Feasibility of post-authorization randomized controlled trials for conditionally authorized anticancer medicines – a multistakeholder perspective

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Abstract

To generate comprehensive evidence for anticancer medicines that have been granted a conditional marketing authorization (CMA) based on single-arm trial (SAT) data, often, post-authorization randomized controlled trials (RCTs) are imposed. However, these PA-RCTs are sometimes delayed or not completed, thus raising questions on their feasibility and how this is assessed at time of marketing authorization. Here, we prospectively explored conditions and factors that contribute to or hamper the feasibility of PA-RCTs, from the perspective of various stakeholders that are directly involved in the conduct and approval of PA-RCTs. As such, a combination of qualitative research methods, i.e., exploratory interviews and focus groups with patients, physicians, medical ethicists and pharmaceutical industry was applied. Thematic analysis of the data obtained from the focus groups confirmed the three initial main themes that seem to directly determine the feasibility of PA-RCT: (i) design (i.e., trial aim and complexity), (ii) conduct (i.e., data collection, competition), and (iii) motivations to participate in, conduct, or approve a PA-RCT. Stakeholders' motivations differed among them, but generally regarded their motivations to contribute to comprehensive evidence generation. Additionally, 'conditioning factors' were identified that may modify the relevance of the PA-RCT specific feasibility main themes, namely (i) cancer indication; (ii) promise of new product; (iii) need for evidence; (iv) development plan; (v) access to the product; (vi) location of trial. Mainly, perceived clinical equipoise, patient recruitment, and burden for patients and physicians may be concepts that overarch these feasibility considerations. Altogether, this exploratory study may contribute to advance PA-RCT feasibility assessments.

Plain language summary

New medicines to treat cancer are highly needed, but before a medicine can be used by all patients, it must receive a market authorization from the European Medicines Agency. Before getting marketing authorization, there must be evidence that the medicine is safe and effective. Therefore, clinical trials are performed to gather evidence about its safety (i.e., how safe is the medicine) and efficacy (i.e., how well does the medicine work).

To get medicines earlier to the market and enable earlier patient access to new medicines, the EMA has a so-called 'conditional marketing authorization' (CMA). A CMA can be given to a medicine if there are no complete clinical trial data available (yet), but only 'incomprehensive' (i.e., incomplete) data. Based on this data, the EMA can give a CMA if they consider the benefit-risk of a medicine positive (i.e., the desired effects are greater than the undesired effects).

However, one condition to this 'conditional' authorization is that the pharmaceutical company must gather additional evidence about the medicine's safety and efficacy, because there are uncertainties about that. Therefore, the EMA often requests that the company performs a 'randomized controlled trial' (RCT), in which the medicine is compared to a placebo or other treatment (i.e., the 'comparator', e.g., standard therapy, the best therapy). And participants (i.e., patients that participate) are randomized (i.e., randomly allocated) to either one of the treatments. RCTs are considered the strongest type of evidence.

So, performing an RCT after the medicine is conditionally authorized is very important. And although it may seem feasible to perform a RCT post-authorization (PA) (i.e., when given CMA), these RCTs are sometimes delayed or not completed.

Therefore, with this research study, we aimed to understand the feasibility of these so-called 'PA-RCTs'. Which factors or aspects may contribute or hamper the conduct of a PA-RCT, making it either more or less feasible.

To study this, we held interviews and focus group discussions with four stakeholders that conduct or approve PA-RCTs, namely patients, physicians, medical ethicists, and pharmaceutical companies.

Overall, we found that how these stakeholders view the uncertainties about the medicine (i.e., 'clinical equipoise) is important. For instance, if a medicine seems very promising, and it is available outside the trial, then patients and physicians would not want to participate in or perform a trial, because this is more burdensome, while it seems already clear that it works. In addition, we found that various other factors influence whether enough patients will participate, for instance, how good and fair the comparator treatment is, and if patients will already participate if the trial starts before the CMA is given. Moreover, how the trial is designed and will be conducted seemed to influence its feasibility directly.

Altogether it appears to be important that many factors, circumstances, and aspects are considered for a PA-RCT when a medicine may be given a CMA. The findings of our study, in which we explored and identified these factors, circumstances, and aspects, may enable better estimation of the feasibility. And importantly, to ensure that these RCTs are finished so that the uncertainties may be resolved.

Introduction

To enable early patient access to innovative therapies that address an unmet medical need, expedited regulatory pathways have been established by regulatory authorities such as the European Medicines Agency (EMA) [1,2]. The European pathway that has been increasingly used since its implementation is 2006 is the conditional marketing authorization (CMA) pathway. The CMA pathway facilitates authorization based on non-comprehensive evidence for a medicine with a positive benefit-risk [Box 1]. So far, until 2016, oncologic indications accounted for more than half of all CMAs granted (2 , Bloem LT *et al.,* unpublished results).

In oncology, between 2010 and 2019, one in every four (24%) medicines with a new active substance was granted a CMA [3], often (38%) exclusively based on data from a single-arm trial (SAT) [4]. This trend is present for targeted therapies in particular despite the lack of clear guidance for when SATs are acceptable as pivotal evidence for regulatory assessment (5, Bloem LT *et al*., unpublished results). However, SATs have been more likely acceptable if the mechanism of action was understood (such as is characteristic for targeted therapies); if the trial population was well-characterized; and, if the SAT population was considered of sufficient size [5]. These features, together with an 'unprecedented' and durable overall response rate (ORR), are expected to translate into clinical benefit [5].

Nonetheless, when a CMA is granted on the basis of such SAT data, it remains obligatory to provide comprehensive evidence that is intended to confirm the benefit-risk post-authorization [1,6]. Specific obligations (SOBs) are imposed to achieve comprehensive evidence [Box 1]. Generally, SOBs include randomized controlled trials (RCTs), typically phase III (n=32/77), for post-authorization (PA) comparative evidence generation [2]. An exemplary therapeutic area in this context of targeted therapies with SAT-based CMAs is non-small cell lung carcinoma (NSCLC). NSCLC is the most frequently reported indication in this regard and SOBs often require performing an RCT post-authorization [7,8] [Supplementary Material S5].

Whether the applicant will be able to perform such PA-RCTs (or other PA-studies) in a timely manner is an important prerequisite for granting a CMA [1]. The responsibility for the initial feasibility assessment of a PA-RCT is considered the applicant's [1,9]. The applicant's claims on the feasibility are assessed by the EMA's Committee for Medicinal Products for Human Use (CHMP)[1]. This feasibility assessment is a vital element, because if deemed unfeasible, marketing authorization under exceptional circumstances would be more appropriate [6]. And formally, this may be reason to withhold granting the CMA [1]. However, in general, regulatory guidelines provide limited to no guidance for this feasibility assessment [1]. And details of feasibility assessments for PA-studies as part of SOBs are rarely described in EMA's European public assessment reports (EPARs) [1,9,10].

Still, even though considered feasible, requirements for PA-evidence are often delayed (between 2010 and 2016, 44% of SOB changes were initial due date extensions) or left incomplete [11–14]. Consequently, better criteria for the feasibility assessment of PA-studies, and particularly PA-RCTs for CMA may be required [11–14].

Overall, successfully designing and conducting RCTs can be complex, both pre- and post-authorization [15,16]. RCTs may be subject to low recruitment and retention rates, have suboptimal study designs (e.g., not able of demonstrating efficacy and safety), or may be poorly conducted [15,16]. For PA-RCTs, some aspects may be more prominent, related to the rarity of the disease, the loss of clinical equipoise, tight timelines, and other (ethical and logistical) patient recruitment challenges [5,9,12,17–20].

Similar issues have risen around PA-RCTs for CMA in particular, leading to delays or unsatisfactory conduct. Some studies suggested that this is related to the lack of scientific interest of investigators for such trials [12]. Others suggested a lack of incentive for companies, and a lack of

patients' willingness to participate if a medicine is marketed [14].

In an effort to contribute to better feasibility assessments of PA-RCTs as part of CMA SOBs, this study aims to prospectively explore and identify conditions and factors that may facilitate or impede their feasibility. A combination of qualitative research methods was applied to account for the perspectives of relevant stakeholders that are primarily involved in the conduct and approval of PA-RCTs. As such, we included the perspectives of patients, physicians, medical ethicists, and the pharmaceutical industry.

Box 1 – Conditional marketing authorization (CMA) & Specific Obligations (SOBs)

Since its implementation in 2006, the CMA pathway has been increasingly used [2], facilitating authorization based on non-comprehensive evidence, according to European Commission Regulation (EC) No 507/2006 [6].

Eligible medicines for CMA are those that are intended for "seriously debilitating diseases or life-threatening diseases"; those that are "to be used in emergency situations"; or are an "orphan medicinal product" [1]. This eligibility should be justified by the applicant (i.e., sponsor), as well as the expectation why the requirements for CMA will be met:

(i) "the benefit-risk balance of the product is positive";
(ii) "it is likely that the applicant will be able to provide comprehensive data";
(iii) "fulfilment of unmet medical need";
(iv) "the benefits to public health of the immediate availability of the medicinal product outweigh the risks inherent in the fact that additional data are still required" [1,6].

Upon a positive CHMP opinion, the European Commission can grant the CMA [6].

As legally binding conditions to the marketing authorization (MA), specific obligations (SOBs) are imposed. Typically, these concern new or ongoing studies that are to be performed once the medicine is conditionally authorized [10]. For comparative evidence generation, randomized controlled trials (RCTs) are considered the gold standard approach [10]. Consequently, RCTs are typically imposed post-authorization as part of SOBs [1]. The required additional data and their submission due dates stipulations are published in Annex II of the medicine's Summary of Product Characteristics (SmPC) [1].

Generally, comprehensive data is requested "intended to confirm that the benefit-risk balance is positive", i.e., that the benefits (i.e., 'desired effects') are considered to outweigh the risks (i.e., 'undesired effects'), to meet requirement (ii) and (iv [1].

A CMA has a 1-year validity that may be annually renewed [6]. To that aim, the marketing authorization holder (MAH, i.e., the sponsor) must submit "an interim report on the fulfilment of the SOBs to which it [the medicinal product] is subject" [1]. Compliance with the SOBs is then reviewed and assessed by the CHMP. A positive opinion on the benefit-risk is critical for maintaining the CMA. Upon fulfilling of the SOBs, the CMA is converted to a standard MA with a 5-year validity while no longer subject to SOBs [1,6].

Methods

Qualitative Approach and Study Design

To identify feasibility conditions from the perspectives of four key stakeholder groups, qualitative research methods (interviews and focus groups) were performed [Figure 1]. Purposive and snowball sampling was applied to identify potential respondents and organizations, and respondent eligibility was assessed based on their expertise through the research team's networks as well as national and European networks and organizations. The study protocol was approved by the Institutional Review Board (IRB) of Utrecht University Pharmacy Practice Education and Research (UPPER (UPF2210). Detailed description of the methodology are found in Supplementary Materials S1 [Extended Methods].

Focus Group Script Development and Data Collection

In total, 14 semi-structured exploratory interviews (i.e., 2 per stakeholder group) were performed with decision-making organizations (i.e., regulators, HTA organizations, clinical benefit-assessing committees) and four key stakeholders involved in the conduct and approval of PA-RCTs (i.e., patients, physicians, medical ethicists, pharmaceutical industry representatives). Interview data were thematically analyzed [21]. Identified themes were aggregated into three main themes that were informed by the framework as described by Gadke *et al.* (2021) [22], including (i) design, (ii) conduct, and (iii) motivations for PA-RCTs. This informed the development of the script for the subsequent focus group discussions with the four key stakeholders. During two-hour, online or hybrid focus groups via a teleconference tool (Webex® (Cisco Systems, CA, USA)) per stakeholder group, respondents were asked to reflect upon the recognizability of the themes and what aspects they regarded important.

Data Analysis

Video-recordings of the discussions were transcribed verbatim and pseudonymized to prevent reasonable participant identification. Transcripts were thematically analyzed and coded using NVivo software (QSR International, version 12, Burlington, MA, USA) [21]. Upon analysis, transcript data were coded deductively for the three main themes from the interviews, as well as a miscellaneous category, to ensure an open coding approach [21]. Within these main themes, subthemes were identified inductively [21]. The open coding phase was performed by C.H., and was and will be checked by A.J. Axial coding was proposed by C.H., and structuring of the themes was iteratively discussed with all members of the research team. Codes were categorized and aggregated while accounting for relationships between them.

