Gerkens et al., 2017; Macaulay and Jamali, 2015), partly because this type of convention presents a significant financial and administrative burden for the parties involved (Adamski et al., 2010; Carlson et al., 2009; Gerkens et al., 2017; Neumann et al., 2011).

It remains to be seen whether the volume of treatment optimisation studies needed would exceed payers' capacity to follow up on their outcomes effectively, and if so, how it should be decided which research questions to prioritise. Furthermore, in past examples of outcome-based MEAs as well as MEAs in general, the conditions for coverage often eventually remained unchanged, even when insufficient evidence was provided by the manufacturer at the end of the initial period of reimbursement (Bishop and Lexchin, 2013; Gerkens et al., 2017; Lewis et al., 2015; Mortimer et al., 2011). It would seem that payers are reluctant to act upon the data collected in such schemes, in

part due to ethical objections surrounding the cessation of reimbursement, which defeats the purpose of organising them in the first place. Applied research should be able to lead to changes in the way health technologies are utilised in clinical practice.

4.2 Momentum for change

In order to enact the policy options listed in the previous section, the applicable legislative frameworks will have to be modified, which in turn will require significant political effort. A first important step towards realising such legal changes is to raise awareness of the existence of the research gap among all actors involved in the process of developing new treatments and integrating them into clinical practice. A truly patient-centred paradigm that includes treatment optimisation can only be realised once all stakeholders understand the extent of the underlying problem that it strives to address. To achieve this, more inter-stakeholder discussion and collaboration are needed, since the fragmented nature of the current drug development and marketing system contributes to the lack of data informing decision-making in a real-world clinical environment (Kempf et al., 2017).

An example of a useful initiative in this regard is the parallel consultation procedure (EMA, 2017b) coordinated by the EMA and the European Network for Health Technology Assessment (EUnetHTA). Through this mechanism, pharmaceutical companies can consult both EMA and HTA bodies simultaneously for feedback on their plans to produce the evidence required to secure regulatory approval as well as reimbursement. In addition, patient representatives and healthcare professionals can also be involved in the discussion.

This allows each actor to voice their needs and listen to those of others, thereby highlighting any contrasts that may exist between them. As parallel consultation is only initiated at the request of the manufacturer, a potential policy action could be to promote its utilisation by the industry and expand its application. For instance, it could fully replace the EMA's scientific advice programme, in which the applicant receives guidance from the regulator alone, since parallel consultation features input from a broader range of actors. It could also be incentivised by lowering the associated fees. Additional measures could be taken in other areas to facilitate interaction between the different stakeholders.

Once enough momentum for change has been gained through the setup of collaborative platforms and the organisation of other efforts to increase awareness of the research gap, one of the abovementioned policy actions can be legally implemented.

4.2.1 Policy option 1

For policy option 1, the legislation of relevance is Regulation (EC) No 726/2004, in which, among other things, the centralised procedure for obtaining a marketing authorisation is established. This Regulation stipulates that to receive regulatory approval via the centralised procedure, the conditions listed in Directive 2001/83/EC have to be fulfilled by the applicant. More specifically, Annex 1 to this Directive gives an overview of the evidence required by the regulator. Here, treatment optimisation studies could be added under Module 5. This means that data acquired from such trials would become a mandatory part of the application dossier that the manufacturer has to submit to the EMA. However, the Directive does not go into detail on the design of any evidence-generating studies. Hence, a separate methodological guideline for applied research would have to be composed by the EMA.

4.2.2 Policy option 2

Policy option 2 could be implemented by adapting Regulation (EC) No 507/2006, which outlines the conditional marketing authorisation procedure. In particular, the scope of the Regulation as

described in Article 2 would need to be broadened and the requirements in Article 4 would have to be loosened to allow treatment optimisation studies to be requested for any therapeutic intervention, not just the ones addressing an unmet medical need. Additionally, the specific obligations covered under Article 5 should be imposed not only if there is insufficient evidence available on safety and efficacy as Article 4 states, but also when the clinical utility of the product is inadequately characterised. Since the Regulation does not specify what these obligations may entail, it is up to the EMA to demand the conduct of applied research in such situations as a condition for receiving an indefinite regulatory approval. To this end, an official EMA guideline on treatment optimisation methodology will again be necessary.

4.2.3 Policy option 3

As policy option 3 makes the payers responsible for ensuring that applied research is being carried out when appropriate, it cannot be actualised via changes in the European legal framework, since decision-making relating to the pricing and reimbursement of medicines is a Member State competence. Each country individually specifies in their national legislation the terms and conditions under which managed entry agreements may be initiated (Gerkens et al., 2017). For example, in Belgium, the legal basis for setting up such conventions is provided by Article 35bis § 7 of the Law of 7 July 1994 on compulsory health insurance, the execution of which is detailed in Articles 111 to 117 of the Royal Decree of 1 February 2018.

