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Factors affecting the feasibility of post-authorisation RCTs for conditionally authorised anticancer medicines: a multistakeholder perspective from a qualitative focus group study

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ABSTRACT

Objective The collection of comprehensive data from post-authorisation trials for conditionally authorised anticancer medicines is frequently delayed. This raises questions about the feasibility of post-authorisation randomised controlled trials (RCTs) that aim to address remaining uncertainties. Therefore, this study explored factors that facilitate or impede the feasibility of post-authorisation RCTs from the perspective of stakeholders directly involved in the design, medical-ethical approval, and conduct of these RCTs.

Design We conducted four qualitative focus groups (FGs).

Setting FG discussions focused on the oncology setting in European context.

Participants Twenty-eight European patients, physicians, medical ethicists and pharmaceutical industry representatives participated in the FGs.

Intervention Respondents were informed about the topic and the purpose of the FGs before and at the start of FG discussions. An FG script was used to guide the discussion, which was informed by 14 semi-structured interviews with various stakeholders.

Results We identified factors with the potential to impact feasibility related to trial design, trial conduct, factors external to a trial and post-authorisation interaction with regulators. Factors that may be particularly relevant for the post-authorisation setting include the choice of relevant endpoints and the inclusion of a fair comparator (trial design), strategies to increase patients' and physicians' willingness to participate (trial conduct), and external factors relating to a medicine's commercial availability, the presence of competing medicines and trials and the perceptions about clinical equipoise. Post-authorisation interaction with regulators about how to obtain comprehensive data was deemed necessary in cases where a post-authorisation RCT seems infeasible.

Conclusions Based on the identified factors, our findings suggest that patient recruitment and retention could be assessed more in-depth during regulatory feasibility assessments at the time of granting conditional marketing authorisation and that sponsors and regulators should better inform patients and physicians about the remaining uncertainties for conditionally authorised medicines and the necessity for post-authorisation RCTs. By enhancing the evaluation of trial feasibility, timely completion of post-authorisation RCTs may be facilitated to resolve the remaining uncertainties within a reasonable timeframe.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Focus group discussions allowed for the identification of complementary perspectives from patients, physicians, medical ethicists and pharmaceutical industry representatives.
⇒ The current study focusses on the oncology setting in European context, but our results are expected to be relevant for other geographical regions and therapeutic areas where expedited approval pathways are used.
⇒ Distinguishing feasibility factors specific to post-authorisation randomised controlled trials (RCTs) for medicines with a conditional marketing authorisation and for post-authorisation RCTs in general is challenging.
⇒ This study took an exploratory approach: a quantification of the most important impediments to post-authorisation RCTs and defining strategies to optimise feasibility assessments require future research, which should include the perspectives of regulators and health technology assessors.

INTRODUCTION

For medicines that are authorised on the basis of non-comprehensive data through an expedited pathway—such as the European Medicines Agency's (EMA) conditional marketing authorisation (CMA) and the US Food and Drug Administration's (FDA) accelerated approval[1–3] (box 1), typically more uncertainties are accepted compared with a standard marketing authorisation. In the European Union, CMAs have increasingly been granted

Box 1 Conditional marketing authorisation and specific obligations

Since its implementation in 2006, the conditional marketing authorisation (CMA) pathway has been used in the European Union with the intention of accelerating patient access to novel medicines that address an unmet medical need.[9 11] As stipulated in European Commission Regulation No 507/2006, the CMA pathway enables authorisation based on non-comprehensive evidence.[1]

Medicines eligible 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'.[2]

The following additional requirements should be met[1 2]:

(i) The benefit-risk balance of the medicine is positive.

(ii) It is likely that the applicant will be able to provide comprehensive data in a timely manner.

(iii) An unmet medical need will be fulfilled.

(iv) The benefits to public health of the immediate availability of the medicine outweigh the risks inherent in the fact that additional data are still required.

The European Commission can grant the CMA upon a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).[1]

Specific obligations are imposed as legally binding conditions for marketing authorisation. Typically, the obligations concern new or ongoing randomised controlled trials (although other designs could be considered).[27] These specific obligations and their submission due dates are stipulated in Annex II of a medicine's Summary of Product Characteristics.[1]

A CMA has a 1-year validity, which is required to be annually renewed.[1] To that end, the marketing authorisation holder must submit a report on the fulfilment of the specific obligations.[2] Compliance with the specific obligations is then reviewed and assessed by the CHMP. A continued positive benefit-risk balance is critical for maintaining the CMA. Upon fulfilling the specific obligations, the CMA is converted to a standard marketing authorisation with an initial 5-year validity.[1 2]

based on single-arm trial (SAT) data as pivotal evidence, particularly for targeted therapies in oncology settings.[4–10] Consequently, specific obligations imposed by the EMA to generate additional, comprehensive, evidence typically include randomised controlled trials (RCTs).[2 11]

However, the feasibility of conducting RCTs in the post-authorisation setting is considered challenging, complicating evidence generation for regulatory, reimbursement and clinical decision making purposes.[12–15] For example, recruitment of trial participants—particularly those who are covered by the authorised indication—may be difficult when the medicine in question is already available to patients.[2 16–18] This is recognised in the European public assessment report (EPAR) of olaratumab (CMA for soft tissue sarcoma, which was later retracted based on a negative post-authorisation RCT) and detailed that 'once a country has approved the medicine, no further patients would likely be included in the study from that region'.[19] Additionally, the EPAR for pixantrone (for non-Hodgkin B-cell lymphoma), which was granted CMA based on data from a non-Western European population, detailed that immediate availability on the European market 'will hamper the clarification of relevant scientific questions such as the benefit in a (Western) European population'.[20]