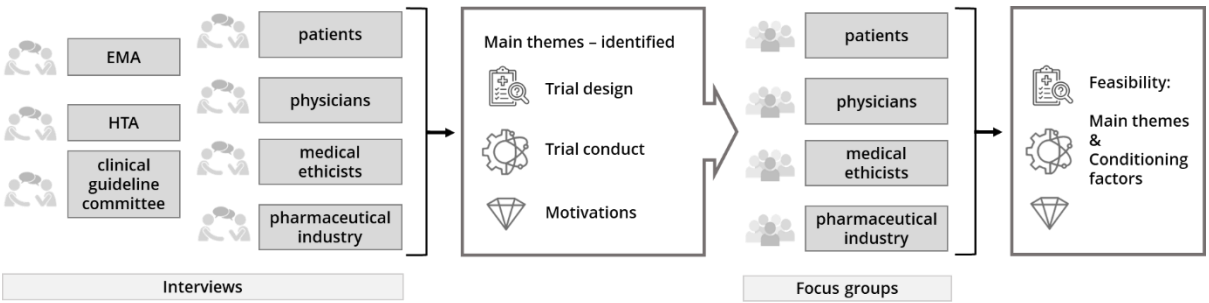

Figure 1. Overview of study design. First, exploratory interviews with decision making organizations and key stakeholders that are directly involved in the conduct and approval PA-RCTs. Second, focus groups were organized to further discuss the main themes identified from the exploratory interviews.

Results

Characteristics of interview respondents

Characteristics for the exploratory interview respondents with decision-making organizations and the key stakeholders involved in the conduct and approval of PA-RCTs were obtained from the pre-interview questionnaires [Supplementary Material S3].

Characteristics of focus group respondents

Characteristics were obtained for 25 of the 28 participants [Table 1]. Three participants did not fill out the pre-focus group questionnaire. Focus group numbers ranged from 5 (patients) to 11 (pharmaceutical companies). Various Dutch and European organizations were represented for patients, physicians, medical ethicists, and pharmaceutical industry. These Dutch and European patient organizations; Dutch academic and peripheral hospitals; medical ethics and research ethics (i.e., they assess not only clinical trials) committees; and multinational pharmaceutical companies based in Europe were represented. One pharmaceutical industry representant indicated no experience, as that person was not a cancer patient. Medical ethicists generally reported that they had no experience in designing clinical trials, possibly because their role is to assess them [Table 1].

***Table 1. Characteristics of focus group respondents**.*

	Patients	**Physicians**	**Medical ethicists**	**Pharmaceutical industry**
Number of respondents (n (% of total))	5 (18%)	6 (21%)	6 (21%)	11 (39%)
Experience in role (median years(range))	4 (3 - 5)	15 (5 - 19)	25,5 (8 - 40)	25 (8 - 35)
Experience with (n for 'yes')				
Cancer in general	2	2	5	6
Specific cancer	2	4	1	4
Experience with clinical research (median years(range))				
Participating	0 (0 - 4)	15 (5 - 31)	0 (0 - 37)	0 (0 - 35)
Designing	2 (0 - 2)	12 (5 - 31)	0 (0 - 37)	10 (0 - 30)
Understanding of regulatory system (self-rated 1-5 (median(range))	4 (3 - 5)	3 (3 - 4)	4 (3 - 5)	4 (2 - 5)

Qualitative Results from Thematic Analysis

Data obtained from the focus groups confirmed the three initially main themes that seem to directly determine the feasibility of PA-RCTs: (i) design, (ii) conduct, and (iii) motivations. Additionally, we identified ‘conditioning factors’, which were broader conditions that may modify the relevance of PA-RCT specific feasibility aspects and considerations about these aspects [Figure 2].

Figure 2. Overview of identified conditioning factors and feasibility aspects for a PA-RCT as part of SOBs for conditionally authorized anticancer medicine. A distinction was made between six conditioning factors and three main themes about feasibility aspects that determine PA-RCT feasibility more directly.

Conditioning factors

Conditioning factors represent factors that may modify the relevance and applicability of aspects specific for PA-RCT feasibility of (i) design, (ii) conduct, and (iii) motivations for a PA-RCT. We identified the following conditioning factors: (i) cancer indication, (ii) promise of new product; (iii) need for evidence; (iv) development plan; (v) access to the product; (vi) location of trial [Figure 2].

The type of cancer (i) for which a product is being developed was identified as a conditioning factor. The prevalence of the cancer indication, the acute or chronic character of the disease, as well as the (non-)solid tumor nature influences further decisions. For instance, biomarker-based patient selection was considered easier for breast cancer than for lung cancer.

The promise of the product (ii) is associated with the biological rationale (i.e., understood mechanism of action for targeted therapies). If this understanding is accompanied by an outstanding response rate, this may translate into a more subjective component 'enthusiasm'. Moreover, the promise is emphasized by a lack of alternative treatment options.

Third, the need for additional evidence (iii), and more specifically, how this need is perceived by the stakeholders. A diversity of views was displayed on which uncertainties and needs for evidence remain at time of CMA and whether and how these should be addressed. The nature of the uncertainties determine which methodology is appropriate to generate comprehensive PA-evidence. As such, different methodologies were proposed in all focus groups.

For a medicine's development plan (iv), respondents recommended timely anticipation and planning of CMA and its obligations for comprehensive evidence generation. As such, initiating a PA-RCT prior to MAA was recommended.

Moreover, the status of access to the product (v) after being granted CMA influences most other considerations for a PA-RCT. Respondents raised issues related to the access, (e.g., via trials, routine care, managed entry agreements), the reimbursement status, and the certain requirements to have access (e.g., trial participation, or registry enrolment). Primarily, respondents reported that once reimbursement is in place, the willingness of patients, physicians, and industry to conduct or to participate in a PA-RCT would generally be less. However, differences between countries provide opportunities, as an industry representative indicated:

> "*sometimes access may take quite a while. So, before patients have access, you have a longer time. You can also provide, or get some more patients in those countries where access might be delayed*." – (industry, 3.7)

Interdependent with access, the location of the trial (vi) (e.g., in which countries and (type of) hospitals) was considered to shape further considerations on aspects on the trial design and conduct.

Feasibility aspects

Upon setting the scene for a PA-RCT, stakeholders considered that the following aspects related to (i) design, (ii) conduct, and (iii) motivations determine the feasibility of PA-RCTs more directly [Figure 2].

i. Design

Design aspects for a PA-RCT can be clustered into those related to trial aim or trial complexity. In all focus groups, the aim of the PA-RCT was considered an important aspect that influences feasibility. However, diverse views existed on which aims and research questions were considered relevant. Industrial sponsors indicated confirmation of clinical benefit, while physicians indicated (dose) optimization, placement in line of therapy, and comparison to other products.

First, considerations on relevant absolute and surrogate endpoints varied across the focus groups. Overall survival (OS) was deemed relevant, although patient representatives highlighted also more patient-relevant surrogate or alternative endpoints, such as time-to-metastasis, -pain, -progression, treatment-free-period, or progression-free survival (PFS). For instance, one patient representative reflected on quality-of-life measures:

> "*I would say quality of life is really key, at least the patients [with rare tumors] that I represent. That is their main concern.*" – (patient representative)

Generally, surrogate endpoints were considered more relevant or feasible even, if OS data would take too long. However, the extent of using surrogates was questioned, and physicians regarded OS as the ultimate goal.

Second, randomization to the conditionally authorized medicine or a comparator arm was reason for discussion. On one side, all stakeholders argued for the choice of a good comparator, with different ideas on what would be 'good' and 'fair'. Respondents deemed standard-of-care or best therapy available relevant, although these may differ between countries. However, placebo has its drawbacks, as a physician and medical ethicist indicated:

> "*as the benefits [of the medicine] are better than the risks and the results are better than before. […] I think that we should not think on any kind of introduction of placebo in these studies, for there is a lot of treatment regimes. So a placebo is not in the place for the moment*." – (medical ethicist)

> "*Because, if it really is a promising medication and the comparator is, well, inferior in the views of many people, then it will be, I think, very difficult to find people for such a trial*" – (physician)

On the other side, respondents considered the fairness of randomization relevant, due to a possibly 'inferior' arm. This impacts ethics since equipoise may be considered broken, and (thereby) the willingness of patients and physicians to participate. However, for both, physicians indicated that the willingness would be increased if cross-over to the other (possibly superior) arm is intended as part of the design. However, they acknowledged that OS and PFS endpoints as well as data quality could in turn be comprised, in case of non-differential cross-over.

Third, the eligible trial population and line of therapy envisioned for the PA-RCT were deemed relevant. If a trial design entails that participants are selected based on biomarkers that are not measured as part of routine practice, this may complicate trial conduct. Additionally, respondents raised the generalizability of the results as important. Moreover, pharmaceutical industry representatives considered a PA-RCT in the conditionally authorized indication as very difficult, especially if that is an end-stage or last-in-line setting. Performing a PA-RCT in an earlier line was deemed more feasible, as one respondent proposed:

> "*When you go one level [of therapy] up where you have an established standard already […] then things from a recruitment and from a trial contact point of view become usually much more simple because you're doing a comparative trial, [with] the standard of care, and that's usually feasible*." - (pharmaceutical industry representative)

Next, respondents mentioned the complexity of a trial design, such as the type and the amount of data collection that is required. Complexity of such data collection procedures might be decreased if they are already of routine clinical practice. In that regard, physicians noted that a 'lean trial set-up'

enhances feasibility.

Another complexity issue that respondents mentioned in all discussions, was the relevance and need for involving multiple stakeholders in the design of a PA-RCT. Respondents suggested that this may improve feasibility though a design that is meaningful and relevant for all stakeholders, and not only for regulators and sponsors.

Consequently, involving multiple stakeholders may lead to a trial design that is better applicable to serve multiple purposes. However, as one pharmaceutical company representative pointed out:

> "*we cater to many stakeholders. We have regional control arms, we sometimes even have regional endpoints. And as a statistician you then get all these kind of requirements and then there's the ask: and now until next week, you design a trial that caters for all this. This is very, very difficult, believe me*." – (pharmaceutical industry representative)

ii. Conduct

Bringing trial design into practice by conduct of the PA-RCT raised complementary considerations about feasibility. For data collection procedures, minimizing the burden of (additional) procedures and tests, for participants and physicians was deemed critical. For participants, this would be relevant given their situation and state of disease. Physicians especially reflected on the differences between hospitals – academic hospitals have the expertise and the research support in place, whereas the peripheral may lack this support while they typically treat the most patients that would be eligible. Illustratively, one physician indicated:

> "*I mean, well, we in the <academic medical centre> crumble too under all the trials. We really have to select more critically and assess what, yes, what fits us? Where is our strength? And that will not always be, yes, well this kind of post-authorization studies*." – physician

In contrast, availability of resources were considered self-evident for pharmaceutical companies.

Second, respondents considered that potential competition for PA-RCTs would hamper its feasibility. This concerns competition with other trials in general and specific trials for patients in the same (sub)population (e.g., with the same mutation-driven tumors); and competition for available resources and interest of hospitals and physicians. Overall, the expected participant enrolment was identified as being dependent on multiple factors.

iii. Motivations

Motivations are aspects that were considered valuable in relation to the willingness to participate in, conduct, or approve a PA-RCT. Stakeholders commented on their own role, responsibilities, and considerations for their involvement in a PA-RCT, as well as on others' [Table 2].

Patients. Patient participation was considered related to a variety of factors, with agreement between stakeholders on altruistic (i.e., for other/future patients) reasons; the burden of participating; awareness; and informed consent (i.e., understanding of CMA and implications for trial participation); and promise of the new product.