The latter does not explicitly state which types of studies may be imposed on the manufacturer as part of an outcome-based agreement. This means that, from a legal point of view, the payer is already allowed to ask the pharmaceutical company in question to collect supplementary data derived from treatment optimisation studies in the context of the conditional reimbursement mechanism. The Royal Decree therefore does not have to be modified. Nevertheless, the situation may be different in other Member States. An increased degree of international cooperation between the European payer authorities could lead to more harmonisation and help expand applied research to the larger European setting. The Benelux Initiative (Benelux Initiative, 2018), which brings together representatives of the Ministries of Health of Belgium, the Netherlands, Luxembourg, Austria and Ireland, can serve as a model for such cross-country collaboration.

5. Limitations of the study and conclusions

This study suffers from three main limitations. Firstly, due to the large number of targeted stakeholder groups, the interviews could not be conducted until data saturation was reached for each individual group. Nevertheless, the multi-stakeholder approach enabled a diverse range of opinions to be captured. Secondly, the expertise of the interviewees was limited to oncology, hematology, rheumatology or respiratory, so their views and remarks may not be as relevant for other areas of research. Additionally, Western Europe was overrepresented in the list of EU Member States included, which could indicate that the participants' observations and answers may not be reflective of the situation in other European regions. Thirdly, the analysis of the interview data was performed by a single person as opposed to multiple researchers in parallel, meaning there was no opportunity to validate the coded transcripts by carrying out cross-checks as prescribed by Gale et al. (2013). Despite this, any uncertainties that emerged during the coding process were discussed with one of the principal investigators.

The following key points can be concluded from the interviews:

- A majority of interviewees (22 out of 26) thought drug development research is not sufficiently patient-centred, but there was no agreement on whether it is also too drug-centred. For instance, some participants highlighted that the current drug-focused attitude may be needed to obtain a marketing authorisation from the regulatory authorities. However, they also stressed that the two types of approaches are not incompatible with one another. Others thought that the system is already undergoing a major shift towards implementing a paradigm that puts the patient at the centre of the development process.
- The interviewees who believed that the current drug development paradigm is too drug-centred were convinced that the present approach severely complicates decision-making for regulators, HTA agencies, payers and clinicians. Moreover, it results in missed opportunities for patients and allows treatments with a limited clinical utility to enter the market.
- The majority of participants (18 out of 26) agreed with the statement that there is a lack of real-world evidence for the use of many drugs on the market today. A number of reasons were given for this apparent scarcity:
 - Real-world data collection is complex and costly;
 - The evidentiary demands of regulators and HTA agencies/payers differ too much between each other;
 - Real-world data is perceived to be of poor quality;
 - No stakeholder is responsible for collecting real-world data, and there are no incentives for doing so spontaneously.
- When asked who should be responsible for performing treatment optimisation studies, most interviewees gave one of the following two answers:
 - They should be undertaken by academia and not-for-profit organisations to ensure their conduct remains independent from any commercial interests. Nevertheless, the industry could still provide support by supplying the study drug free of charge.
 - They should be carried out by consortia comprised of all relevant stakeholders as their results will benefit every actor involved in the drug development process.
- The majority of participants (16 out of 26) saw combinations of public and private funding as either a viable or the most viable option for financing treatment optimisation research. One of the main arguments given in support of this position was that the conduct of these studies should be independent from the commercial pressure of the pharmaceutical industry in order to prevent bias, but that at the

same time, academia or not-for-profit organisations do not have the means to fund them fully on a sufficiently large scale.

- No matter how treatment optimisation is going to be financed, choices will have to be made regarding which research topics and medicines to focus on, as there will not be infinite resources to spend on these studies.
- There was no clear consensus among the experts interviewed concerning the optimal timing of treatment optimisation studies. Some participants were convinced that they could already be initiated before the therapy has been approved by the regulatory authorities, while others considered the post-authorisation conduct of these trials to be the most realistic option. Nevertheless, several of the interviewees that saw treatment optimisation taking place exclusively in the post-approval stage of the drug development process emphasised that the questions to address and the type of information to collect should be defined prospectively, preferably as early as possible, so that applied research can start immediately after the therapy enters the market.
- When asked which features treatment optimisation should ideally have, the interviewees listed the following elements:
 - They should have fewer inclusion and exclusion criteria than the classical clinical trials;
 - They should employ the standard of care or the best available alternative treatments as comparators;
 - They should implement outcome measures that are relevant for patients;
 - Some participants believed randomisation would be necessary to reduce bias and ensure the robustness of the results, while others saw it as a barrier to simulating real-world conditions;
 - Some interviewees thought blinding would be needed to increase the validity of the outcomes, while others preferred an open-label design because it more closely approaches real-life clinical practice;
 - All results should be published, regardless of whether they reflect well upon the therapy or not.
 - Most participants did not express a preference for a particular setting in which treatment optimisation studies should ideally take place, stating that this is something that must be decided on a case-by-case basis, since it depends on the type of disease and intervention that are being investigated in the trial. However, for those interviewees who did explicitly favour one of the suggested options, a national setting was seen as the most appropriate alternative for carrying out applied research. The most commonly cited motivation behind this answer was that standards of care vary widely between countries, making it difficult to design studies with overarching objectives that are relevant for most EU Member States. Nevertheless, the majority of the interviewees who preferred a national setting indicated that international coordination and oversight of nationally organised treatment optimisation studies still remains possible.
- There was broad support among the participants for inter-stakeholder collaboration and discussion during the design and conduct of treatment optimisation studies.
- Most participants named the same group of stakeholders when asked who should be present at the table during the planning of treatment optimisation studies, namely:
 - Patients and/or patient organisations;
 - Physicians and clinicians (from both academic and community hospitals);
 - Academia and independent research organisations;
 - Pharmaceutical industry;
 - Payers;
 - HTA agencies;
 - Regulators.