Timely provision of comprehensive data is one of the prerequisites for granting CMA and extension of the due date for providing the additional evidence is only allowed when feasibility issues were not foreseen at the time of granting CMA.[2] However, analyses have shown that the submission of post-authorisation data is frequently delayed.[21–26] For example, for medicines granted CMA between 2010 and 2016, the majority of changes to specific obligations (34 out of 39) were due date extensions.[24] Therefore, it is essential that the feasibility of post-authorisation RCTs is thoroughly assessed by the EMA's Committee for Medicinal Products for Human Use (CHMP).[2]

Regulatory guidelines provide limited guidance as to what feasibility assessments entail, and details of feasibility assessments as performed by the CHMP are rarely described in the EPARs.[2 16 27] Consequently, it is not sufficiently clear which factors are relevant for feasibility assessments of post-authorisation RCTs. Therefore, this exploratory study aims to identify factors that facilitate or impede the feasibility of post-authorisation RCTs for anticancer medicines that are conditionally authorised based on non-comprehensive data from SATs from the perspective of those stakeholders involved in the design, medical-ethical approval and conduct of these RCTs.

METHODS

Study context and design

To identify factors that, from the perspective of stakeholders, facilitate or impede the feasibility of post-authorisation RCTs for anticancer medicines granted CMA based on SAT data, we performed an exploratory qualitative focus group (FG) study. In light of the CMA requirement to provide comprehensive data in a timely manner,[2] feasibility is defined as the expectation to conduct a post-authorisation RCT within a reasonable timeframe.[2 28] We focused on the oncology setting as CMAs on the basis of non-randomised SAT data are most frequently granted to anticancer medicines.[8 9]

For this study, FG discussions were conducted with each of four stakeholder groups directly involved in the design, medical-ethical approval and conduct of post-authorisation RCTs: (i) patient representatives, (ii) medical ethicists, (iii) physicians (ie, (hemato-) oncologists) and (iv) pharmaceutical industry representatives. These FGs allow for interaction between respondents, fostering the exchange of experiences, ideas and solutions.[29]

Focus groups

Potential respondents were identified through professional organisations, the research team's network and respondents' recommendations. Respondents had to be familiar with anticancer medicinal product development

or medical oncology and proficient in the Dutch and/or English language. Eligibility was not based on respondents' seniority or experience with (post-authorisation) clinical research. Respondents were asked to share their own perspectives based on professional experience rather than representing views of their respective organisations.

Data collection

From August to October 2022, eligible respondents were invited to participate in FG discussions in October 2022. FGs lasted for approximately 2 hours and were conducted separately with each stakeholder group. After a round of introductions and introducing the purpose of the FG, the respondents were asked to discuss various topics, which were introduced separately by a research team member. The FG script was informed by 14 semi-structured, individual, 1 hour pilot interviews with medical ethicists, physicians and representatives from regulatory authorities, health technology assessment (HTA) organisations, clinical guideline committees, patient advocacy groups and the pharmaceutical industry (online supplemental 1 and 2). The main topics included (i) trial design, (ii) trial conduct and (iii) motivations (online supplemental 3). Data on respondent characteristics were collected through an online questionnaire that was shared prior to the FG.

Data analysis

The FG discussions were transcribed verbatim and analysed through thematic analysis using NVivo 12 PRO (QSR International, version 14, Burlington, MA, USA).[30] Themes and individual factors were identified both deductively (informed by the topics from the interviews: trial design, trial conduct and motivations) and inductively in an iterative manner. Factors that impede or facilitate the conduct of post-authorisation RCTs were grouped under the themes and visualised in an Ishikawa diagram. The FG transcripts were coded independently by two researchers (CCvH and AJdJ), after which the coding structure was discussed iteratively within the research team. Due to differences in interests and areas of expertise, not all topics were discussed to the same extent across all FGs. Consequently, if no reference is made to a stakeholder group in the results, this should not be understood as a fundamental difference between stakeholders.

Patient and public involvement

Through patient organisations and public engagement offices, we were able to involve patient representatives in the conduct of this research. Patient organisations helped recruiting respondents for the FG with patient representatives and one patient representative who helped in the recruitment also critically reviewed the manuscript (see Acknowledgements). We plan to actively disseminate the study findings to patients and the public through social media and plain-language summaries and infographics on the websites of the authors' affiliated organisations. Herein, we plan to involve patient representatives. The study findings will furthermore be shared at research institutions, regulatory agencies and academic conferences.

RESULTS

Respondent characteristics and main themes

After reaching out to 199 individuals and organisations, 28 respondents agreed to participate, 45 respondents indicated that they were not interested in participating due to time constraints, perceived limited knowledge of the topic, or other reasons, and others did not respond. In total, 28 European respondents participated in one of the FGs: patient representatives (n=5), medical ethicists (n=6), physicians (n=6) and pharmaceutical industry representatives (n=11) (table 1).

Themes

We identified four main themes from the FG transcripts: trial design, trial conduct, factors external to a trial and post-authorisation interaction with regulators tables 2–5). Under these themes, we grouped the main facilitating and impeding feasibility factors as reported during the FGs as displayed in figure 1.

Trial design

Feasibility factors regarding trial design reported by the FG respondents relate to the indication of interest, endpoints, the amount of data to be collected, the use of blinding, the comparator and the enrolment status of a post-authorisation RCT (figure 1, table 2). First, part of the oncology indications concerns rare diseases or specific subpopulations for which it may be difficult to identify patients, as was reiterated in all FGs. This was especially considered true for indications of targeted therapies. Additionally, the lack of standardised manners for collecting biomarker data (eg, molecular diagnostics) was mentioned by physicians to impede patient identification.

Second, respondents mentioned that there is a trade-off between generating data relatively fast, using surrogate endpoints (eg, progression-free survival), and generating data on clinically relevant endpoints (eg, overall survival and quality of life). Respondents furthermore mentioned that the inclusion of clinically relevant endpoints in a post-authorisation RCT enhances the willingness of patients and investigators to participate in these trials (FG patients, physicians).

