

A regulator's view on AIT clinical trials in the United States and Europe: Why successful studies fail to support licensure



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Clinical studies demonstrate that efficacy and safety in allergen immunotherapy (AIT) are linked to a multiplicity of factors decisively influencing success or failure. In recent years, numerous trials were performed with correspondent study results published. Yet, the number of AIT products successfully obtaining licensure in the analogous time frame is comparably limited. Essential for licensure is that the AIT product investigated remains comparable in its qualitative and quantitative composition throughout the clinical development. Verification of efficacy is not solely demonstrated by a statistically significant difference between the test and control populations; it must also be shown to be clinically relevant. Choice of meaningful inclusion and end-point criteria is critical. *Post hoc* or subgroup analysis can be supportive but needs verification as predefined criteria in additional studies. Data analysis may be presented on varying analysis populations, while it should be based on the intention-to-treat population for

regulatory review to allow objective assessment of the treatment effect on the overall study population. Apparently conflicting interpretations of clinical data between publications and regulatory review are frequently based on their inherently different objectives, with regulatory review taking into considerations the full data sets of all relevant clinical studies for the concerned AIT product to allow an informed decision on licensure. (*J Allergy Clin Immunol* 2022;149:812-8.)

Key words: Allergen immunotherapy, clinical trials, regulation

Allergic disease affects millions of people. Although there are many approved treatments for allergy symptoms, only allergen immunotherapy (AIT) offers the possibility of reversing the underlying pathology.¹ Regulatory agencies in both the United States and the European Union (EU) require that medicinal products be proven safe, efficacious, and of adequate quality. This is especially relevant for AIT products that are usually repetitively administered for several years. Evidence for safety and effectiveness of any given product is demonstrated in a multistep clinical development program that typically includes 2 sets of randomized double-blind placebo-controlled trials.² Phase 2 studies are designed to identify an optimal, safe, and effective dose, and larger phase 3 trials are intended to unequivocally demonstrate safety and efficacy.

In the last few decades, the field of allergy has seen tremendous changes, including an unprecedented number of controlled clinical trials for many AIT products. In the EU, many of these trials have occurred as a result of the German Therapy Allergen Ordinance.³ This regulation requires AIT manufacturers to apply for marketing authorization for AIT products for the treatment of allergies that were considered to affect a high number of patients in Germany, and for which the execution of a clinical development program was considered feasible and reasonable. With these marketing authorization applications, the manufacturers must conduct state-of-the-art clinical development programs to prove that their products are safe and effective even if the product had been distributed without marketing authorization before modern requirements for demonstration of safety and efficacy existed. In the United States, the efforts to secure licensure of 5 new AIT products in the United States (Oralair, Grastek, Ragwitek, Odactra, and Palforzia) have generated several published controlled studies to support rational and safe AIT usage, at least for the newly licensed products.⁴⁻⁸ It should be noted that the term “licensure” as being applied in the United States essentially

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Abbreviations used

AIT:	Allergen immunotherapy
EU:	European Union
FDA:	Food and Drug Administration
IMP:	Investigational Medicinal Product
IND:	Investigational New Drug
IP:	Investigational product
ITT:	Intention to treat
NCA:	National competent authority
PP:	Per protocol

corresponds to a “marketing authorization” in the EU. For the sake of readability, the term licensure is used consistently throughout this review.

For many clinical trials, their design and key results are published after conclusion of the trial. Yet, although openly accessible clinical trials registers⁹⁻¹¹ show that numerous AIT clinical trials have been completed, many go unpublished and comparably few AIT products are eventually authorized in Europe or the United States. For example, of the 123 AIT products for which marketing authorization procedures were initiated in response to the German Therapy Allergen Ordinance in Germany, only 2 have obtained an authorization so far, with 50 products still pending authorization and 73 products no longer under consideration (either due to rejection by the competent authority or due to withdrawal by the applicant).