Notably, patient representatives did not raise the promise of the new product as a specific reason (not) to participate. They instead highlighted that the willingness of patients would be higher if the unmet medical need for their disease was greater, and if fewer (novel) therapies and concurrent possible trials were in place. Understanding the importance of participation of patients in a trial was also considered a motivation, as one patient representative explained:

> *"How aware would a patient be that if there are no more data, that you could lose this drug? That is especially important if it's a real new one and you need the new data (…). If they understand that, they may be motivated to participate even more." – (patient representative)*

Similarly, medical ethicists reflected on the 'hypes' that may push patients towards trial participation, and the 'danger' of therapeutic misconception (i.e., the expectation that participation is in principle beneficial for the patient).

Moreover, medical ethicists suggested that voluntary participation and patients' autonomy to choose (not) to participate are values they regard highly. Especially in double-blinded trial design, ethicists mentioned that uncertainty about which treatment participants receive, could decrease patients' willingness. In turn, patients may be reassured if they are convinced (by their physicians) that the comparator arm offers a good alternative, and cross-over is possible. Besides, patients' and industry's interest may differ, and consequent choices and decisions would not always align.

***Physicians*.** For physicians, motivations on participation in a PA-RCT were mostly related to the trial aim. If "meaningful and clinically relevant", physicians could be interested. However, as mentioned by industry representatives and medical ethicists, scientific interest is crucial, as physicians are typically more interested in more experimental and novel trials than confirmatory trials. In a way, this was confirmed by physicians, but related primarily to the expertise and resources hospitals have in place for early-phase rather than PA-trials. Altogether, regulator-imposed trials seem not to necessarily reflect the aims of investigator-initiated trials.

Furthermore, physicians take into account the promise of the new product and the possible enthusiasm in the field for it. Additionally, along with benefits and risks, the burden for patients was also deemed relevant for physicians. Moreover, physicians tend to be more willing to participate if a PA-RCT is simple, not burdensome to physicians, and if the expected patient accrual is sufficient within the set timeframe. For similar reasons as patient representatives, intended cross-over could interest physicians as well. Besides, medical ethicists mentioned that compensation and publishable results upon participation could be motivations. Altogether, medical ethicists and patient representatives considered physicians' professional obligation and physician-patient trust-relationship as a motivation for physicians. In turn, they considered physicians in a way responsible to motivate patients to participate.. Additionally, physicians called upon their own responsibility to be more critical towards industrial sponsors, to ensure meaningful PA-RCTs.

Medical ethicists. Although ethical concerns and considerations were raised throughout the discussions medical ethicists were the only stakeholder who specifically reflected upon the role and responsibilities for ethics committees to approve the conduct of PA-RCT. In their considerations for approval of a PA-RCT, therapeutic misconception (i.e., the tendency of patient participants to think that trial participation will benefit them) was essential, as one respondent stated:.

> "*But for me, […] always the main concern with this kind of study [i.e., PA-RCTs] is therapeutic misconception. […] And to just do whatever is necessary to try to ward that off*," – medical ethicist

Another aspect was the tendency of medical ethics committees to patronize patients. There was a diversity of views amongst medical ethicists on the extent to which a patient should be protected from even having a PA-RCT proposed to her/him. Voluntary participation and the autonomy to choose (not) to participate were important values for their assessment of a PA-RCTs. Therefore, it was suggested that ethicists could or should define, albeit subjective and arbitrary, limits for a medicine's profile for a patient to decide on hers/his participation. Especially for PA-RCTs, where

clinical equipoise is unclear, medical ethicists mentioned that ultimately this may be more the potential participants' choice than when there is clear equipoise.

> "*but I think that that for a randomized controlled trial after conditional authorization, the concept of equipoise is essential. […] It is essential, important, and I also agree that it's very very difficult to assess. An ethicist cannot do that on his her own. You really need a multidisciplinary company of the research ethics committee. And then, there is also in this concept, a certain kind of arbitrariness*" – medical ethicist

Specifically for PA-RCTs, informed consent and ensured commitment on the side of investigators was important for approval of a PA-RCT, as well as a good and fair comparator. However, medical ethicists raised their concerns on their limited access to the scientific background of a medicine. This limitation complicates their evaluation on whether the comparison and promise of the product is 'fair'.

***Pharmaceutical industry*.** For a pharmaceutical company to conduct a PA-RCT after being granted the CMA as a sponsor, the legal obligation is the first and foremost reason, as indicated:

> "*the motivation is clear, right? It's to get your approval. You have no choice to do. Whether it's an RCT or any post-approval activity, you have to do it to finally get your product fully approved.*" – (pharmaceutical industry representative)

However, performing a PA-RCT was not only considered a regulator-imposed obligation, it also translates to taking accountability for a medicine, as industry representatives discussed. Second, increasing the evidence base and knowledge about the medicine was considered relevant, as this will strengthen the basis for clinical benefit as well as a sponsor's reimbursement negotiations with HTA and payers. And thirdly, not unimportantly, if a PA-RCT is performed in a different line of treatment than the conditionally authorized indication, gaining a possible extra authorized indication was also considered a motivation.

Moreover, a weak commercial case of a medicine may limit sponsor's motivations to perform a PA-RCT, as they indicated. Alternatively, physicians mentioned that financial incentives or penalties may be required to increase the sponsor's typically low willingness if the medicine is already marketed. To a further extent, they assumed that reimbursement of a conditionally authorized medicine would diminish any financial incentives for a company to perform a PA-RCT.

Lastly, physicians and medical ethicists expressed their general concerns on the presentation and 'framing' of a medicine's benefit. This regards particularly that comparison with other therapies may not be as positive or negative as the sponsor presents them.

Table 2. Motivations per stakeholder to participate in, conduct, or approve a PA-RCT.

	Subtheme	Definition of subtheme	Supporting quotes
Patients			
Altruism	Altruism	Altruistic reasons for patients to participate, namely to contribute to good scientific standards for all medicines, and helping future patients	"Why would people enter the trial if the drug is already available, I would say because you care and you want to sort of help other patients. You're not, like there are a lot of patients that are, you know, they are sick and they feel like the next generation of patients should have it better than they have it themselves." – (patient)
Unmet medical need	No new treatment and trials available in past years	The number of possible trials and new treatment options that have emerged in the past years	"And I guess also it's really like the first new treatment that is available for a patient group that has been waiting years for a new treatment. I'm sure the willingness will also be higher than, let's say there are maybe tens such trials available." – (patient)
	Trial landscape	How many trials are or will soon become available for patients to participate in	
	Cancer with high unmet medical need		"And I think a reason to participate is, I guess, if there's really an unmet need, I think the more unmet need there is, or the more unmet need that he patient feels he or she faces, the higher the willingness would be to participate." – (patient)
	Wanting new medicine		
Burden	Burden of participation	Burden of participation, mostly related to the data collection procedures (e.g., hospital visits, tests) and if they are more than routine care.	"So it should not be a real burden for a patient, because then why should they participate? So, not too many extra visits to the hospital, extra, what is it, bone marrow things, etc. Don't do it too often." – (patient)
	Data collection procedures	Which procedures are required (e.g., types of tests) and the ability and willingness of patients to cope with/handle these procedures that come with it	"But there's also a question of whether the patients want to participate in the trial because they have to commit themselves to the study, […], checkpoints and tests. And if the drug is on the market, they don't necessarily want to do it or you get poor quality data because, […], they commit at the beginning, but, […], they don't do it. And then you have to follow up for scans for checks. And it just poses a challenge […], difficulty for your quality of your study. And very often you have very little power over it as a company or as an industry."- (industry)
Awareness	Awareness & understanding	The extent to which a patient is aware of opportunities to participate in clinical research and PA-RCTs specifically. Higher awareness and understanding of trials may increase likeliness and willingness for patient participation	"(…) but it all relates to awareness. Most, the average patient is probably not aware. Because the average patient thinks the doctor he or she knows because he's a doctor. And I'm just a layman." - (patient)
	Importance of participation	To what extent patients understand and are aware of the importance of their participation in a PA-RCT and the understanding of a the conditionality of a CMA-authorized medicine	"How aware would a patient be that if there are no more data, that you could lose this drug? That is especially important if it's a real new one and you need the new data (…). If they understand that, they may be motivated to participate even more." – (patient)
Informed consent	Voluntariness	Whether and how voluntary is trial participation, and is this compromised or influenced somehow	
	Autonomy	To what extent do patients have their own autonomy and freedom of choice for deciding on trial participation	"And if a patient is, a person or patient, is invited to participate in the randomized trial, of course he has to be informed, he or she has to be informed on the different ways of treatment, drug, surgery or different drugs, etc., etc.. And, then it is his or her choice to say, I will join on the condition that I am randomized to a specific arm of that therapy." – (medical ethicist)

Uncertainty	Blinding	The uncertainty that comes with participation in a blinded trial and the not knowing of the treatment they receive	"If a patient does not does not want to have this uncertainty and he can say, no, I do not want to go to the study, I would like to have the normal treatment to which I am accustomed and which I am very, very comfortable [with]." (medical ethicist)
	Therapeutic misconception	The tendency of participants to think that participation in a PA-RCT will benefit them	
	Cross-over		"And that is what you see with lung cancer, that that the cross-over is just super important, that that you actually see in those targeted therapy, that it almost does not matter when they receive it, as long as they receive it. So if they first had received the standard chemo or the standard of care one time, and thereafter they go to a targeted therapy, that those people perform eventually just as good on the overall survival as the patients that first received targeted and then something else. So, and like this you can of course enthuse people, of, the product is not yet there yet, but if you participate in this study, and it doesn't matter if you first get the standard of care or not, you always get that [new] product, that then, those trials will go better, I think" – (physician)
Physicians			
Meaningful aim	Meaningful & clinically relevant aim	The notion that a PA-RCT must have a clinically relevant aim, according to physicians	"And then there must be some kind of idea that it will add something meaningful: clinically relevant with not too much effort." - (physicians)
Scientific interest	Little interest of physicians in confirmatory trials	The (expected) tendency of physicians to be more interested in novel trials, not confirmatory trials	"If you have a post-marketing study, post-approval study, the principal investigators are not necessarily always keen to participate. […] just because the key investigators, […] are interested in, […], new things and the drugs which are going heading for approval […] not necessarily something which is a post-approval marketing study." – (industry)
	Promise of new product	How promising the product is, according to the different stakeholders	"If itis very promising and it is already available outside the trial, then forget it, yes, and if it is a little promising with a lot of tox, then no one will participate." – (physician)
	Expected patient accrual	Within the given timeframe, how many eligible patients may be expected to be recruited	"And we also assess is, what is the lead time of the trial, how many people do you expect to recruit. If that are less than five, then we often do not participate. That relates to how many patients are there." (physicians, R1.2)
	Simple trial	Lean set-up, little trial complexity	"That is the other thing, there are no resources. Hospitals are all overflowing with the standard care. So everything needs to be simple." – (physician)
	Compensation for participation	Being rewarded for contributing to a trial	"Yes, researchers this might be interesting. That's the question as, as a research question. And there might be other motivations, still there is motivation of money. If you grant money for that or also. Or if you can have publishable results." – (medical ethicist)
	Publishable results	Scientifically interesting results	
Expected professional obligation for patient care	Expected helping and guiding of patients in PA-RCT	The expectation that patients rely on their physicians to help and guide them when they (consider to) participate in the trial	"(…) the essence is that the experts who will treat the patients they should know and (…) they should address patients and ask them. 'There is a new medication that is conditional, but it may be something for you', because they know if it's something for the patient […]. So they should address the patient and ask and motivate them. (…) 'I will help you. I will take you by the hand. Whatever is needed and I will get you in. And I'll monitor you. I will be with you.'." – (patient)
	Trust-relationship with patients	Responsibility for a good trust relationship between patients and physicians, reason both to participate	"If you have a real good relation with the people who treated you as a patient, then it's easier to get there. (…) And you can also help patients to understand. But then, you have to build that relation, I think with the doctors." – (patient)
	Explaining need for more participants in trial and motivate patients	The responsibility of physicians to explain the trial and motivate patients for trial participation	"But if a doctor can explain it properly why he or she needs a bit more patients in the trial, then it might be a motivation." – (patients)
	Cross-over	If cross-over is intended as part of the trial design	"And what was said before, a cross-over possibility enlarges of course the motivation to participate, both for physicians as well as for patients" – (physicians)