Third, collecting only essential data was deemed a particular facilitating factor in post-authorisation settings, specifically when an RCT aims to include different locally requested endpoints and comparator arms to cater to multiple regulatory bodies (FG industry). In terms of broad inclusion criteria and trial procedures that align with routine care, employing more pragmatic RCT elements was frequently mentioned as facilitating for post-authorisation data generation (FG patients, physicians, industry).

Fourth, the 'risk' of randomisation to the (perceived inferior) control arm instead of a 'fair' comparator was

Table 1 Characteristics of focus group respondents

	Patient representatives	Medical ethicists	Physicians	Industry representatives
No. respondents*	5	6	6	11
No. individuals and organisations invited (acceptance rate)	23 (22%)	118 (5%)	39 (15%)	19 (58%)
Experience in role – median years (range)	4 (3–5)	26 (8–40)	15 (5–19)	25 (8–35)
Role	Lived experience (n=1) Professional expertise (n=4)	Member of medical ethics and/or research ethics committee (n=6) Research position (medical) ethics (n=6)	Hemato-oncology (n=2) Lung cancer (n=2) Breast cancer (n=1) GI cancer (n=1)	Regulatory affairs (n=6) Medical oncology (n=2) Statistician (n=2) Policy affairs (n=1)
Cancer expertise†‡				
Cancer in general	2	5	2	6
Specific cancer	2	1	4	4
Level of understanding of regulatory system – median (range)§	4 (3–5)	4 (3–5)	3 (3–4)	4 (2–5)

*Of these, three respondents (ie, one physician and two patient representatives) did not fill out the voluntary online questionnaire.
†Respondents indicated whether they had experience with (conducting trials for) cancer, in general and/or for a specific cancer type.
‡One industry representative and one medical ethicist indicated no experience with cancer.
§Self-rated from 1 (limited understanding) to 5 (perfect understanding).
GI, gastrointestinal.

discussed in all FGs and was deemed to impede feasibility, especially when a trial is not blinded by design.

Fifth, early planning of an RCT may result in an ongoing trial at the time of granting CMA with patient recruitment started or even finished before a CMA is granted. This was deemed to enhance feasibility (FG physicians, industry). In general, respondents mentioned that involving various stakeholders in the design of a post-authorisation RCT is key for trials to be meaningful for more stakeholders (FG physicians, patients, industry).

Trial conduct

Feasibility factors regarding the conduct of a trial identified from all FG discussions relate to the willingness to participate in a post-authorisation RCT and incentives for pharmaceutical companies to conduct a post-authorisation RCT (figure 1, table 3).

First, specific to post-authorisation settings, investigators' willingness to participate was deemed crucial. Industry representatives indicated that it can be difficult to involve clinical investigators for post-authorisation RCTs because of low scientific interest as the medicine is already authorised. Physicians indicated that a clinically relevant research question and enabling patient access to the medicine in question are particularly important for their participation in post-authorisation trials. As further discussed with physicians, the administrative and data collection burden impedes their participation in these trials. Respondents mentioned that investigators' willingness is generally supported by a physician's professional responsibility (FG patients, ethicists), financial compensation and the possibility that participation will result in a publication (FG ethicists). Although not specific to post-authorisation RCTs, research capacity and related availability of sufficient resources and research infrastructure in the participating centres were considered pivotal to facilitate trial conduct (FG physicians).

Second, respondents indicated that patients' willingness to participate is affected by factors that are more apparent in a post-authorisation setting including the chance for randomisation to the control arm, possible cross-over to the intervention arm and available treatment alternatives (FG patients, ethicists, physicians). General factors that may affect patients' willingness include access to the medicine in question, altruism, a patient's relationship with the investigator, the involvement of patient representatives in the trial design, while weighing potential treatment benefits and possible side effects (FG patients, ethicists, physicians). Generally, the burden for patients to participate in a clinical trial was considered impeding, while pragmatic trial elements, such as data collection alongside routine clinical care, were considered facilitating (FG patients, ethicists, physicians). Patients' awareness and understanding of trial participation options, as well as other methods for informing patients about participation opportunities aside from communication through physicians, were considered important for participant recruitment (FG patients).

Table 2 Factors regarding trial design that facilitate or impede the feasibility of post-authorisation randomised controlled trials as identified from the focus groups

Facilitating factor	Illustrative quote	Impeding factor	Illustrative quote
Trial design			
Indication with a large patient population	*And if it* (the medicine) *is so promising, then I think you should demand, if it is a really large population, that there is a good randomised trial. But then you first need to know that you have a sufficiently large patient population*. (Physician)	**Difficulty identifying eligible patients** (eg, for rare indications) due to technical barriers (eg, biomarker tests are not available or suitable)	*I was thinking about lung cancer because that is a case of niche indications for very specific, rare subgroups. And potentially this will also be the case for other tumours, but that very much depends, I think, on how the tumour is driven; be it on DNA mutation level, or for example, epigenetic, then it becomes all a bit more blurry*. (Physician) *The biomarker development goes super-fast. You cannot actually keep up. So, I am in doubt whether one should invest in that path*. (…) *But yes, they will of course be very important for the further personalisation of healthcare*. (Physician)
Inclusion of **clinically relevant endpoints** may support patients' and investigators' willingness to participate*	*For them* [patients] *it's all about the time that they have, spending that in good quality and getting access to the novel treatments* (…). *So I would say quality of life measures, that would be really, really key. And, of course, overall survival as well*. (Patient representative)	**Difficulty enrolling and retaining participants** who are randomised to the control arm in unblinded trials	*So there is, for example, the CheckMate 37 trial where blinding was not feasible. So, 20% of patients randomised to the control immediately left the trial because they had many other trials with PD-L1 compounds they could get*. (Industry representative)
Low data collection burden with a focus on essential data and using pragmatic trial designs	*An RCT is about randomisation, but we can always define how much data we collect in an RCT. And I think this development towards pragmatic trials is something that I really see with excitement and it's something that we should also pursue*. (…) *It all boils down to the scientific question we are trying to answer*. (…) *Very often, I think, we could chop a lot from the RCTs and then we could move towards pragmatic trials and answer questions in a much more efficient way*. (Industry representative) *If that* [trial participation] *is more bothersome for patients than the normal treatment, I think you'll have the problem getting patients into the trial. 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 bone marrow things et cetera. Don't do it too often*. (Patient representative)		
Fair comparator	*I think it is important to randomise them against the best comparator, so not placebo-controlled, that setting is not useful anymore, but really put it next to the best comparator*. (Physician)		