A careful reader of these published study results would be surprised that only a small number of promising published studies lead to licensure. A recent review by de Kam et al¹² addresses some of the major challenges for phase 3 clinical development of aeroallergen AIT products. Although some promising products fail to come to market for reasons unrelated to regulatory considerations (eg, whether the product will be financially profitable), some products simply fail to meet the appropriately high expectations of regulatory agencies for safety, efficacy, and product quality. As a result, regulatory agencies may come to conclude that the overall benefit-risk ratio is not positive, and that the product should not be authorized. To address some reasons that products fail licensure, we first provide an overview of key regulatory aspects of clinical trials in the EU and the United States, followed by an overview of problems and critical issues identified in regulatory assessments with data obtained from clinical trials.

OVERVIEW OF CRITICAL REGULATORY REQUIREMENTS FOR CLINICAL TRIALS IN THE EU AND THE UNITED STATES

Generally, the regulatory authorities in the EU and the United States have different procedures for granting permission to proceed with a proposed clinical trial. Since 2004, the assessment of clinical trials in the EU has been regulated on the basis of EU Clinical Trials Directive 2001/20/EC¹³ and Directive 2005/28/EC,¹⁴ defining the minimum standards for the procedures conducted in every member state (Fig 1). In accordance with these directives, a sponsor must submit a clinical trial application to the national competent authority (NCA) and the national ethics committee(s) of each EU member state concerned, thereby receiving separate decisions per member state.

Regulation of clinical trials in the EU has recently undergone a major change as the Clinical Trial Regulation (No. 536/2014), adopted by the European Parliament in 2014, came into effect on January 31, 2022.¹⁵ Since this date, the Clinical Trials Information System, a combination of portal and database, is the core and single entry point of harmonized clinical trial regulation throughout the EU.¹⁶ For example, sponsors have to submit only 1 clinical trial application via the Clinical Trials Information System, split into Part I (scientific and medicinal product documentation, eg, investigator's brochure, dossier on the quality of the product to be tested, and clinical trial protocol) and Part II (national documentation, eg, informed consent form). This allows a joint assessment of Part I by the NCA and ethics committee and a single decision from each member state concerned on both parts of the submission. As before, the formal permission to proceed with the clinical trial and the monitoring of clinical trials is within the responsibility of the concerned member states. Apart from harmonization, main improvements are the substantially shortened time frames for completion of the application procedure as well as the increased public availability of information on each clinical trial conducted in the EU. All in all, it is expected that the new regulation will increase both transparency and the number of clinical trials conducted in the EU in upcoming years.¹⁷

In the United States, clinical investigations in which a drug or biological product is administered to human subjects must be conducted under an Investigational New Drug (IND) application per Part 312 of Title 21 of the US Code of Federal Regulations (21 CFR 312). The Food and Drug Administration (FDA) oversees the IND application review process. Similar to the EU, components of the IND submission include but are not limited to preclinical data; chemistry, manufacturing, and controls information (of which the amount of detail required increases as clinical development progresses); clinical trial protocols; and up-to-date investigator information, informed consent forms, and investigator's brochures. Results of preclinical testing in laboratory animals are submitted either before or with the initial clinical trial protocol, and determination of whether it is reasonably safe for the sponsor to move forward with testing of the investigational product (IP) in humans is made on the basis of these results. Subsequent clinical development of the IP, elaborated upon below, occurs in at least 2 to 3 phases, before submission of the licensure application.

PROBLEMS AND CONSIDERATIONS FOR CLINICAL STUDIES

The design and execution of a clinical trial is highly complex, and its success is substantially dependent on intrinsic and extrinsic factors other than the safety and effectiveness of the product. Numerous issues come into play that may jeopardize the eligibility of data obtained from a clinical trial. On a general level, such issues can be related to product quality, trial design, and trial execution.

Quality aspects

In the clinical trial, the AIT product is called an *Investigational Medicinal Product* (IMP) in the EU and an IND in the United States (IP in this review). Under both regulatory authorities, quality requirements for investigational products are