	Patient benefit-risk-burden acceptable	If the trial is acceptable in the balance between benefits, risks and burden for a patient	"I would ask my patient and tell him, very clearly, you have a chance of a benefit in general, risks are, and burdens are. We very often forget burdens, but risk and burden are different. […] And if physicians say "your drug is, has a lot of burden, it is fine, but it is a lot of burden when it is applied to patients". And then the pharmaceutical companies are interested to see what can we do to change the drug in a way that the benefits are hold or even improved, that the risks are lowered and the burdens are lowered. And therefore, in general, I think there is a good motivation to join and to perform trials, even after authorization." – (medical ethicist)
Medical ethicists			
Voluntariness	How voluntary is patients' participation in a trial	For medical ethicists to consider how patients view participation in a PA-RCT, whether and how voluntary that is, and is this compromised or influenced somehow	"I've heard of examples of certain treatments or certain technologies not being accessible to patients unless they participate in a study." – (medical ethicist)
	Valid informed consent	How well patients are informed upon trial participation	"So I'm less concerned, so long as the informed consent is clearly written and there's clear commitment on part of the researchers to enroll people in a way that clearly communicates that to them, that, I don't see such a problem." (medical ethicist, R4.6)
Paternalism	Ethical (arbitrary) limits	Defining limits for a medicine's profile before a patient chooses whether or not to participate	"I think there's a lot of subjectivity in arbitrarity yeah. So, for instance, is it ethical to propose a drug that gives 80% chance of one month life prolongation at the cost of a 40% increase in toxicity? Make it 90%, make it 50%. It's almost impossible to weigh, you weigh different things. Now research Ethics Committee, I think, should set a limit, complex, subjective and arbitrary as it may be, within this limit, it is up to the, up to the patient."– (medical ethicists)
	Proposing PA-RCT as trial participation option	The extent to which proposing a trial to patients may be prevented due to ethics	"Question that research ethics committees ask themselves is, […] Is it ethical to propose this to our population? That's a question that goes, that precedes submitting the patient information leaflet to the patient."– (medical ethicist)
	In case of unclear equipoise – different for PA-RCTs	Whether patronizing patients is acceptable (or: ethical) in case of unclear equipoise	"And so I don't want to get too far off-track or to suggest that comments I made about patronizing participants or whatever had to do with those other cases, because I feel like they're very different from the case where you have, you know, equipoise and you're trying to compare a drug where there's some evidence that it's safe and somewhat efficacious against the gold standard. I feel like that's a very different issue."- (medical ethicist)
Clinical equipoise		The uncertainty in the balance of whether a treatment will be beneficial or harmful to patients	"but I think that that for a randomized controlled trial after conditional authorization, the concept of equipoise is essential. I developed this point of view in the last one and a half hour. It is essential, important, and I also agree that it's very very difficult to assess. An ethicist cannot do that on his her own. You really need a multidisciplinary company of the Research Ethics Committee. And then, there is also, in this concept, a certain kind of arbitrariness ."- (medical ethicists)
Therapeutic misconception	Misunderstanding of patients' hopes and expectations for participation in a PA-RCT	The tendency of patients to think that participation in the trial will benefit them, must be warded off according to medical ethicists	"But for me, I guess always the main concern with this kind of study is therapeutic misconception. And to just do whatever is necessary to try to ward that off, even if it comes down to something like the name of the study, you know, they've chosen an acronym that spells out the letters 'cure' or something like that."- (medical ethicist)
Comparator arm	Appropriate comparator arm	If the comparator arm is not appropriate according to the medical ethics committee, this must be changed	"And the most important question is, what is a comparator, if there is any? And the research ethics committee can and they do it, believe me, they do it, they can accept the comparator or they can say, no, this is not a good comparator, you should change your protocol unless there will not be a favorable opinion of the ethics committee." – (medical ethicist)
Quality of scientific evidence	As framed by pharmaceutical companies	How pharmaceutical companies present a medicine's performance in clinical trial data	"And I feel like there for me at least, the thing I would most worry about, is that drug companies would try to game the system by framing the comparisons in ways that benefited them and led to market authorization in a favorable way for them. But that did not lead to the best scientific evidence for the efficacy of one drug or another, or that led to drugs that had a low quality of life profile relative to the costs." – (medical ethicist)
	Access to scientific background	To what extent medical ethicists can understand and have access to the scientific background of a medicine	"And I feel like as a as an ethicist on a single committee, it's extremely difficult for me to have access to the broad scientific and market background, to be able to assess those kinds of things. In fact, nothing that I'm asked to assess has anything to do with it ultimately. So that's, I feel like that's the big ethical issue. But I don't think it concerns my work as

			some, as an ethicist on a medical ethics research ethics committee, because that's not what I'm really being asked about to assess." – (medical ethicist)
Commitment of investigators	Along with informed consent	Ensuring that investigators, physicians, sponsors are committed to conducting the PA-RCT and do as is expected according to the informed consent	"I think if people understand what they're getting into, it's okay to allow, you know, to allow adult, adults to take risks and to do so out of an altruistic hope that some scientific benefit will come for other patients. So I'm less concerned, so long as the informed consent is clearly written and there's clear commitment on part of the researchers to enroll people in a way that clearly communicates that to them, that, I don't see such a problem." - (medical ethicist)
Pharmaceutical industry			
Obligation	Legal obligation as part of SOBs to perform PA-RCT	The obligation was indicated as important for the industry.	"You know, if you ask about the motivation of the industry as a stakeholder in this case, you know, the motivation is clear, right? It's to get your approval. You have no choice to do. Whether it's an RCT or any post-approval activity, you have to do it to to finally get your product fully approved. (…) If we want to get the product on the market fully, fully approved, you have to do this RCT or whatever alternative model you choose." – (industry)
	Responsibility	The responsibility for performing the CMA obligation lays with MAH	"The, uh, uh, medicines authority could, could ask anything else, like, doing the placebo controlled, randomized trial even, or other type of clinical trials and so on. So the obligations, obligation is on the holder of marketing authorization because this guy is making money from it. So (…) it has to have some obligations." – (medical ethicists)
Financial	Strong vs. weak commercial case	Whether it is commercially and financially interesting for a pharmaceutical company to perform a PA-RCT	"Now, I have to say that I have one example where we ultimately decided, not in oncology, by the way, not to complete an RCT, because the commercial case was too weak. And that is certainly what you don't want as a company, Right, because you invest a lot of money in the development of a product and then close to the finish line or even beyond the finish line, you say, well, you withdraw. And, so that's definitely not a preferred situation." – (industry)
	Other indication	Interest of industry enhanced if PA-RCT is to be performed in another (earlier) line of treatment – extension of the indication.	"And I think also not unimportantly, especially if we do it in a different light [line?] of treatment, it also may give us another indication." – (industry)
	Financial incentives	To fulfill the requirements for a PA-RCT, or motivate pharmaceutical industry (additional) financial incentives (as penalties or positive incentives…) may be required	
	Reimbursed product – generate income	When reimbursement is in place, this generates income for the sponsor	"Because yes, I can imagine that the company does not always have an interest to rapidly provide those data, because, once its reimbursed, then the cash flows" – (physician)
Evidence-base	Enhance evidence base for further negotiations	More comprehensive evidence provides stronger basis for the sponsor during further negotiations (e.g., for reimbursement)	"when we think about conditional approval and then the confirmatory trial, we think that's a requirement from regulators and maybe HTA, but it may be not only in the interest of regulators and HTA to perform such a trial and to get that information out. At the end, when you bring a new a new medicine onto the market, you have to answer two questions. One is why a patient should take it, and the other one is why a society should pay for it or should pay that much for it. And for that you need in both cases, you need really good data. And when you go for a conditional marketing authorization, you have limited and incomplete data and it's in the interest also of the company." – (industry)
	Taking accountability	The responsibility of being accountable for a medicine	"But I do think what is important, and I think we're willing as a sponsor ecosystem to take accountability for our products and answering and confirming benefit and doing it in a way that's responsible to patients." – (industry)
Promises	Actual conducting PA-RCT upon regulator-request…	Perception of problem by physicians: promises are not kept for a well-performed trial…	"But yes, the company can promise all sort of things, such as, we will open more sites and those will accrue, but subsequently, they don't do they best. So I think that that primarily the big problem is why this is discussed here, that a company can make promises for a well-conducted trial, but that you cannot keep them accountable for it." – (physician)
Resources in place		If the sponsor has sufficient resources to perform the PA-RCT	"And there, is I cannot that would be terrible situation if the authorization is given with some conditions requiring certain type of clinical trials and then you as sponsor just say to the authority: "Oh no thank you, I do not want the marketing authorization because I do not have the capacity and I cannot do the trials and I could not, be, cannot meet your expectations, my good medicines authority"." – (medical ethicist)

Discussion

With this study, we aimed to explore and identify conditions that may influence the feasibility of PA-RCTs for anticancer medicines with a SAT-based CMA. PA-RCTs are typically imposed to achieve comprehensive evidence on the benefit-risk balance. A combination of interviews and focus group discussions was performed to identify various perspectives of stakeholders that are directly involved in the conduct and approval of PA-RCTS, i.e., patients, physicians, medical ethicists, and representants of the pharmaceutical industry.

We identified three major/main themes that represent feasibility aspects: design, conduct, and motivations for a PA-RCT. In additional, we identified conditioning factors (conditions, situations, and perceptions) that affect the relevance of these feasibility aspects: the (i) cancer indication, (ii) promise of new product; (iii) need for evidence; (iv) development plan; (v) access to the product, (vi) location of trial.

Importantly, our main findings concern concepts that are interrelated with all conditioning factors. As such, we identified ethical considerations, and specifically, the perceived clinical equipoise. How clinical equipoise is perceived influences how stakeholders perceive the need for evidence and the promise of the new product. Consequently, clinical equipoise impacts the aim of a PA-RCT and which uncertainties it should address (e.g., which line of therapy is meaningful). Additionally, clinical equipoise impacts stakeholders' motivations, while it is differently perceived among them. Typically, the uncertainties for conditionally authorized medicines are clear from a regulators' perspective, as discussed in the respective EPARs. Interestingly, we found that stakeholders not necessarily perceive these uncertainties in a similar manner. Illustratively, Kesselheim *et al*. (2019) clarified the discrepancy between physicians' perception and the actual reality of regulatory decisions [23]. They found that, while physicians value the high evidence standards for market authorizations, an increasing number of approvals was based on SAT data [23]. Similarly, we found that physicians' perception of which comprehensive evidence should be required (e.g., optimization studies) was not necessarily the same as regulators' (i.e., additional efficacy and safety data) [12]. Moreover, a recent publication by Vokinger *et al.* (2022) highlighted the therapeutic value of anticancer medicines with a CMA, indicating that these are typically low, while in line with our findings, this is not always reflected in stakeholders' views [24].

A second major finding is the variety of factors that influence patient recruitment for a PA-RCT. First, it depends on aspects inherent to the envisioned patient population in a certain line of therapy. However, conditions which are not directly related to the PA-RCT itself modify patient recruitment, such as the development plan and consequent timing of initiating patient enrolment. If enrolment starts after being granted CMA, the window of opportunity may narrow if the medicine is (soon to be) marketed and reimbursed. However, this raises the question whether sponsors delay reimbursement applications in certain countries to enlarge this window. The status of a PA-study (ongoing or newly started) and the number of enrolled patients were considered in the EPARs of SAT-based CMAs for NSCLC [Supplementary Material S5]. However, details are lacking on expectations for acquiring sufficient patient numbers. So, recruitment is a more complex issue than currently may be assessed according to the EPARs. Interestingly, Rittberg *et al.* (2021) simulated hypothetical RCTs as alternatives to SATs and conclude that most SAT-based FDA approvals would have been feasible in a timely manner [25]. Although promising, they did not consider differences for a post- or pre-authorization setting, although they acknowledged that the window of opportunity was lost after accelerated approval (i.e., FDA equivalent of CMA) [25]. Based on our findings, this theoretical approach would not reflect the reality of PA-RCTs.

The third main finding regards the burden for patients and physicians to participate in a PA-RCT, which is reflected in the design, conduct, and motivations. For patients, this is dependent on their indication and stage of disease; and consequently, if participation would require procedures that add to the routine care for instance. For physicians, burden was reflected in hospitals' limited availability of resources and expertise, and in whether data collection procedures were necessary and part of clinical practice routines. Minimizing burden for both was recommended for a more feasible PA-RCT design and subsequent conduct, as this ultimately improves their motivations.