Continued

Table 2 Continued

Facilitating factor	Illustrative quote	Impeding factor	Illustrative quote
Early planned trial for patient enrolment before CMA is granted, by anticipating a post-authorisation RCT	*And then the earlier you start* [the trial] *the better it this. And I would even argue that* (…) *when you get onto the market and you have fully recruited your trial, most of the patients have finished the treatment*. (Industry representative)		
Involvement of relevant stakeholders in designing the post-authorisation RCT	*Scientific advice, which may involve also HTA agencies, could be a helpful way to plan for the right evidence*. (Industry representative)		

*Some factors that were identified to facilitate feasibility may contradict each other. For example, collecting clinically relevant endpoints (eg, overall survival) may limit the possibilities for cross-over to the intervention arm.
HTA, health technology assessment; RCT, randomised controlled trial.

Third, divergent views existed regarding the incentives for pharmaceutical companies to conduct post-authorisation RCTs. Ethicists and physicians indicated that it is not necessarily in a sponsor's interest to conduct these studies as the benefit-risk balance could become negative. On the other hand, industry representatives mentioned that performing post-authorisation RCTs is not only a regulator-imposed obligation but would also increase the evidence base, which strengthens the conclusion on clinical benefit and aids sponsors in reimbursement negotiations. Additionally, if a post-authorisation RCT is performed in a different line of treatment than the conditionally authorised indication, this could lead to an extension of the indication (FG industry).

External factors

Factors external to the post-authorisation trial itself may change over time and affect trial feasibility. External factors that stakeholders reported included competition with other medicines or trials, commercial availability of the medicine and the related (perceived) clinical equipoise (figure 1, table 4).

Particularly in the post-authorisation setting, competition with other available medicines (particularly those of the same class) and other clinical trials were mentioned as impeding factors for participant recruitment (FG patients, physicians, industry). Additionally, the commercial availability of the medicine—which, in Europe, is dependent on reimbursement decision-making supported by national HTA organisations—was mentioned as impactful on the motivation to participate in a post-authorisation RCT, as the medicine is accessible outside the context of a trial (all FGs). Respondents indicated that post-authorisation RCTs may be conducted in countries where the authorised medicine is not commercially available, which can in turn raise questions on ethics and generalisability (FG ethicists, physicians, industry). In the oncology setting, differences in genetics, pretreatment regimes and standards of care were deemed to influence the generalisability of trial results to clinical practice.

Furthermore, clinical equipoise (ie, 'a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial'[31]) and how it is perceived was mentioned as a feasibility factor. Several aspects relate to clinical equipoise, including the expected benefit of the new medicine, the availability of a fair comparator and trial participants' perceptions. The expected benefit was noted to be determined by the effect size observed in pre-authorisation data (ie, SATs) and the biological rationale (FG physicians), which in turn affect both patients' and investigators' motivations to participate. Nonetheless, physicians indicated that they could be more critical when appraising trial outcomes. Additionally, respondents indicated that, particularly for post-authorisation trials with conditionally authorised medicines, therapeutic misconception (ie, the tendency of participants to think that trial participation will benefit them) should be prevented by clarifying the uncertainties related to both the expected benefits and risks (FG patients, ethicists).

Clinical equipoise further depends on the choice of a 'fair' comparator. In general, respondents in all FGs mentioned that randomisation to the best available care, including the best supportive care when treatment options are exhausted, should be considered. A fair comparator further facilitates the evaluation of the new medicine's added clinical benefit relevant for clinical practice (FG physicians). On the other hand, choosing a fair comparator for post-authorisation RCTs was indicated to be challenging due to the dynamic treatment landscape and varying standards of care across countries (FG industry).

Although others were hesitant, some ethicists indicated that eligible patients should be empowered to make decisions themselves about participation in case it is difficult to weigh the benefits and risks. Clinical trial applications should not be declined beforehand by ethics committees when uncertainties are difficult to weigh, which could be the case for conditionally authorised medicines.

Table 3 Factors regarding trial conduct that facilitate or impede the feasibility of post-authorisation randomised controlled trials as identified from the focus groups