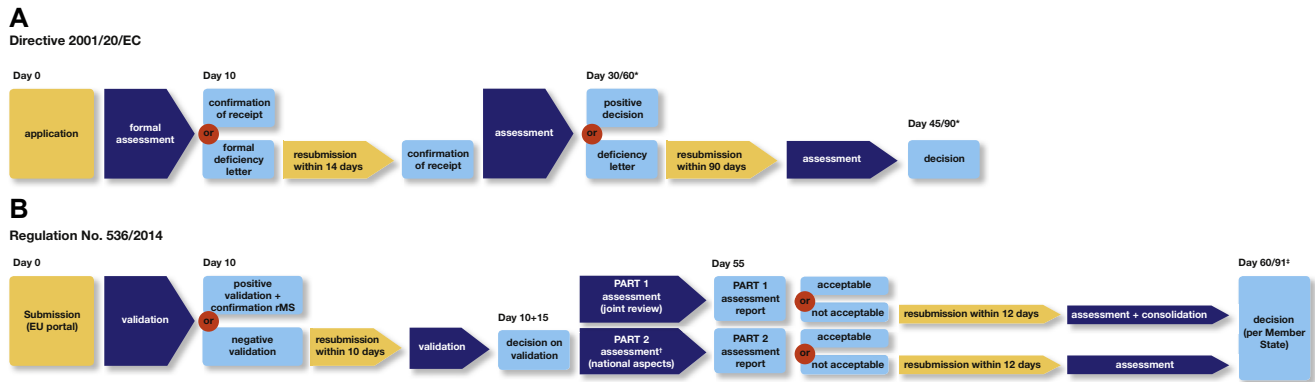


FIG 1. Overview on the formal procedure for granting permission to proceed with a clinical trial in the EU. **A**, Since 2004, the assessment of clinical trials in the EU has been regulated on the basis of EU Clinical Trials Directive 2001/20/EC. The sponsor submits a clinical trial application to each member state separately, which then each make an independent decision. **B**, With the implementation of Clinical Trial Regulation (No. 536/2014) in early 2022, only 1 application needs to be submitted to a common submission portal, resulting in a joint assessment and a single decision by the concerned member states. *Biological products containing material of human/animal origin. †Either in parallel to Part 1 or sequential (maximum 2 years between assessments). ‡If resubmission was necessary. rMS, Reference Member State.

phase-dependent, with minimal requirements at early stages and highly demanding requirements as products advance to pivotal studies and licensure. At the earliest phases of study, regulators focus on safety, sufficient product characterization, and stability to support meaningful human study. As investigators progress to more advanced phases of study, regulators expect that the applicant will have made progress toward reliable potency unitage and qualified methods for ascertaining potency, robust manufacturing procedures to include reliable source material supply chains, in-process testing protocols and standards, and specifications to assess product quality at release. At licensure, the candidate product should have fully validated processes and procedures; potency measures that ensure that the manufactured product reflects the product's testing in pivotal trials; and a mature manufacturing procedure that reflects a stable quality-based corporate culture. By this time, the IMP/IP needs to be extensively characterized to verify its quality such that it is representative of the product intended to be authorized, and that the clinical data obtained inform regulatory agencies on the clinical performance of the actual product to be authorized.

Given the complex nature of many AIT products, the necessary depth of characterization can be challenging. Numerous guidelines and regulations are available to guide investigators and manufacturers in this process. For the EU, the *Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials*¹⁸ can be considered as especially relevant. For more detailed information on these requirements, reference to other publications is made.¹⁹⁻²¹ FDA's approach to product characterization in early phases of clinical development is described in *Guidance for Industry: CGMP for Phase 1 Investigational Drugs* (July 2008).²² Details on product quality requirements in later stages can be found in the US Code of Federal Regulations [21 CFR 312.23(a)(7)(i) – (iv)], with specific guidance provided by FDA, as needed, in the pre-IND and IND process.

Despite the challenges associated with generating this quality data, it is the responsibility of the sponsor of a clinical trial to ensure that the manufactured and distributed AIT product will perform after licensure as expected on the basis of clinical trial

data. With insufficient IMP/IP characterization, verification of the investigational AIT product's comparability to the product to be licensed can be challenging or even impossible after the fact. Critical aspects in this regard are presented in [Table 1](#) and may include AIT products for which basic analytical methods had not been applied (eg, the characterization of crosslinked allergoids), analytical methods that were applied without adequate validation, or methods that were used that are not in compliance with relevant guidelines or good scientific practice. Furthermore, where previously applied analytical methods have been subject to fundamental changes in their performance without conducting a proper comparability study, previously obtained data may no longer be comparable to data obtained after such changes.