- There was broad support among the participants for regulatory measures to facilitate treatment optimisation, although there was no agreement on the optimal size, scale and nature of these initiatives. Some interviewees favoured strong action and wanted to make it mandatory for the industry to undertake applied research, while others preferred a policy of incentivisation.
- Some of the advantages and opportunities of treatment optimisation studies that were mentioned by the interviewees include:
 - They could employ clinically relevant outcome measures and generate more personalised treatments, both of which would benefit patients directly;
 - They could achieve major cost savings for healthcare systems;
 - They could allow therapies with an added clinical value to be rewarded;
 - If they are performed early on in the drug development process, they could enable companies to better evaluate the marketability of their products and already anticipate the outcomes of the HTA assessments;
 - They could lead to the registration of additional drug indications in specific subpopulations and produce new combinations of active substances;
 - They could more accurately predict the occurrence of unacceptable side effects in the real-world patient population which were not observed in the strictly homogeneous sample of subjects included in the conventional clinical trials;
 - Their findings could improve clinical decision-making;
 - Their findings could improve HTA and payer decision-making;
 - Patient accrual rates could be faster due to the lack of selection criteria;
 - They could give a company's products a major marketing advantage over those of their competitors;
 - They could fill the evidence gaps that are left by the conventional clinical trials.

- Some of the disadvantages and challenges of treatment optimisation studies that were mentioned by the interviewees include:
- There is a lack of funding for applied research;
- There is no methodological framework available yet for these trials;
- Clinicians might be reluctant to recruit patients due to competition with commercial trials;
- The industry might be reluctant to invest in such research due to the associated business risks;
- The infrastructure needed for a multi-stakeholder, international setting is missing for now;
- They could raise ethical issues due to the potential for conflicts of interest to arise;
- They could raise legal issues concerning who would be liable for any side effects occurring during the study as well as who should be able to request changes to the drug label based on the results of these trials;
- If they are performed before approval, they could delay patients' access to innovative treatments;
- If they are performed after approval, patients would not want to participate due to the risk of being assigned to the control group when the therapy can also be accessed outside of a research environment at that point;
- If they are performed by the industry, this could result in increased drug prices.
- The request for additional evidence in the form of data derived from treatment optimisation studies should be balanced with patients' and clinicians' demand for access to novel therapies.
- Most interviewees (18 out of 26) believed the evidence strength of well-designed treatment optimisation studies that are performed according to rigorous quality standards is greater than or at least equal to that of classical registrational trials.
- There was a strong consensus among the experts interviewed that the results of treatment optimisation studies should be taken into account during the decision-making of regulators, payers and/or clinicians.
- If treatment optimisation studies are performed before the therapeutic intervention has entered the market, their findings should be part of the evidence that is evaluated during the drug approval and/or reimbursement procedures.
- If treatment optimisation studies are performed after the therapeutic intervention has entered the market, their findings should be able to trigger revisions of the decision to reimburse the health technology. The marketing authorisation should not be re-evaluated to ensure the access of patients to the medicine is not undermined. Clinicians should examine the results of applied research and decide for themselves whether or not to administer the drug to a particular patient.
- Treatment optimisation studies could be implemented into the drug development paradigm by imposing their conduct as part of the evidence required to successfully complete the regular approval procedure, conditional approval procedure or conditional reimbursement procedure. To achieve this, the applicable national or European legislative frameworks will need to be modified, which will require significant political effort.

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The current drug development paradigm is too drug-centred and does not sufficiently take account of the patients that will receive the new therapy. This has led to the emergence of a research gap between the pre-approval development of medicines and their post-approval use in real-world conditions. This gap could potentially be bridged by transitioning towards a patient-focused framework that places strong emphasis on treatment optimisation, which strives to optimise the way health treatments are applied in clinical practice.

Questions remain regarding the ideal features of treatment optimisation studies and their acceptability among key stakeholders. In this qualitative research study, semi-structured interviews were performed with 26 experts across 5 stakeholder groups and 10 different EU Member States. The results offer an overview of the concept of treatment optimisation. A set of policy options is also presented that could help enable implementation of treatment optimisation.

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