Besides, we identified aspects that are inherent to the conduct of RCTs and other clinical trials that are not specifically part of CMA SOBs. These include the choice of trial population; duration of treatment (e.g., relevant for optimization trials); choice of comparator; choice of relevant endpoints. The work of Cipriani *et al.* (2020) complements and underscores the identified conduct aspects in our study [9]. For instance, they describe that a clinically relevant active comparator was important in a PA-setting [9]. However, conditions for when comparative PA-evidence generation was deemed feasible were not further specified. Furthermore, competition between trials is likely to be more pronounced the PA-context. As was indicated during the focus groups, hospitals must choose which trials they focus on. Regarding ethics, prioritizing recruitment for certain trials is vital and 'ethically permissible', as Gelinas *et al.* (2017) argue [26]. With clinical equipoise and warding-off therapeutic misconception in mind, they recommend prioritizing treatment based on sound measures for (expected clinical benefit) in a competitive trial landscape, which may be relevant for PA-RCTs as well [26].

Lastly, stakeholders' motivations are not always aligned, as respondents acknowledged themselves. Overall, they were motivated to generate comprehensive evidence. For physicians, patient-care and scientific interest were motivations to contribute, and for patients, altruism and ensuring good scientific basis were motivations. For industry, having comprehensive evidence in reimbursement negotiations was a motivation. However, while industry representants discussed the limited scientific interest for physicians to contribute to a confirmatory trial, medical ethicists and physicians appeared to contradict this.

Although this study beholds a regulatory focus, a broader context may exist for PA-evidence needs . For informed decision-making for Health Technology Assessment (HTA) organizations and clinical guideline committees, RCTs generally provide the preferred type of data [27]. For reimbursement decisions, RCTs are required, but acknowledged as not being always [27]. So, for conditionally authorized medicines, providing PA-RCT data may benefit their decisions as well. A recent study from our group indicates that aligning regulatory and HTA requirements for PA-evidence generation may be key to facilitate timely patient access and improve decision-making [28]. And in turn, this may support PA-RCTs for regulatory decisions.

To our knowledge, this is the first qualitative study focusing on the feasibility of PA-RCTs. By means of interviews and focus groups, we explored various stakeholders' perspectives that are key in the conduct and approval of PA-RCTs. As such, we provided insights on the aspects they consider relevant for PA-RCT feasibility and how they perceive clinical equipoise for conditionally authorized medicines.. Inherent to qualitative research is the limited generalizability, as data is obtained from focus groups with limited sample size. However, we considered stakeholders' views as complementary to each other. Furthermore, their views represent expert opinions since most respondents were experts in their respective roles. Although a minimum understanding of the European regulatory system was not required to be eligible, some invited respondents considered themselves not equipped for participation. As such, stakeholders may have been represented more diversely. Moreover, although eligibility was neither restricted to Dutch organizations, and European

organizations were invited as well, the first were more represented in the focus groups. Still, given the recruitment challenges within the time and resources available, we considered the data richness satisfactory for this exploratory study. Nonetheless, findings presented here require additional coding validation, in accordance with our study protocol.

To further explore the completeness of the identified feasibility aspects, additional (multistakeholder) focus groups and interviews may be held with these four stakeholders (more European representation of physicians and patients), as well as others (e.g., contract research organizations (CROs), payers). To explore the (relative) importance, a quantitative survey may prove insightful. Our exploration may provide grounds to further explore the relevance of regulatory decision-making for the development of novel anticancer medicines.

Altogether, this study aimed to contribute to advance feasibility assessments of PA-RCTs for anticancer medicines with SAT-based CMAs to provide comprehensive data on the benefit-risk balance. As such, we identified feasibility aspects closely related to the trial. These are in turn influenced by overarching conditioning factors of perceptions, conditions, and circumstances in which the PA-RCT is set. Differences in the perceived clinical equipoise and the various relevant factors for patient recruitment ultimately determine whether the requirements for a CMA can be met: if (i) comprehensive evidence can be provided in a timely manner, while the (ii) the benefits outweigh the risks of incomprehensive evidence. So, this study may offer recommendations to advance feasibility assessment of PA-RCTs, to ensure that trial are not only initiated, they are finished as well.

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Supplementary Material S1 – Extended Methods

Study Design

To identify conditions for the feasibility of PA-RCTs from a multistakeholder perspective, qualitative research methods (interviews and focus groups) were used. For insight into the decision-making context, two exploratory interviews were held per decision-making organization (i.e., regulators, HTA organizations, and clinical benefit-assessing organizations). With key stakeholders involved in the conduct and approval of PA-RCTs (i.e., patients, physicians, medical ethicists, pharmaceutical industry representatives), two exploratory interviews were held as well. Specific, semi-structured interview guides were prepared, based on literature review on the feasibility of post-authorization evidence generation, and included a framework of feasibility dimensions for interventional studies as described by Gadke *et al.* (2021) [22]. The interview guides were discussed with the research team [Supplementary Material S2].

For both the interviews and focus groups, purposive and snowball sampling was applied to identify potential respondents and organizations. Respondent eligibility was assessed based on their expertise through the research team's networks and national and European networks and organizations.

Potential respondents, networks and organizations were contacted and invited by e-mail, through a formal standardized information letter. For the interviews, contact was sought between July and September 2022, and interviews were performed during this period by A.J. and/or C.H. For the focus groups, eligible respondents were invited from August to October 2022, for the discussions in October 2022. Before the interviews and focus groups, respondents received standardized additional information on the topic. Respondents provided verbal and/or written (digital) consent. Participants were requested to fill out a short questionnaire (via LimeSurvey tool (Hamburg, Germany) on professional characteristics, with specified questions for decision-making organizations or key stakeholders. For each interview, a field-note based summary was shared with each respective respondent to reflect upon and correct if he/she deemed that necessary.

Interview-based Focus Group Script Development

Ultimately, exploratory interviews were held to inform the development of a focus group script. To that aim, a total of 14 (i.e., 2 per stakeholder group) semi-structured interviews were held with representatives of decision-making organizations and key stakeholders involved in the conduct and approval of PA-RCTs [Supplementary Material S3]. Audio-recordings of the interviews were transcribed verbatim and pseudonymized to prevent reasonable respondent identification. Comparing with the framework from Gadke *et al.* (2021) interview data were thematically analyzed using NVivo software (QSR International, version 12, Burlington, MA, USA). Identified themes were aggregated into three main themes, i.e., (i) design, (ii) conduct, and (iii) motivations, that were informed by the framework as described by Gadke *et al.* (2021) [22]. The first three interview scripts were double-coded (i.e., independently by two researchers), and were compared until consensus was reached.

These main themes informed the development of the focus group scripts for the discussions with each of the four key stakeholders. Focus groups were chosen as the next qualitative research method as they allow for interaction between respondents, enhancing the exchange of experiences and generation of ideas and solutions [29]. Besides, the focus of this paper is on the focus group-derived data [Figure 1].

Data Collection

At the start of each focus group session, practicalities were introduced, as well as a personal introduction of the respondents and present research team members, and the background and goal for the focus group were introduced. Focus groups took 2 hours, and after a 25-45 minutes of discussion, the next main theme was introduced. Respondents were asked to reflect on whether the introduced theme was recognizable and what was important for them regarding this theme. The moderator ensured that all respondents had the opportunity to speak, and additional questions could be asked by the research team. Discussions were guided according to the focus group script that was iteratively discussed within the research team beforehand [Supplementary Material S4]. Given the international character and represented nationalities, all respondents participated online, by joining a Webex® meeting (Cisco Systems, CA, USA). Only during the patient focus group, one of the participants joined on-site. All focus groups were moderated by A.J. or C.H. and comprised between 5 and 11 respondents [Table 1].

Data Analysis

The focus groups were video-recorded and transcribed verbatim using an automated transcription service (Amberscript software, Amsterdam, the Netherlands). Transcripts were pseudonymized to prevent reasonable respondent identification. Subsequently, transcripts were thematically analyzed and coded using NVivo software (QSR International, version 12) [21].

All transcripts were coded sequentially for each of the following steps. Data were coded for stakeholders or parties involved in the context of PA-RCTs as mentioned by the respondents. Codes were generated in close resemblance to the transcript text. Next, a distinction was made for comments that concern 'PA-RCTs specifically' or 'clinical trials in general'. If a segment was not applicable to these categories, the transcript was left uncoded there. Subsequently, transcript data were coded deductively for the three main themes from the interviews, as well as a miscellaneous category, to ensure an open coding approach [21]. Within these main themes, subthemes were identified inductively [21].

This open coding phase was performed by C.H., and was and will be checked by A.J. Axial coding was proposed by C.H., and structuring of the themes was iteratively discussed with all members of the research team. At the end of this step, codes were categorized and grouped while accounting for relationships between them.

Characteristics of pivotal trials and trials as part of SOBs for anticancer medicines for the treatment of NSCLC that were granted a CMA based on SAT-data (2006-2021).

To contextualize the current landscape of medicines granted a CMA in a competitive landscape, key characteristics were collected for medicinal products that were granted a CMA for an NSCLC indication. Those medicines that were granted CMA by the European Commission between 2006 (when the CMA was implemented) to June 2022 were included, as described in the respective EPARs and SmPCs (Annex II) as published on the EMA website (www.ema.europe.eu). Characteristics were collected for the pivotal trials and trials as part of SOBs [Supplementary Material S5].

Supplementary Material S2– Semi-structured interview guides

Feasibility of post-authorization randomized controlled trials

Definition of concepts

In these interview guides, we use several concepts as listed below.

Conditional marketing authorization (CMA): this type of marketing authorizations allows the timely market access of a medicines for severe, often rare, diseases for which an unmet medical need (i.e., there is no appropriate therapy available) exists, but for which comprehensive data is lacking. The market access is on the condition that comprehensive evidence will become available in a timely manner while the medicine is marketed, and the benefit-risk balance for the medicine is positive [30].

Post-authorization (PA): after a medicine is granted (conditional) market authorisation based on the opinion of regulatory agencies, so once the medicine has acquired market access [31].

Randomized controlled trial (RCT): a clinical trial that uses randomization when allocating people to different arms of the study. Each person has an equal chance of being allocated to one of the study arms. One of the interventions is the control group, which is for instance a placebo, or standard of care at that time. This type of study is considered one of the most powerful instruments in clinical research [32].

Single-arm trial (SAT): a nonrandomized clinical trial in which patients with the intended medical condition/disease are all allocated to one arm (group) to receive the novel therapy. The response to this treatment is followed over time. This type of clinical study is different than the abovementioned RCT, because there is only an intervention-arm and no internal control group [7].

Benefit/risk: The balance of the desired effects ('benefits') of a medicine in compared to its undesired effects ('risks'). A positive balance, in which the benefits outweigh the risks, forms the basis for determining whether a medicine can be granted (conditional) market authorization [33].

Part I: Interview guide decision makers

The objective of this interview guide is to explore the decision-making context regarding the feasibility of post-authorization randomized controlled clinical trials and conditions that influence the (request and) conduct of post-authorization RCTs of several decision-making bodies including regulators, health technology assessment (HTA) bodies, and clinical guideline committees. To that end, exploratory interviews will be held.

The data from these exploratory interviews will be used in the data analysis and the design of focus groups with patients, physicians, medical ethicists, and pharmaceutical company representatives, respectively. These focus groups will be used to confirm, reflect, and expand on the findings observed in the interviews.

Notably, the exploratory interviews will be held in either English or Dutch, for which the questions in this guide will be translated accordingly.

A pre-interview questionnaire will be sent to the respondents, including questions regarding their relation to the different decision-making bodies, experience with/expertise in oncology, experience with (participating in, or designing) clinical research.

Interview format: one-hour, in-person or online, semi-structured interview.