Typically, the manufacturing process for a medicinal product evolves throughout the preclinical and clinical development program. Such changes need to be closely monitored for their effects on product quality, especially manufacturing process optimizations, changes in the composition of the IMP/IP, and modifications associated with the increased scale of manufacture that inevitably occur as products advance to licensure. At all stages of development, the manufacturer must ensure that the AIT product remains consistent by performing well-designed comparability analyses. Although the fundamental quality requirements and implications regarding clinical trials are also applicable for nonallergen medicinal products (eg, comparability of the IMP/IP throughout the clinical development), other aspects such as the product-specific potency determination are unique to allergens and must be considered with respective care. Also, because the biological potency (predominantly IgE-reactivity) of the individual products is typically analyzed with manufacturer-specific in-house assays, these products are often labeled with arbitrary units that are therefore not directly comparable to other manufacturer's medicinal products, even when targeting the same type of allergy. Notably, quality requirements for AIT products are generally independent of the selected allergen.

It should be noted that some product quality issues may not be fully resolved even at the successful conclusion of the pivotal clinical trial. The level of detail required on the manufacturing process and the product characterization (including, but not

TABLE I. Critical aspects in characterization of IMPs intended for AIT

Problem observed	Potential impact
Insufficient characterization of allergenic source materials	Substantial batch-to-batch variation for the IMP
Insufficient validation of the manufacturing process	- Typically, full validation of the manufacturing process is not documented for early-phase clinical trials - Risk that problems in the manufacturing are observed only at late stages of clinical development
Unsuitable or incomplete specifications for the final IMP or intermediates	Quality data may not be suitable to secure eligibility of the IMP to demonstrate safety and efficacy for the product to be authorized
Insufficient or incomplete validation of analytical methods for characterization of the IMP or intermediates	Data obtained for the IMP may not be based on validated methods and eligibility of the IMP to demonstrate safety and efficacy for the product to be authorized may not be given
Changes in the manufacturing process during clinical development (eg, in composition, specifications, manufacturing procedures, and analytical methods)	Requirement to demonstrate eligibility of prechange and postchange data by providing data from a comparability analysis. If no comparability is demonstrated, eligibility of the IMP to demonstrate safety and efficacy for the product to be authorized may not be given
Insufficient data on the stability of the IMP	- Approval for a clinical trial not possible where stability of the IMP and relevant intermediates is not demonstrated - Eligibility of IMP may be questionable
Insufficient characterization or procedures for changes regarding reference standards	Data obtained from analytical characterization of the IMP may be questionable

limited to, process validation or analytical method validation) for the initiation and completion of a clinical trial may be less than needed for successful licensure. For example, tabulated summaries of validation results are sufficient for clinical trial approval in the EU even for phase 3 clinical trials, even though full method validation already must be completed at this stage. Furthermore, in Europe, different clinical trials may be performed and authorized in different countries, resulting in the possibility that the full data package is available to a competent authority only once a marketing authorization procedure has been started. As a result, although promising data may have been obtained in a clinical trial, the applicability of these data for a specific product may still be in question due to critical aspects identified in the full assessment during the marketing authorization procedure. In the United States, this is not generally an issue.

Clinical aspects

The *Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases*²³ provides the main regulatory framework with regard to clinical aspects for AIT products in the EU. According to this guideline, the primary end point for a confirmatory study to prove efficacy of an AIT product for treatment of respiratory allergies must reflect both symptom severity and the intake of rescue medication (Combined Symptom-Medication-Score). In recent years, the Combined Symptom-Medication-Score as proposed in a position paper by the European Academy of Allergy and Clinical Immunology²⁴ has been used more commonly in clinical trials, contributing to better comparability between different trials, because comparison of different scores typically does not allow reliable conclusions. Similar to all other scores, the score proposed in the European Academy of Allergy and Clinical Immunology position paper is not yet validated. In spite of this, combined scores incorporate both reduction in symptoms and medication use and will likely give a better reflection of AIT efficacy. In the United States, several Guidance for Industry documents,^{25,26} collaboratively written by centers within the FDA, provide the regulatory framework for clinical trial development. Although these guidance documents are not specific to AIT products, the general

principles provided in these documents are relevant to their clinical development.