Facilitating factor	Illustrative quote	Impeding factor	Illustrative quote
Trial conduct			
Investigators' willingness to participate may be supported by physicians' professional responsibility, enabling patient access to new medicines, a clinically relevant research question, financial compensation and possibly publishable results	*There is the motivation of money; if you grant money or if you can have publishable results. There are many other kind of useful motivations in research*. (Ethicist)	**Lack of investigators' willingness to participate** may be due to low scientific interest of investigators in post-authorisation studies, administrative burden and burden of data collection and limited research capacity for in clinical centres	*We are also competing with low scientific interest* [when studying] *something which was already available. And you have* (…) *specific obligations, so it has to be done in a timely manner. And yet, you can't engage the good quality investigators*. (Industry representative) *I got a study this week we wanted to participate in, with the request if I wanted to register myself in seven different portals and could do the accessory trainings. And this is no exemption. So, I just took next week off*. (Physician) *And the difficulty is that academic hospitals, which often have more support options for research, focus more on phase 1 trials, and less on these kind of phase 3/4 trials*. (…) *We* [in academic hospital] *really need to select and see what fits with us: what is our strength? And that will not always be these kind of post-authorisation trials*. (Physician)
Patients' willingness to participate may be supported by ensuring a good relationship between patient and investigator, access to the new medicine when reimbursement is not arranged, involving patient representatives in designing the trial, limiting participation burden, increasing randomisation ratios, allowing for cross-over to the intervention arm* and increasing awareness about the importance of these trials (to avoid therapeutic misconception)	*For patients it is of course important to get access to these things* (new medicines). *Through such a study there is the possibility to get access to the new product, while the reimbursement is not yet arranged. That are reasons why patients would be willing to participate*. (Physician)	**Limited incentive for industry to conduct post-authorisation RCT** (eg, due to the lack of financial benefit, potentially negative benefit-risk balance)	*I don't know if this is usually the case, but I can imagine that pharma companies do not always benefit from making that data available quickly. Because as soon as it* [the medicine] *is reimbursed, the cash comes in*. (Physician)
Clear and complete information for patients including information on the remaining uncertainties, trial rationale and possibilities for participation	*Patients themselves now are finding access to the trials. That is really good and that should help*. (Patient representative)		

Continued

Table 3 Continued

Facilitating factor	Illustrative quote	Impeding factor	Illustrative quote
Incentives for industry to conduct a trial may be strict regulatory requirements, a stronger evidence base for HTA and reimbursement negotiations or the prospect of a potential extension of the indication	*I think there's sometimes a misperception that sponsors don't want to do randomised studies, and I just want to clarify that oftentimes that that's the most rigorous way, sometimes, to answer the question. And it gives us confidence as well to further invest in clinical development planning and answer questions definitively. And it is convincing then to patients and stakeholders that that your drug is doing something and is worth not only taking but paying for*. (Industry representative) *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. Whether it's an RCT or any post-approval activity, you have to do it to finally get your product fully approved*. (Industry representative)		

*Some factors that were identified to facilitate feasibility may contradict each other. For example, collecting clinically relevant endpoints (eg, overall survival) may limit the possibilities for cross-over to the intervention arm.
RCT, randomised controlled trial.

Post-authorisation interaction with regulators

If a post-authorisation RCT is deemed infeasible, further discussion with regulators may be required (figure 1, table 5). For instance, if the medicine is accessible outside the context of a trial, respondents suggested conducting the post-authorisation RCT in an earlier line of treatment (FG ethicists, physicians, industry); this was also suggested to maintain clinical equipoise. For the same reason, treatment optimisation trials (eg, those that investigate a different dose or a shorter treatment period) allow for randomisation in the line(s) of treatment of the authorised indication according to the respondents (FG patients, physicians). Additionally, for generating comprehensive data, alternatives to post-authorisation RCTs were proposed in all FGs, particularly in the context of rare indications. These alternatives included contextualising SAT results with external controls, registry-based studies and studies based on data obtained from drug access protocols, such as the DRUG Access Protocol in the Netherlands (ie, for anticancer medicines that are not yet reimbursed).[32] Nonetheless, respondents also reiterated the disadvantages of such alternatives, including potential confounding bias, lack of high-quality databases in which the variables of interest are captured and continuously changing standards of care.

DISCUSSION

When CMAs are granted, sponsors are required to address uncertainties in a timely manner through the generation of post-authorisation evidence.[2] However, as generation of post-authorisation evidence is frequently delayed, increased understanding and enhancement of the feasibility of post-authorisation RCTs are needed in the context of CMA, particularly for anticancer medicines.[2 16 24 27] In the current study, we identified factors that, from the perspective of multiple stakeholders, affect the feasibility of post-authorisation RCTs for conditionally authorised anticancer medicines (figure 2).

Feasibility factors specific to the post-authorisation setting

Some of the feasibility factors we identified are not specific to the post-authorisation setting but relevant for all RCTs, for example, recruitment difficulties due to the chance of randomisation to a control arm or more burdensome treatment, or the logistical, mental and administrative burden of participating in a clinical trial.[33–36] However, the choice of comparator and endpoints, the trial population in relation to the one covered by the authorised indication, competition with other trials and medicines and a lack of scientific interest on the part of investigators seem more relevant to the post-authorisation setting.[16 17 22 24 37]

As was also mentioned by the respondents, there are two potential situations to consider in relation to a post-authorisation RCT: either (i) the post-authorisation RCT is ongoing at the time of CMA—in which case the sponsor has recruited (most of) the participants of the post-authorisation RCT—or (ii) the post-authorisation RCT is newly initiated, as seen for lapatinib (for breast

Table 4 External factors that facilitate or impede the feasibility of post-authorisation randomised controlled trials as identified from the focus groups

Facilitating factor	Illustrative quote	Impeding factor	Illustrative quote
External factors			
Conducting post-authorisation RCTs in countries where the **medicine is not commercially available**	*If you get an EMA approval of a new oncology compound, there might be a time like of two years between the first market, let's say Germany, and the last market*. (…) *And then an ethical question pops up again, but it gives you the opportunity to do the confirmatory trial in the country where the product is not yet commercially available. And that is something you might consider*. (Industry representative)	**Medicine is commercially available** outside the context of a clinical trial	*It's a common issue to recruit patients if you have a targeted therapy which is available on the market and has some efficacy* (…) *where the therapeutic alternative is not necessarily as palatable as the targeted therapy*. (Industry representative)
Empowered patients to weigh benefits and risks	*I think there's a lot of subjectivity. For instance, is it ethical to propose a medicine that gives an 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*. (…) *Research ethics committees, I think, should set a limit, as complex, subjective, and arbitrary as it may be. Within this limit, it is up to the patient*. (Ethicist)	**Competing medicines and trials** hinder the enrollment of participants	*If there are lots of products with exactly the same mechanism competing for the same patients, I think that is also a topic that would definitely influence your ability to enroll these confirmatory trials*. (Industry representative)
		High expectations about the clinical benefit of the new medicine based on the biological rationale and evidence from pre-authorisation data	*The extent to which it is feasible, depends, I think, on the enthusiasm in the field about the new product. Because if it is a very promising product and the comparator is, well, in the eyes of a lot of people, inferior, then it will be very difficult to find people for such a trial*. (Physician)
		Dynamic, **fast-changing treatment landscape**	*As a sponsor, of course, should a new standard emerge, it's very difficult to do that*(set up a post-authorisation RCT)*for a number of reasons. One is, of course, the length of studies, the availability of IMP, the cost of the approach, et cetera. So as a sponsor, I say that's a real issue for us. As a clinician, we would love to have that incorporated*. (Industry representative)