Regulators	
Topic	**Question**
Grand tour questions	What can you tell me about your experience with regulatory decision making based on single arm trials? What can you tell me about your experience with conditional marketing authorizations?
Feasibility assessment	Do you consider a feasibility assessment of a (post-authorization) study important? And why? What aspects of feasibility should be considered when you make decisions for products that may be granted CMA? How is the feasibility of a post-authorization trial currently assessed when granting conditional marketing authorizations? (general vs oncology) • Is the feasibility of such a PA-trial sufficiently assessed, in your view? • Who would you say is responsible for assessing the feasibility? (regulator vs. applicant) • According to CMA criterium (ii): when do you consider that an applicant will be 'likely to provide comprehensive data post-authorization'? And to what extent is the timeliness of obtaining the comprehensive data discussed and assessed? • Do you consider data typically obtained from PA-RCTs after CMA sufficiently informative to extend the CMA or convert it to a SMA?

HTA organizations	
Topic	**Question**
Grand tour questions	What can you tell me about your experience with reimbursement decision making based on single arm trials?

	What can you tell me about your experience with conditional marketing authorizations?
Feasibility assessment	Do you consider a feasibility assessment of a (post-authorization) study important? And why? What aspects of feasibility should be considered when you make decisions for products that are granted CMA (based on SATs)? How is the feasibility of a post-authorization trial currently assessed when granting conditional marketing authorizations? (general vs oncology) • Is the feasibility of such a trial sufficiently assessed, in your view? • Who would you say is responsible for assessing the feasibility? (regulator vs. applicant) • In your view, do you consider data typically obtained from PA-RCTs after CMA sufficiently informative for making reimbursement decisions?

Clinical guideline committees	
Topic	**Question**
Grand tour questions	What can you tell me about your experience with decision making regarding implementation in clinical guidelines based on single arm trials? What can you tell me about your experience with conditional marketing authorizations?
Feasibility assessment	Do you consider a feasibility assessment of a (post-authorization) study important? And why? What aspects of feasibility do you consider (or should be considered) when you make decisions for products that are granted CMA (based on SATs)? How is the feasibility of a post-authorization trial currently assessed when granting conditional marketing authorizations? (general vs oncology) • Is the feasibility of such a trial sufficiently assessed, in your view? • Who would you say is responsible for assessing the feasibility? (regulator vs. applicant) • In your view, do you consider data typically obtained from PA-RCTs after CMA sufficiently informative for decision-making?

Part II: Interview guide stakeholders involved in the conduct and approval of PA-RCTs

The objective of these interview guides is to identify feasibility conditions for post-authorization randomized controlled clinical trials to confirm the benefit-risk of anticancer medicinal products granted conditional marketing authorization from various stakeholder perspectives including patients, physicians, medical ethicists, and pharmaceutical company representatives. To that end, exploratory interviews will be held, using the interview guide corresponding to the stakeholder group. The data from these exploratory interviews will be used in the data analysis and the design of focus groups, which will be used to confirm, reflect, and expand on the findings observed in the interviews.

Notably, the exploratory interviews will be held in either English or Dutch, for which the questions in these guides will be translated accordingly.

A pre-interview questionnaire will be sent to the respondents, including questions regarding their relation to the different decision-making bodies, experience with/expertise in oncology, experience with (participating in, or designing) clinical research.

Interview format: one-hour, in-person or online, semi-structured interview.

Patients	
Topic	**Question**
Grand tour question	What can you tell me about your experience with products granted CMA?
Feasibility aspects	What would you say is the importance of assessing the feasibility of PA-RCTs (studies requested after a conditional marketing authorization)? What aspects should be thought of when determining the feasibility of a PA-RCT? (in the context of NSCLC vs. anticancer products in general) • When, would you say, do you (not) need post-authorization RCTs? • When would you participate in a PA-RCT? • When would you consider a post-authorization RCT (in)feasible? ➔ What is your experience with this? Could you describe an example of a situation in which this was the case?

Probes	Topics for probes when topic is mentioned by respondents:
	• Recruitment capability
	  ○ Based on your experience, is it possible to recruit participants appropriate for typical post-authorization RCTs for products granted CMA? Why (not)?
	  ▪ In your view, what are the most important obstacles for recruitment of participants in PA-RCTs? And what are obstacles or reasons not to participate in a PA-RCT?
	• Data collection procedures
	  ○ Do you find data collection procedures typically used in PA-RCTs appropriate? Do you think of them as a burden? Why (not)?
	• Design procedures
	  ○ What design features (e.g., endpoints, comparator, patient group) of an RCT affect its feasibility when seen in the context of products granted CMA?
	(And how do these features affect the feasibility to conduct the RCT post-authorization?)

	• Social validity
	  ○ Under which conditions, or on which terms, would patients participate in a PA-RCT? And in your regard/experience? When would you participate yourself?
	• Practicality
	  ○ In your view, do (pharmaceutical) sponsors have the resources (and ability) to manage PA-RCTs? (regarding the available resources, time, training, and materials)
	  ○ In your opinion, is it ethical to conduct PA-RCTs in the context of products granted CMA/authorized based on single arm trials? Under what conditions?
	• Integration into existing systems
	  ○ Which existing systems (e.g., interactions between stakeholders, health-care practice, education, regulatory, reimbursement, etc.) support or hinder conduct of PA-RCTs? And how, what aspects play a role? Why?
	  ○ To what extent do PA-RCTs fit or compete with other (ongoing) studies? (To what extent do PA-RCTs fit the standard of care?)
	  And is the integration dependent on line of treatment for which the medicine is evaluated?
	• Adaptability
	  ○ When can a PA-RCT be adjusted (e.g., for country-specific needs or changes over time), while still achieving study objectives? And how does the degree of adaptability affect the feasibility of a PA-RCT?
	• Implementation
	  ○ When, under what conditions, are you, as a patient, willing to participate in a PA-RCT?
	• Effectiveness
	  ○ In your view, do PA-RCTs sufficiently confirm the benefit-risk of anticancer medicines as assessed at time of CMA approval? On which conditions is this dependent?
	• Generalizability
	  ○ When do PA-RCTs provide possibilities to (better) improve the generalizability of the study results as compared to pre-authorization RCTs results? (or pre-authorization SATs?)

Physicians	
Topic	**Question**
Grand tour question	What can you tell me about your experience with products granted CMA?
Feasibility aspects	What would you say is the importance of assessing the feasibility of PA-RCTs (studies requested after a conditional marketing authorization)? What aspects should be thought of when determining the feasibility of a PA-RCT? (in the context of NSCLC vs. anticancer products in general) • When, would you say, do you (not) need post-authorization RCTs? • When would you participate in a PA-RCT? • When would you consider a post-authorization RCT (in)feasible?

	➔ What is your experience with this? Could you describe an example of a situation in which this was the case?

Probes	Topics for probes when topic is mentioned by respondents:
	• Recruitment capability
	  ○ Based on your experience, is it possible to recruit participants appropriate for typical post-authorization RCTs for products granted CMA? Why (not)?
	  ▪ In your view, what are the most important obstacles for recruitment of participants in PA-RCTs? ? And what are obstacles or reasons not to participate in a PA-RCT?
	• Data collection procedures
	  ○ Do you find data collection procedures typically used in PA-RCTs appropriate? Do you think of them as a burden? Why (not)?
	• Design procedures
	  ○ What design features (e.g., endpoints, comparator, patient group) of an RCT affect its feasibility when seen in the context of products granted CMA?
	  (And how do these features affect the feasibility to conduct the RCT post-authorization?)
	• Social validity
	  ○ Under which conditions, or on which terms, would patients participate in a PA-RCT? And in your regard/experience? When would you participate yourself?
	• Practicality
	  ○ In your view, do (pharmaceutical) sponsors have the resources (and ability) to manage PA-RCTs? (regarding the available resources, time, training, and materials)
	  ○ In your opinion, is it ethical to conduct PA-RCTs in the context of products granted CMA/authorized based on single arm trials? Under what conditions?
	• Integration into existing systems
	  ○ Which existing systems (e.g., interactions between stakeholders, health-care practice, education, regulatory, reimbursement, etc.) support or hinder conduct of PA-RCTs? And how, what aspects play a role? Why?
	  ○ To what extent do PA-RCTs fit or compete with other (ongoing) studies? (To what extent do PA-RCTs fit the standard of care?)
	  And is the integration dependent on line of treatment for which the medicine is evaluated?
	• Adaptability
	  ○ When can a PA-RCT be adjusted (e.g., for country-specific needs or changes over time), while still achieving study objectives? And how does the degree of adaptability affect the feasibility of a PA-RCT?
	• Implementation
	  ○ When, under what conditions, are you, as investigator, willing to participate in PA-RCTs?
	• Effectiveness
	  ○ In your view, do PA-RCTs sufficiently confirm the benefit-risk of anticancer medicines as assessed at time of CMA approval? On which conditions is this dependent?
	• Generalizability

	○ When do PA-RCTs provide possibilities to (better) improve the generalizability of the study results as compared to pre-authorization RCTs results? (or pre-authorization SATs?)

Medical ethicists	
Topic	**Question**
Grand tour question	What can you tell me about your experience with products granted CMA?
Feasibility aspects	What would you say is the importance of (adequately) assessing the feasibility of RCTs requested post-authorization? What aspects should be taken into consideration when determining the feasibility of a PA-RCT? (in the context of NSCLC vs. anticancer products in general) • When do you (not) need post-authorization RCTs? • When would you approve the conduct of a PA-RCT (in terms of feasibility)? • When would you consider a post-authorization RCT (in)feasible?
Probes	Topics for probes when topic is mentioned by respondents: • Recruitment capability ○ Based on your experience, is it possible to recruit participants appropriate for typical post-authorization RCTs for products granted CMA (hereafter, PA-RCTs)? Why (not)? ▪ In your view, what are the most important obstacles for recruitment of participants in PA-RCTs? ? And what are obstacles or reasons not to participate in a PA-RCT? • Data collection procedures ○ Do you find data collection procedures typically used in PA-RCTs appropriate? Do you think of them as a burden? Why (not)? • Design procedures ○ What design features (e.g., endpoints, comparator, patient group) of an RCT affect its feasibility when seen in the context of products granted CMA? (And how do these features affect the feasibility to conduct the RCT post-authorization?) • Social validity ○ Under which conditions, or on which terms, would patients participate in a PA-RCT? And in your regard/experience? When would you participate yourself? • Practicality ○ In your view, do (pharmaceutical) sponsors have the resources (and ability) to manage PA-RCTs? (regarding the available resources, time, training, and materials) ○ In your opinion, is it ethical to conduct PA-RCTs in the context of products granted CMA/authorized based on single arm trials? Under what conditions? • Integration into existing systems ○ Which existing systems (e.g., interactions between stakeholders, health-care practice, education, regulatory, reimbursement, etc.) support or hinder conduct of PA-RCTs? And how, what aspects play a role? Why?

	○ To what extent do PA-RCTs fit or compete with other (ongoing) studies? (To what extent do PA-RCTs fit the standard of care?) And is the integration dependent on line of treatment for which the medicine is evaluated? • Adaptability ○ When can a PA-RCT be adjusted (e.g., for country-specific needs or changes over time), while still achieving study objectives? And how does the degree of adaptability affect the feasibility of a PA-RCT? • Implementation ○ When are you, under what conditions, as medical ethicists, willing or inclined to approve PA-RCTs? • Effectiveness ○ In your view, do PA-RCTs sufficiently confirm the benefit-risk of anticancer medicines as assessed at time of CMA approval? On which conditions is this dependent? • Generalizability ○ When do PA-RCTs provide possibilities to (better) improve the generalizability of the study results as compared to pre-authorization RCTs results? (or pre-authorization SATs?)