For phase 3 clinical efficacy trials in both the EU and the United States, the major objective is to demonstrate a statistically significant difference between the test and control populations; however, statistical significance alone may not be sufficient to demonstrate efficacy. The difference between the treatment and control populations must also be shown to be clinically relevant (ie, represent a clinically meaningful impact of the IMP/IP on the disease or condition for which the applicant seeks an indication). This clinically relevant difference must be predefined and justified by the applicant,²³ and must be factored into the design of phase 3 efficacy trials. The predefined clinically relevant difference is required for any phase 3 trial intended to demonstrate efficacy of the IP concerned, independent of the type of allergen targeted (eg, respiratory or food allergen) or of the route of administration. As such, clinical trial results may show a statistically significant difference between test and control populations, but if the results do not meet the predefined clinically relevant criteria chosen to represent a clinically meaningful outcome, the clinical trial results may not be considered supportive of licensure. Specific cutoffs for the minimum clinically relevant effect have been proposed in the EU,²⁷ but experience has shown that this aspect must be assessed on a case-by-case basis because it is strongly dependent on several trial-specific factors, such as the respective Combined Symptom-Medication-Score used and data from additional secondary end points or additional supportive trials. Likewise, in the United States, the predefined clinically relevant difference is evaluated specifically for each IP and the proposed indication.

Further aspects may become critical when assessing data from a published AIT clinical trial (Fig 2). One issue is that published trials may not be fully transparent about the details of the statistical analyses related to the primary end point of the study, and the type of analysis conducted can result in severe bias (such that the overall effect appears exaggerated). For example, data may be presented for analysis populations other than the intention-to-treat (ITT) population or full analysis set (commonly defined as all subjects who receive 1 dose of the IMP/IP in a clinical trial),