EMA, European Medicines Agency; IMP, investigational medicinal product; RCT, randomised controlled trial.

Table 5 Factors regarding post-authorisation interaction with regulators that facilitate or impede the feasibility of post-authorisation randomised controlled trials as identified from the focus groups

Facilitating factor	Illustrative quote	Impeding factor	Illustrative quote
Post-authorisation interaction with regulators			
Optimisation trials in the authorised line(s) of treatment allow for randomisation (eg, different dose, a shorter treatment period)	*For example, you have a medicine that you have used for a stage 4 but you think 'okay, but is that dose okay? Can we lower that dose or can we shorten it? Or can it be administered another way?' Those are excellent studies that you could perform post-authorisation*. (Physician)	**Possibility for alternatives** to RCTs	*An RCT, of course, that's the gold standard, but the key message, or the key question behind, is that you need more data. And if you can generate the data in a different way, maybe that that's open for discussion*. (…) *We also could replace them* (RCTs) *by registries or managed access programs, provided you do proper data gathering in an unbiased way of course. So it's not the proper replacement of an RCT, but in the case that these are actually not possible, you can think of alternatives*. (Industry representative)
Trial in an **earlier line of treatment** could lead to an extension of the indication	*So for me, the standard situation we should face is that the confirmatory trial is actually put into a different setting, into a slightly different population, and then things from a recruitment and from a trial design point of view become easier*. (Industry representative)		

RCT, randomised controlled trial.

cancer).[38] In the latter situation respondents noted that a lack of reimbursement or reimbursement conditional on trial participation may increase the feasibility of the post-authorisation RCT because the medicine is otherwise not accessible. However, the ethics and feasibility of such approaches remain to be addressed in a broad societal discussion.[39]

Our findings suggest that employing more pragmatic trial elements could particularly facilitate trial conduct in the post-authorisation setting. Pragmatic—and

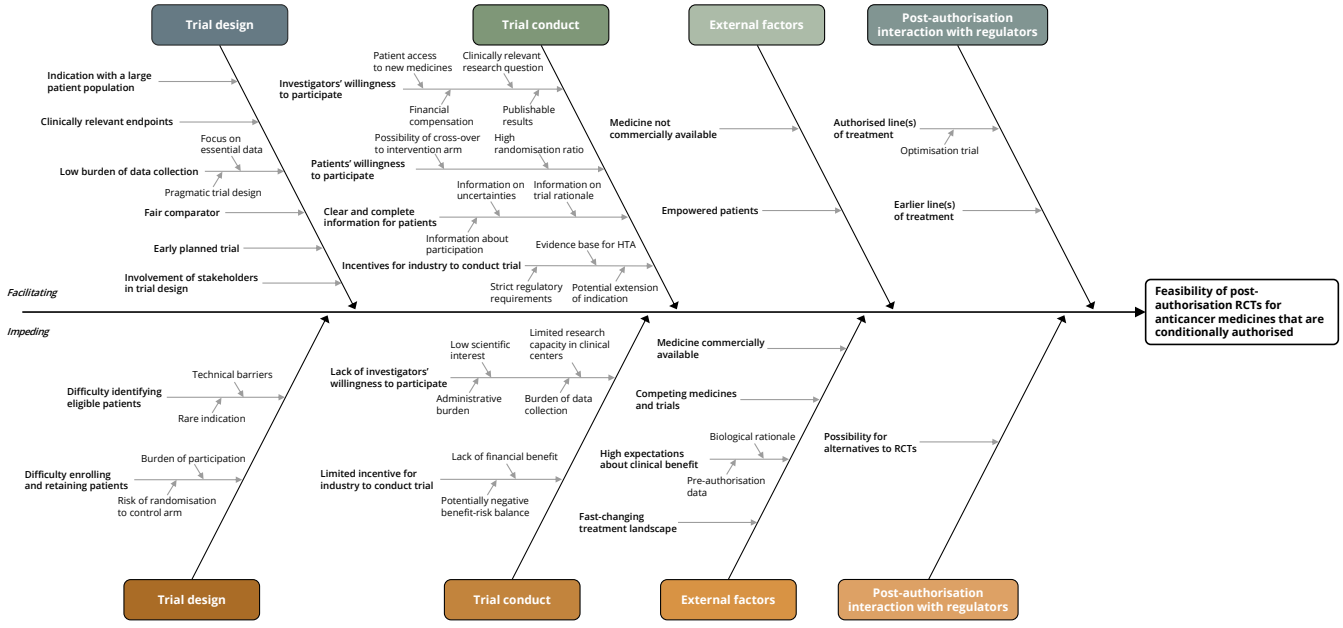

Figure 1 Ishikawa diagram showing factors that facilitate or impede the feasibility of post-authorisation randomised controlled trials for anticancer medicines that are conditionally authorised, as identified from the focus groups. HTA, health technology assessment; RCT, randomised controlled trial; SAT, single-arm trial.