Pharmaceutical company	
Topic	**Question**
Grand tour question	What can you tell me about your experience with products granted CMA?
Feasibility aspects	What would you say is the importance of (adequately) assessing the feasibility of RCTs requested post-authorization? What aspects should be taken into consideration when determining the feasibility of a PA-RCT? (in the context of NSCLC vs. anticancer products in general) • When do you (not) need post-authorization RCTs? • When would you agree to execute a post-authorization RCT? (related to feasibility) • When would you consider a post-authorization RCT (in)feasible?
Probes	Topics for probes when topic is mentioned by respondents: • Recruitment capability ○ Based on your experience, is it possible to recruit participants appropriate for typical post-authorization RCTs for products granted CMA (hereafter, PA-RCTs)? Why (not)? ▪ In your view, what are the most important obstacles for recruitment of participants in PA-RCTs? ? And what are obstacles or reasons not to participate in a PA-RCT? • Data collection procedures ○ Do you find data collection procedures typically used in PA-RCTs appropriate? Do you think of them as a burden? Why (not)?Have you applied for scientific advice on PA-RCTs? What topics were frequently discussed? Were these related to the feasibility to conduct the PA-RCT? • Design procedures

	○ What design features (e.g., endpoints, comparator, patient group) of an RCT affect its feasibility when seen in the context of products granted CMA? ○ (And how do these features affect the feasibility to conduct the RCT post-authorization?) • Social validity ○ Under which conditions, or on which terms, would patients participate in a PA-RCT? And in your regard/experience? When would you participate yourself? • Practicality ○ In your view, do you, as (pharmaceutical) sponsors, have the resources (and ability) to manage PA-RCTs? (regarding the available resources, time, training, and materials) ○ In your opinion, is it ethical to conduct PA-RCTs in the context of products granted CMA/authorized based on single arm trials? Under what conditions? • Integration into existing systems ○ Which existing systems (e.g., interactions between stakeholders, health-care practice, education, regulatory, reimbursement, etc.) support or hinder conduct of PA-RCTs? And how, what aspects play a role? Why? ○ To what extent do PA-RCTs fit or compete with other (ongoing) studies? (To what extent do PA-RCTs fit the standard of care?) And is the integration dependent on line of treatment for which the medicine is evaluated? • Adaptability ○ When can a PA-RCT be adjusted (e.g., for country-specific needs or changes over time), while still achieving study objectives? And how does the degree of adaptability affect the feasibility of a PA-RCT • Implementation ○ When, under what conditions, are you, as applicant, willing to execute PA-RCTs? • Effectiveness ○ In your view, do PA-RCTs sufficiently confirm the benefit-risk of anticancer medicines as assessed at time of CMA approval? On which conditions is this dependent? • Generalizability ○ When do PA-RCTs provide possibilities to (better) improve the generalizability of the study results as compared to pre-authorization RCTs results? (or pre-authorization SATs?)

Supplementary Material S3 – Characteristics of interview respondents

	Regulators	HTA	Clinical guideline committee	Total
Number of interviewees (n)	2	2	5	10
Experience in drug development (median years)	14	12.5	31.5	15
Experience with (n for 'yes')				
Cancer in general	0	2	1	3
Specific cancer	1	0	1	2
Experience with clinical research (median years)				
Designing	1	1	16.5	1
Evaluating	12	12.5	31.5	15
Understanding of regulatory system (self-rated 1-5 (median))	1	4.5	4	4

	Patients	Physicians	Medical ethicists	Pharmaceutical company	Total
Number of interviewees (n)	2	2	2	2	8
Interviewees (% of total)	25.0	25.0	25.0	25.0	100.0
Experience in role (median years)	9.5	12.5	15	5.25	7.5
Experience with (n for 'yes')					
Cancer in general	1	1	1	2	5
Specific cancer	0	1	1	0	3
Experience with clinical research (median years)					
Participating	0.5	12.5	0	3.75	0.5
Designing	3	7.5	0	2.75	2
Understanding of regulatory system (self-rated 1-5 (median))	4.5	3	2.5	4	4

Supplementary Material S4– Focus group script

I. Practicalities

1. Recruitment

- Aim for 6 respondents, 10 respondents maximum
- 4 stakeholder focus groups: physicians, patients, medical ethicists, pharmaceutical industry representatives
- Schedule focus groups in time slots of 2 hours [October 2022]

2. Preparations

- Provide the information (i.e., Outlook invite, focus group topics, and pre-focus group questionnaire) to the respondents one week prior to the focus group via e-mail. The pre-focus group questionnaire includes an informed consent form, which can be signed online.
    - **Online focus group:**
- Book a meeting room at the Dutch Medicines Evaluation Board with sufficient space for the research team. Ensure well-working audio-system.
- Provide the online focus group via Webex®, ensure video- and audio-recording of meeting via Webex®.
- Ensure audio recording via telephone and/or voice-recorder on laptop(s).
    - **In-person (hybrid) focus group:**
- Book a meeting room at an accessible location in Utrecht.
- Arrange coffee/tea, etc.
- Provide instructions for respondents to arrive at location and room
- Provide phone number(s) to respondents
- Prepare the online meeting via Webex® for online attending respondents
- Arrange camera for video- and audio-recording of session
-

2. Day of the focus group

- Set up introductory presentation
- Provide writing material
- Check if informed consent questionnaire is filled in by each respondent.
- Open Webex® meeting 5-10 minutes before the starting time.
- Set up audio-recorder on laptop(s)
    - **In-person (hybrid) focus group**
- Set up audio- and video-recorders
-

3. Research team

- Moderator: opens the meeting and moderates the discussion, is overall responsible for the focus group. Provides a high-level summary at the end of the focus group.
- Presenter: provides background information and introduces the research (goals)
- Note taker(s):
    - take(s) notes during the meeting (particularly of non-verbal communication, quotes, key points, follow-up questions that could be asked; alert for novel insights);
    - is/are provided the opportunity to ask additional questions if time allows;
    - is/are responsible for technical assistance with online participants/focus groups, and recording the meeting;

II. Focus group agenda

Text in *italic* is to be said to the respondents, **bold** is timing of actions and slides presented, normal black text is guidance and may be communicated to participants in own words if applicable.

1. **00:00 Slide 1.** Welcome the participants while they arrive

- Provide coffee and tea
- Stimulate small talk before the focus group has started, make people feel comfortable. For online focus groups, interact with the participants while still waiting for others to join.

2. **00:05 Slide 2.** Provide a general introduction to the participants and ask the respondents to sign the informed consent form or to sign the informed consent form online for the online focus groups, if they have not done so already. Further, ask the participants to write their names on a name card/online description. Inform the respondents that the meeting is being recorded for transcription and analysis purposes.

- Welcome to this focus group, my name is [name] and I will be the moderator of this focus group today. I am happy to see that you all made it today and are willing to make time for this focus group. Before we start with introducing ourselves, I would like to start by explaining what we would like to do during this focus group.
    - *My role as a moderator is to guide the discussion. That is, introduce the topics we would like to discuss and to give everybody the opportunity to share their thoughts. Therefore, it is important that one person speaks at a time, and that we create a safe environment where everybody feels free to share their opinion.*
    - *There are no right or wrong answers, but people may differ in their opinion.*
    - *Because it is an informal discussion, we may address each other by the first name that is on the name card in front of us/or which you can see online in the small screens.*
    - *There are also other people from the research team present,* [names]*, who will take notes during the focus group session and will provide technical assistance.*
    - *Because we record the focus group, we would like to ask you to put your phone on silence or to mute yourselves online, if you are unexpectedly disturbed.*
    - *Today, we will discuss different aspects that may impact the feasibility of randomized clinical trials to study new anticancer medicines, after the medicine has been granted a so-called conditional marketing authorization. These concepts will be introduced by* [name] *after we have introduced ourselves.*
    - *We want to have this focus group discussion with you as* [stakeholder]*, because we feel that your opinions, preferences, and experiences are important to increase the feasibility of these studies, thereby potentially improving the clinical development of new medicines.*
    - *This project is organized by Utrecht University and the Dutch Medicines Evaluation Board.*
    - *Based on the interviews we held before, along with this focus group and other focus groups that we will conduct, we will write a report to inform people involved in the request and conduct of such post-authorization trials.*
    - *Please note that anything that will be said during this focus group will be dealt with as confidential information, and any quotes or results will be presented in an aggregated or pseudonymized manner. That is, publicly available reports will never contain any information via which you can be identified. We furthermore aim to share the report with you before making it publicly available.*

- *The focus group will take approximately 2 hours, and we will have a break of 5-10 minutes.*
- *Do you have any questions or concerns about the project or focus group of today?* Give time to raise questions.

2. **00:10 Slide 2.**

- Consent. *We have already started the recording of this session, if that is okay for everybody. Could you each please indicate if you agree with the audio- and video-recording of this meeting? This was also stated in the informed consent form in the questionnaire you have filled in (or not yet, in which case, please do so after this session. We will send a reminder for it..*
- Ask everybody to introduce themselves (including present members of the research team) and provide verbal consent. *And before we start, o get to know each other, could you shortly state your name and mention in which role you are here today? And could you please state if you agree with the recording of this meeting?* Give each respondent the possibility to introduce themselves and confirm verbal consent.
- Thank everyone for their consent and continue to the introduction.

3. **00:15.** Introduction of background and context.

- **Slide 3**. Development of anticancer medicines. The development of novel anticancer medicines typically goes through different phases, in which, after early pre- and clinical studies, studies are conducting involving patients.
- **Slide 4**. Development of anticancer medicines. For diseases such as cancer, there remains a high unmet medical need for therapies to treat these diseases. Market access of these novel medicines or therapies is regulated by the European Medicines Agency (EMA). As you can see in the figure, there is a trade-off between early access to new medicines on one hand, and increasing the knowledge about a medicine, which takes time. To enable earlier market access for novel therapies, the EMA has a procedure called 'conditional marketing authorization' (CMA), which allows market access based on incomprehensive evidence.
- **Slide 5**. Single arm trial. For instance, single arm trials, or SATs, are considered an example. In such a nonrandomized clinical trial, patients with the disease all receive the novel therapy. The response to the treatment is followed over time as an outcome measure. This is different from a randomized controlled trial, to which we'll address soon.
- **Slide 6**. Development of anticancer medicines. Until now, there have a number of CMAs granted on the basis of SAT-data for novel therapies by the EMA, including oncology.
- **Slide 7**. Conditional marketing authorization (CMA). The criteria for a conditional marketing authorization are these: the benefit-risk of the medicine is positive, the medicine fulfills an unmet medical need. And what we are focusing on in this research are the last two criteria: comprehensive evidence will become available in a timely manner while the medicine is marketed. And the benefits of the timely market access actually outweigh the risks of incomprehensive data.
- **Slide 8**. Obligatory conditions to CMA. So, for the criterium that comprehensive evidence must be provided, post-authorization studies are imposed and are to be conducted while the medicine is on the market. These are typically aimed to confirm that the medicine's benefit-risk balance is positive. Often, the requested studies are randomized controlled trials.
- **Slide 9**. Randomized controlled trial (RCT). This is, unlike the SAT, a clinical trial in which patients (or actually, participants) are randomly allocated to either the treatment arm or the control arm. As a control arm, this may be for instance placebo (without active substances)

or standard of care therapy at that time. RCTs are considered the gold standard and one of the most powerful trials in clinical research.

- **Slide 10**. Post-authorization RCTs. However, when requested as a condition to the conditional marketing authorization, we have some questions how and if indeed these conditions can be met and if comprehensive evidence can be provided in a post-authorization setting. It brings up the question how feasible these post-authorization RCTs are.
- **Slide 11**. Case example: Lumykras (sotorasib). As an example of a medicine, we have Lumykras (sotorasib), which is indicated for the treatment of advanced non-small cell lung cancer (NSCLC), with a specific mutation, as a second-line therapy. It was granted a CMA on January 6 this year, based on the outcomes of a single arm trial whiich showed a response of 37%. The key uncertainties the EMA requested to be assessed where:
  Consequently, the obligatory conditions where aimed to confirm the efficacy and safety of Lumykras, for which a post-authorization RCT in the same indication was requested, comparing sotorasib versus chemotherapy. The study is ongoing, and it is due next March.
- Ask if this is all understandable to all participants.
- *If any questions arise during this focus group or some terms are unclear, please let us know.*
- **Slide 12.** Goal project & focus group. So, therefore, the goal of this project and of the focus group of today is to identify which conditions enable or disable the conduct of post-authorization RCT for conditionally approved anticancer medicines, from a multi-stakeholder perspective. So, today we have one with you [stakeholder], and we will also have similar focus group session with [other stakeholders]. Today's discussion will be structured by three main topics: Trial design, Trial conduct, and Motivations to participate in or conduct a PA-RCT. We will introduce each topic with a short definition before we start the discussion.
- *Are there any questions at this point?*

4. **00:25 Slide 13.** Introduce the topic of 'Trial design'

Definition: "*The design features of a post-authorization randomized controlled trial (PA-RCT) may influence its feasibility. Central to the study design is the study aim – that is, the question(s) or uncertainty/-ies one wishes to answer or resolve through a PA-RCT. Further, the study design relates to the choice of intervention and outcome measures/endpoints, (including how these are measured); the included patient population; the extent to which the design can be adapted to changes (e.g., in a changing treatment landscape); the choice of comparator; and whether and how findings can ultimately be generalized (i.e., applied to the population that is intended to be treated). Complementary to these aspects is the possibility of alternatives for PA-RCTs (i.e., other study designs).*"

Question: *Is this 'feasibility theme' recognizable for you and what is important for you regarding this theme?*

Probe: <u>Scenarios</u>. How does your opinion differ for the different scenarios?