Typical course of a clinical study and associated pitfalls

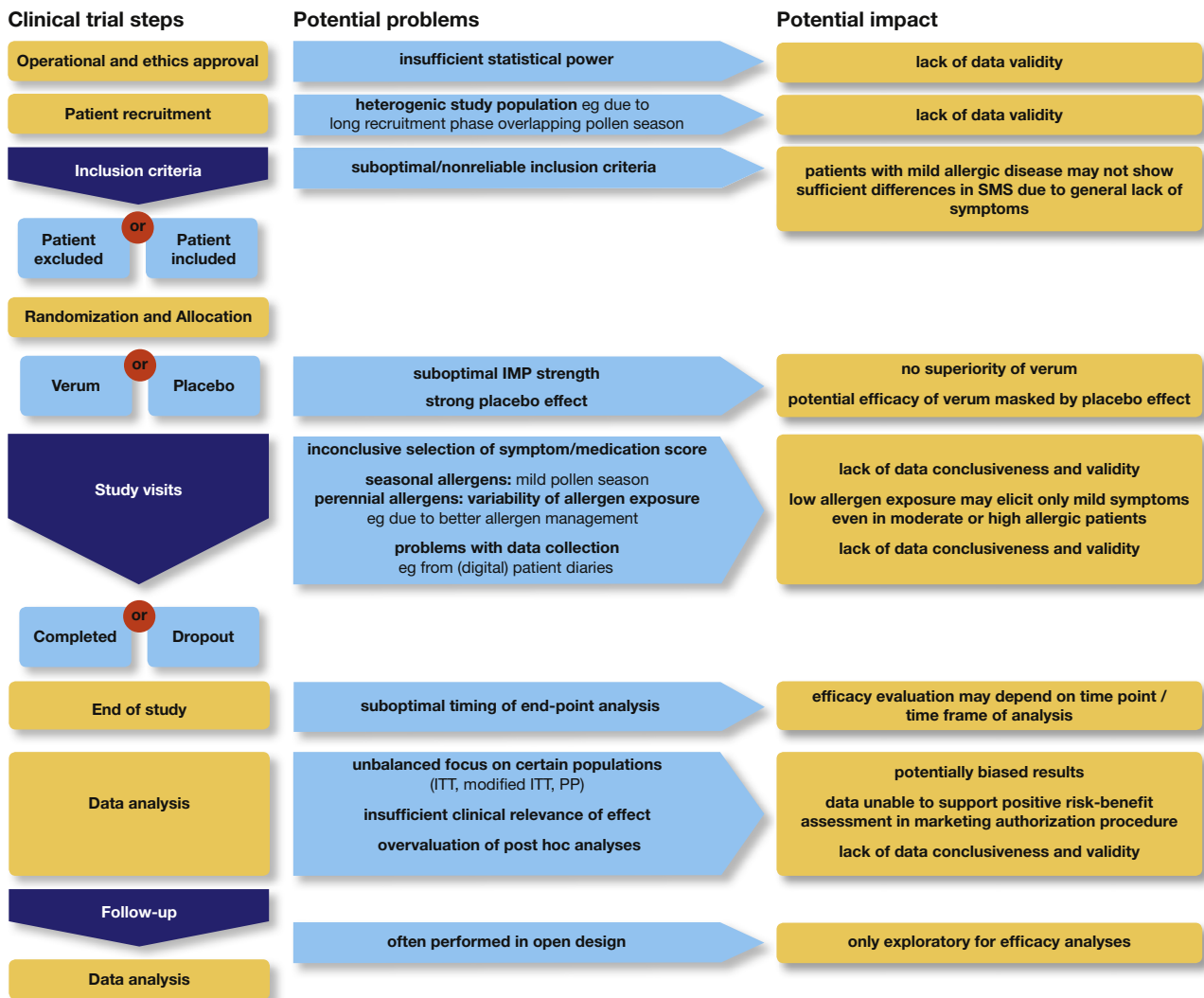


FIG 2. Overview on the course of a typical clinical trial and associated problems that may become relevant at each stage, including potential impacts resulting from these problems. Some of these issues may become relevant at further stages than the examples depicted in the figure. SMS, Symptom Medication Score.

such as the modified ITT population or the per-protocol (PP) group (which is predefined to exclude certain subjects from the population). Analysis of the primary end point using the PP population instead of the ITT population may differ because although subjects in the treatment group who completed the trial may have considerably improved, this improvement was exaggerated by exclusion of data from those who experienced intolerable side effects and were therefore discontinued from or withdrew from the trial (and were therefore, by definition, excluded from the PP analysis). Consequently, the PP analysis does not represent the true risk-benefit ratio of the proposed treatment experienced by the ITT population.

Another issue is that publications may display or overemphasize data only from subgroup or *post hoc* analyses. Such scenarios have been observed in clinical trials that undergo regulatory review. For example, *post hoc* analysis of a more severely ill subgroup may overestimate the effectiveness of the IP. In such case, the severity of the allergic symptoms may be too low in a

certain subset of the patients included in the clinical trial. Only a *post hoc* analysis of a subgroup of patients with more severe symptoms may then show meaningful efficacy, whereas this is not the case for the overall study population. Therefore, data and results obtained from *post hoc* analyses will need to be confirmed by an additional study in which these parameters are predefined in the clinical study protocol.

In addition, study sponsors may report results using clinical end points that overstate the IP's performance. Complicating issues further are trials in which the predefined criteria for a primary end point were not met and only secondary end points were successfully reached.^{28,29} Ideally, such conditions and results are openly addressed in a balanced way in published reports, but this is often not the case.

Further factors that could impede the integrity and meaningfulness of study results are studies that are not sufficiently powered because of insufficient numbers of patients recruited, often resulting in an inability to draw conclusions from the study.

Also, studies in which patient recruitment takes place over a very long time frame can be problematic because it can result in considerable heterogeneity in the study populations, for example, due to differing time frames of participation in the trial in relation to the pollen season. Time frames for patient recruitment may depend on controllable factors (such as a sufficient number of study sites and realistic recruitment milestones) but may also be impacted by extrinsic factors that are outside the control of a sponsor, such as the coronavirus disease 2019 pandemic.

Lastly, permission to proceed with clinical trials can be denied on the basis of incomplete application documents, noncompliance with relevant guidelines, a negative risk-benefit assessment, or noncompliance with the protective regulations concerning particularly vulnerable groups. In contrast, permission to proceed with a clinical trial cannot be denied if the NCA reaches the conclusion that the trial design is unlikely to support a subsequent marketing authorization procedure. Although the competent authority may comment on possible issues such as the selection of a potentially suboptimal IMP dose, these comments will not impede advancement of the clinical trial, and it is the sole decision of the sponsor whether to consider the comments and recommendations provided. Hence, even clinical trial applications that may not be supportive of a marketing authorization procedure are allowed to proceed if the sponsor insists on seeing the trial through as planned. In the United States, the IND regulations provide FDA the authority to delay a proposed clinical investigation or suspend an ongoing investigation. The grounds for imposition of a clinical hold are described in 21 CFR 312.42 and include for a phase 2 or 3 study that the FDA may place the study on hold if the plan or protocol is clearly deficient in design to meet its stated objectives.