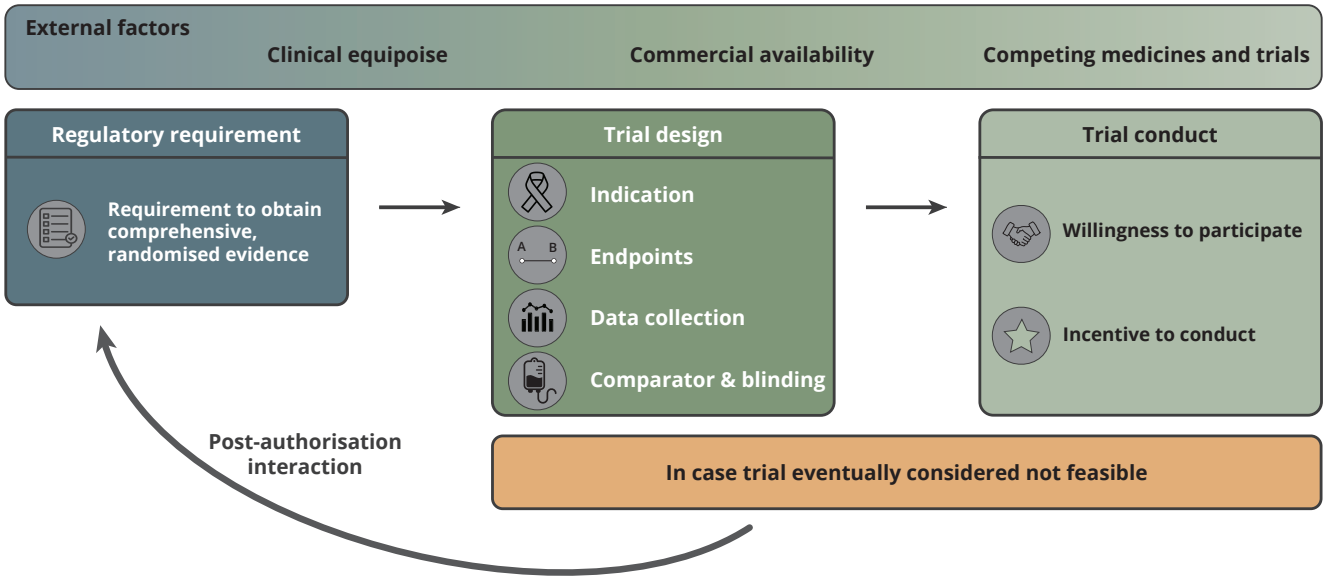

Figure 2 Feasibility of post-authorisation randomised controlled trials: a process visualisation

decentralised—trial elements may allow for data collection alongside clinical practice and the use of broader eligibility criteria and could be considered when compatible with the post-authorisation evidence requirements. This may alleviate participation and data collection burden while increasing the number of eligible and willing patients, ultimately recruiting a more representative population and therefore answering questions (more) relevant to patients and physicians.[40–42] An example is the recently launched Pragmatica-Lung trial for NSCLC in the USA, which applies broad eligibility criteria and aims to alleviate participation burden by collecting only essential data.[42]

Additionally, according to the respondents, clinical equipoise is more evident in a post-authorisation RCT in an earlier line of treatment, which supports patients' and physicians' willingness to participate. In turn, this may provide evidence for a potential extension of the indication. In practice, post-authorisation RCTs in oncology settings are often performed in an earlier line of treatment. For instance, the indications of amivantamab (for NSCLC) and dostarlimab (for endometrial cancer) as monotherapies were extended based on data from the respective post-authorisation RCTs conducted in an earlier line of treatment and as combination therapies.[43–48] However, conducting a trial in a different line of treatment in principle aims to answer a different research question and may thus not allow to resolve the remaining uncertainties.

Impact of uncertainty on perceived clinical equipoise

The available evidence and residual uncertainties may affect how clinical equipoise is perceived. Uncertainties associated with CMAs granted based on SATs may be clear to regulators. A recent EMA reflection paper emphasises important biases that may occur when there is a lack of a control arm, randomisation and blinding.[49] Our findings, however, highlight that other stakeholders may perceive the evidence and uncertainties differently. Patients, physicians and medical ethicists tended to assume that a new medicine is the preferable treatment option for the respective indication once regulators appraise the benefit-risk profile as positive, even though authorisation is conditional. Similarly, previous studies found that US physicians and patients often overestimated the evidence base and underestimated uncertainties for newly authorised medicines, including those with an accelerated approval.[50–52] In turn, our findings suggest that conditional authorisation in combination with high expectations of the medicine may hamper patients' and physicians' willingness to participate in a post-authorisation trial. In addition, respondents indicated the need for scrutiny of therapeutic misconception, especially for patients with limited or no alternative treatment options. Overestimation, difficulty understanding or incorrect interpretation of a medicine's benefits and its risks may compromise patient autonomy.[53] Patients and physicians should thus be better informed about the uncertainties that remain for conditionally authorised medicines that are to be addressed by post-authorisation RCTs.[54]

To maintain clinical equipoise for post-authorisation RCTs, respondents noted that a fair and active comparator should be included. However, in a fast-changing treatment landscape with high unmet medical needs—such as NSCLC, for which more than 330 medicines are in clinical development[55]—identifying an appropriate comparator can become increasingly complex due to a

lack of both directly comparative data and a clear standard of care.[9] To that end, post-authorisation RCTs could involve the use of (adaptive) platform designs that evaluate multiple interventions against one control arm.[56] Such trial designs could also facilitate country-specific assessment of added benefit against a locally available relevant treatment.[57]