- With CMA: *Given the situation that a medicine is conditionally on the market, but not reimbursed how would your opinion differ?*
- Patient access: *Given the situation that a medicine is conditionally on the market, and reimbursed or accessible through access protocols, how would your opinion differ?*
- Enrolment*: If the enrolment of the PA-RCT is ongoing, or nearly completed before the conditional marketing decision, how would your opinion differ?*
- Study not initiated: *If the enrolment of the PA-RCT is not initiated before CMA decision, how would your opinion differ?*

- Other scenarios: *Can you think of scenarios that could affect the importance or relevance of these feasibility aspects?*

Probe: Stakeholders. *How do you view your role towards other stakeholders regarding* [mentioned feasibility aspects]*?*

Examples: ask about specific aspects in definition (to incite discussion)

5. **00:50 Slide 14.** Introduce the topic of 'Trial conduct'

Definition: "*Trial conduct refers to the practical feasibility – or ability – to conduct a PA-RCT. Related aspects that could facilitate or hinder the conduct of a PA-RCT entail the location and time of trial initiation, resource availability – including personnel and procedural capacity -, experience and expertise with conducting clinical studies, potential competing studies, and (burden of) data collection procedures.*"

Question: *Is this 'feasibility theme' recognizable for you and what is important for you regarding this theme?*

Probe: Scenarios. How does your opinion differ for the different scenarios?

- With CMA: *Given the situation that a medicine is conditionally on the market, but not reimbursed how would your opinion differ?*
- Patient access: *Given the situation that a medicine is conditionally on the market, and reimbursed or accessible through access protocols, how would your opinion differ?*
- Enrolment*: If the enrolment of the PA-RCT is ongoing, or nearly completed before the conditional marketing decision, how would your opinion differ?*
- Study not initiated: *If the enrolment of the PA-RCT is not initiated before CMA decision, how would your opinion differ?*
- Other scenarios: *Can you think of scenarios that could affect the importance or relevance of these feasibility aspects?*

Probe: Stakeholders. *How do you view your role in relation to other stakeholders regarding* [mentioned feasibility aspect]*?*

Examples: ask about specific dimensions: treatment landscape, resources (means, experience, expertise, competition with other (ongoing) studies).

6. **01:15 Slide 15.** Introduce 5-10 min break. Mention that the last theme will be discussed after the break. Tea/coffee.

7. **01:25 Slide 16.** Introduce the topic of 'Motivations to participate in or conduct a PA-RCT'

Definition: "*Motivations and willingness (not) to participate or conduct a PA-RCT may differ per stakeholder group. Central to this theme is the relevance and acceptability of the goals of the PA-RCT, and the derived (perceived) benefits for each stakeholder.*"

Question: *Is this 'feasibility theme' recognizable for you and what is important for you regarding this theme?*

Probe: *Why would you and when would you not want to participate in a PA-RCT? What are obstacles or reasons not to participate? And how could they be overcome?*

Probe: Aspects. *The willingness to conduct or participate in a PA-RCT can be related to* clinical equipoise (i.e., similar uncertainty in both treatment arms), product access, altruism, enthusiasm for the new medicine, need to keep the medicine on the market or to broaden the indication. *What do you think about* [aspect]*?*

Probe: Scenarios. How does your opinion differ for the different scenarios?

- With CMA: *Given the situation that a medicine is conditionally on the market, but not reimbursed how would your opinion differ?*
- Patient access: *Given the situation that a medicine is conditionally on the market, and reimbursed or accessible through access protocols, how would your opinion differ?*
- Enrolment*: If the enrolment of the PA-RCT is ongoing, or nearly completed before the conditional marketing decision, how would your opinion differ?*
- Study not initiated: *If the enrolment of the PA-RCT is not initiated before CMA decision, how would your opinion differ?*
- Other scenarios: *Can you think of scenarios that could affect the importance or relevance of these feasibility aspects?*

Probe: Stakeholders. *How do you view your role towards other stakeholders regarding* [mentioned feasibility aspects]*?*

8. **01:50 Slide 17.** Closing remarks

- Summarize lessons learnt and topics discussed – by moderator
- Ask if there are any questions or additional remarks that are important to consider regarding this project at this moment.

9. **Slide 18**. Thank you. Thank all participants for their kind participation and contribution to today's discussion. Mention that they will receive the outcomes of the research project at a later point and that they are free to contact the research team later as well. Wish them a good day ahead (in-person focus group: mention tea and coffee).

- END of the focus group -

10. Collect the following:

- Stop the video- and audio-recordings, check if all the recordings are stored well (with Webex® and other recorders)

Supplementary Material S5 - Characteristics of pivotal trials and trials as part of sobs for anticancer medicines for the treatment of NSCLC that were granted CMA based on SAT-data (2006-2021)

Year	2012	2015	2015	2016	2019	2020	2021	2021	2021
Product	Xalkori	Zykadia	Tagrisso	Alecensa	Lorviqua	Retsevmo	Gavreto	Rybrevant	Lumykras
Active substance	Crizotinib	Ceritinib	Osimertinib	Alectinib	Lorlatinib	Selpercatinib	Pralsetinib	Amivantamab	Sotorasib
Paediatric indication	No	No	No	No	No	No	No	No	No
Indication (subpopulation)	ALK+ Advanced NSCLC	ALK+ Advanced NSCLC	EGFR T790M mutated Locally advanced or metastatic NSCLC	ALK+ Advanced NSCLC	ALK+ Advanced NSCLC	RET-fusion + advanced NSCLC	RET-fusion + advanced NSCLC	EGFR exon 20 mutated advanced NSCLC	KRAS G12C mutated Advanced NSCLC
Authorized line of therapy	2L(+?)	3L	1L+	3L	2L+	2L+	Across all lines	2L+	2L+
Prior therapy	Not specified	Previously treated with crizotinib	N/A	Previously treated with crizotinib	Progressed after alectinib/ceritinib as first ALK TKI or crizotinib and at least one other ALK TKI	Following prior treatment with immunotherapy and/or platinum-based chemotherapy	Not previously treated with RET inhibitor	After failure of platinum-based therapy	Who have progressed after at least one prior line of systemic therapy
CHMP									
Opinion date	19-7-2012	26-2-2015	17-12-2015	15-12-2016	28-2-2019	10-12-2020	16-9-2021	14-10-2021	11-11-2021
Consensus	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
EC Decision	23-10-2012	6-5-2015	2-2-2016	16-2-2017	6-5-2019	11-2-2021	18-11-2021	9-12-2021	6-1-2021
Pivotal trial									
Phase	1/2	1	2, 2	1/2	1/2	1/2	Phase I/II	Phase I	Phase II
Name	A8081001	CLDK378X2101	Pooled analysis: AURA extension (D5160C00001) + AURA-2 (D5160C00002)	NP28761	B7461001	LOXO-RET-17001 (LIBRETTO-001)	BLU-667-1101 (ARROW, NCT03037385, eudract 2016-004390-41)	61186372EDI1001 (EDI1001, CHRYSALIS, NCT02609776)	20170543 (NCT03600883, codebreak 100)
Design	SAT	SAT	SAT	SAT	SAT	SAT	SAT	SAT	SAT
Comparator	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled
Patients (n)	121	163	398	67	139	218	233	114	124
Pivotal trial 2									
Phase	-	-	-	1/2	-	-	-	-	-
Name	-	-	-	NP28673	-	-	-	-	-
Patients (n)				122					
Efficacy									
Efficacy patients (n)	121	163	398	189	139	94	218	233	275
Phase III data (at least interim analysis?)	Top-line summary (supportive) (1007)	No	No	High-level interim analysis results from JO28928 (J-ALEX, supportive)	No	No	No, but acceleret study has started (BLU-667-2303)	No, but PAPILLON (phase 3, 61186372NSC3001) has started	Supportive safety data from 20190009 (Phase 3), study 20190147 (Phase 1), and study 20190135 (combi-nation with tametinib,

									RMC-4630, afatinib, atezolizumab and panitumumab/FOLFIRI)
Primary endpoints	ORR	ORR and dor	ORR (for both studies)	ORR (for both studies)	ORR	ORR	ORR	ORR	ORR
Effect size	60%	56.4% for 8.25 months	66.1%	52.2% and 50.8%	42.9% (cohort EXP-3B) and 38.7% (pooled cohort EXP-4:EXP-5)	56.9%	64.4%	36.8%	37.1%
Interim analysis primary endpoint	No	No	No	No	No	No	No?	38.3%	No
N patients (safety)	588	525	411	253	295	746	528	489	200
Different than efficacy population	No, pivotal and supportive NSCLC studies	No, pivotal and supportive ALK+ NSCLC studies	Same, only pivotal SAT population in NSCLC	Same, only pivotal SAT population in NSCLC	No, only pivotal trial patients	Yes, all patients in pivotal trial	Yes, all patients in pivotal trial + later CCOD	Yes, all patients in pivotal trial	Yes, all patients in pivotal trial
Sobs									
Total nr	**3**	**2**	**1**	**1**	**2**	**2**	2	1	1
SOB aim									
Efficacy	0	2	0	0	1	0	0	0	0
Safety	1	0	0	0	0	0	0	0	0
Efficacy & Safety	2	0	1	1	1	2	2	1	1
Non-efficacy or safety	0	0	0	0	0	0	0	0	0
Study design									
Observational	0	0	0	0	0	0	0	0	0
Interventional	2	2	1	1	2	2	2	1	1
Population	Same	Same	Same	Earlier (1L, comparison against crizotinib)	Earlier / same	Earlier / same	Same & earlier		Same
Status at time of CMA	Ongoing (all 3)	Ongoing (both)?	Ongoing/started	Ongoing	Ongoing / new?	Ongoing	Ongoing / started	Ongoing/started	Ongoing/started
No studies	1 (safety review of all studies)	0	0	0	0	0	0	0	0
Efficacy (1)									
Design	Study 1007 + pivotal and supportive study 1001/1005)	Phase III (A2303)			Prospective SAT				
Comparator		Chemotherapy			Uncontrolled				
Population					Patients progressed after alectinib/ceritinib as first ALK TKI				
Efficacy (2)									
Study design		SAT (A22021)							
Efficacy & safety (1)									
Phase			Phase III (AURA3)	Phase III (ALEX)	Phase III (CROWN 1006)	(LIBRETTO-001)	Phase I/II (BLU-667-1101)	Phase III (61186372NSC3001)	Phase III (codebreak 200)

Comparator	Platinum-based doublet chemotherapy	Crizotinib	Crizotinib			(amivantamab in combination with carboplatin-pemetrexed therapy) vs. Carboplatin-pemetrexed therapy	Docetaxel
Population		Treatment naive ALK + NSCLC	(for the first-line treatment of advanced ALK+ NSCLC)		~116 treatment-naïve NSCLC + more follow-up of the 136 NSCLC previously treated with platinum therapy	Advanced/metastatic NSCLC with activating EGFR exon 20 insertion mutations in first-line setting	Previously treated KRAS G12C-mutated NSCLC
Efficacy & safety (2)							
Phase				Phase III (LIBRETTO-431)	Phase III (BLU-667-2303)		
Comparator				Platinum-based and permetrexed therapy with or without pembrolizumab	Standard-of-care (for first line treatment?)		
Population				Locally advanced/ metastatic, RET-fusion+ non-squamous NSCLC	(First-line treatment of RET-fusion+ metastatic NSCLC)		