Policy implications

In light of these considerations, we propose several actions to enhance the feasibility of post-authorisation RCTs. First, (transparency on) feasibility assessments of post-authorisation RCTs should be strengthened. During these assessments, which are conducted as part of the decision to grant CMA, sponsors and regulators should focus their discussion more explicitly on the identified feasibility factors to increase the likelihood that the sponsor will provide comprehensive data in a timely manner. Admittedly, regulators already consider the enrolment status of post-authorisation RCTs, as described in EPARs,[2] and many of the factors we identified directly and indirectly affect enrolment and retention. These factors could however be described more explicitly in EPARs. Additionally, projects like the US FDA's Front-Runner show the commitment of regulators to generate comprehensive evidence through RCTs.[58] This project aims to determine if a pragmatic trial design in early lines of oncology treatment indeed enhances the feasibility of RCTs in the post-authorisation setting.[58] Furthermore, feasibility assessments and post-authorisation evidence generation should aim to incorporate the evidence needs of HTA organisations and medical societies.[15 59] Such discussions may be facilitated through the parallel joint scientific consultations of the EMA and the European Network for Health Technology Assessment (EUnetHTA) 21 consortium and its successors.[60 61]

Second, trial feasibility and stakeholders' motivation to participate may be enhanced when stakeholders are well-informed, for instance, through informed consent procedures, as to how regulators weigh the remaining uncertainties of conditionally authorised medicines and how these will be addressed by the trial. More transparency is needed on why the post-authorisation RCT is imposed as well as its enrolment status, which could for instance be communicated through the informed consent procedures.[39] Additionally, involving additional stakeholders in the design of post-authorisation RCTs may enhance willingness to participate. For instance, preference studies can be conducted to elicit patient preferences for addressing uncertainties and trial design features.[62]

Third, feasibility of post-authorisation RCTs may be enhanced by providing clearer guidance on what is considered fit-for-purpose evidence generation in specific situations. This includes a clear indication-specific definition of the concept of 'comprehensive evidence', the circumstances under which RCTs are considered paramount, and when alternative study designs, such as observational studies, are acceptable.

Fourth, the reasons of not meeting specific obligations in time[24] and when withdrawing a CMA is considered necessary should be further investigated. For example, in Europe, thus far, the CMAs for three anticancer medicines have been withdrawn: olaratumab has been withdrawn by regulators after 3 years, whereas the indications of rucaparib and vandetanib have been restricted (after four and 11 years, respectively) because post-authorisation RCTs could not confirm the positive benefit-risk balance.[63–66] In comparison, in the USA, clinical benefits remained unconfirmed for almost half (112 out of 253) the medicines that received accelerated approval until 2021, of which 24 await confirmation after more than 5 years on the market and only 16 have been withdrawn.[67] Additionally, potential measures (eg, increased financial penalties or temporary revoking the CMA) to counter such situations should be considered, including an analysis of the legal and policy implications of these measures. Notably, in Japan a type of expedited approval can be granted for a maximum of 7 years, which is automatically withdrawn if the applicant fails to obtain standard approval during that time.[68]

The feasibility for generating additional evidence is an important requirement for granting CMA and a lack of feasibility to obtain such data may be reason for regulators not to grant CMA.[2] The current use of CMA calls for broader discussion about the balance between accepting uncertainties and expediting patient access; that is, the circumstances under which expedited authorisation may be preferred over delaying patient access although there is substantial uncertainty concerning a medicine's benefit-risk profile.[39 69–71] Specifically, the current use of CMA requires discussion on the criteria that must be met before a CMA is granted and how these criteria will be evaluated, including the definition and level of unmet medical need,[72] the level of uncertainty considered acceptable, the observed effect size in pre-authorisation data and the likelihood that the sponsor will be able to provide comprehensive data in a timely manner.[1 2] Alternatively, if generating additional evidence is not deemed feasible at all, granting marketing authorisation under exceptional circumstances may be a more appropriate pathway in Europe, as it would explicitly show involved stakeholders (including patients, physicians) that the uncertainties on a medicine's benefit -risk balance are not deemed resolvable through post-authorisation data generation.[1]

Strengths and limitations

The participation of representatives from various stakeholder groups enabled the identification of feasibility factors for post-authorisation RCTs from complementary perspectives. This study reports respondents' perspectives on factors that are deemed facilitating or impeding, and the overview of factors may be incomplete. Respondents were experts in their respective roles, allowing for

in-depth discussion. Many of the invited respondents considered themselves less equipped for participation because of a limited understanding of the regulatory system, while this might have been representative of their stakeholder group. In addition, only Dutch physicians participated, despite our efforts to include physicians from other European countries as well. Nonetheless, the identified feasibility factors are expected to be relevant for other geographical regions and other therapeutic areas where expedited approval pathways are used. It may, however, be difficult to distinguish between feasibility factors specific to post-authorisation trials for anticancer medicines with a CMA and for post-authorisation RCTs in general. Given the exploratory character of the current study, future studies should aim to quantify the most important impediments to post-authorisation RCTs—from a multistakeholder perspective including regulators and HTA organisations—and identify solutions that could address these. Additionally, strategies to inform patients and physicians about the need for post-authorisation RCTs should be investigated.

CONCLUSIONS

This study identified factors that impact the feasibility of post-authorisation RCTs relating to trial design and conduct, and factors external to a trial from the perspective of various stakeholders. Considering the exploratory nature of this study, we recommend regulators to involve those factors more explicitly in assessing and describing trial recruitment and retention during the feasibility assessment of a proposed post-authorisation RCT and, with that, the possibility for granting a CMA. Moreover, we recommend sponsors and regulators to better inform patients and physicians about remaining uncertainties of conditionally authorised anticancer medicines to empower them to make well-informed decisions and to potentially improve their willingness to participate in post-authorisation RCTs. In line, trial designs should be tailored to the post-authorisation setting, considering the inclusion of clinically relevant endpoints, and a fair comparator.

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Patient consent for publication Consent obtained directly from patient(s).

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