DISCUSSION

Conduct, analysis, and interpretation of clinical trials is a complex task dependent on several variables. Although it is obvious that variables within the control of study sponsors should be considered and planned with exceptional care, some parameters will be beyond such control. It is the responsibility of the sponsors to design the clinical trials in such a way that the efficacy can be objectively demonstrated and that bias is minimized. Notably, most aspects discussed above are basic principles that require consideration independent of the route of administration, the type of allergy targeted, or the complexity of the individual product. Regulatory agencies are available to support in the planning and interpretation of clinical trials through scientific advice in all phases of clinical development. From our perspective, we have observed considerable differences in the quality of study designs among different clinical study protocols.

Because of the complexity of these study protocols, published accounts of the studies rarely include full details, even in the publication appendices. In part, this is to conserve space and preserve the readability of the publication, and often product quality details are proprietary. In addition, such details are rarely of interest to journal readers, reviewers, and editors. However, even minor simplifications of product quality or the clinical trial conduct may obscure issues that will be of major consequence regarding the ultimate safety and effectiveness of the product to be licensed.

Formal failure of a clinical trial (eg, the primary efficacy end point was not reached) does not automatically mean that the

product is not effective. Potential reasons for the observed failure to meet the predefined clinical end point(s) need to be assessed on a case-by-case basis. Parameters that have been observed in the past and may put the validity of data obtained into question include both extrinsic and intrinsic factors and are summarized in Fig 2. Also, van Wijk³⁰ has addressed such factors in a recent review.

Public perception versus regulatory assessment of success or failure for some clinical trials may not always be fully aligned. One reason may be that although core data on clinical studies (such as sponsor name, title of the study, study design, and key end points) are typically available in the respective trial registers, the actual results of such studies are not being consequently published, despite such legal requirements.^{31,32} In the EU, this is likely to change with the coming into force of the EU directive 536/2014 in 2022. Another reason may be that publication of data from clinical trials is usually orchestrated by those linked to success or failure of the investigated product. Even though the peer review process and publication quality criteria are very thorough, unbiased interpretation of a clinical trial data set cannot always be assessed or verified by editors and reviewers. Furthermore, in regulatory review procedures, the full data set under consideration of all clinical trials of the complete clinical development program is assessed. Therefore, journals and publications that take authors' conflict-of-interest statements into account should be appreciated. In contrast, regulatory assessments of the detailed aspects of a marketing authorization/licensure application (or in scientific advice) are confidential until licensure (eg, with the Public Assessment Report made publicly available upon approval in the EU and the Summary Basis for Regulatory Action and other relevant regulatory reviews and documents made publicly available upon licensure in the United States), and the agencies cannot publicly comment on details of specific studies and respective assessments. In the United States, the reviews of failed clinical studies remain confidential and are unavailable for public review, unless the product is subsequently licensed. Although the reasons for refusal of a marketing authorization in the EU can be made public by the NCA, this rarely occurs, because the applicant will typically withdraw a marketing authorization application before refusal.

AIT clinical trials are challenging and complex, in part because they may require years to complete. Therefore, suggestions on alternative approaches or modifications are available or being actively developed.³³ One such suggestion is to increase reliance on allergen exposure chambers.^{34,35} In particular, the European Medicines Agency is exploring potential ways forward with regard to studies in children³⁶ and new guidances.³⁷ Alternatively, hybrid allergen exposure chamber/natural exposure trials or novel statistical approaches may increase the feasibility of these trials.³⁸ In-depth discussions on applicability and requirements concerning allergen exposure chambers have been published previously.³⁹⁻⁴¹ Recently, use of real-world data and real-world evidence has gained much attention. The extent of applicability of data obtained from real-world data/real-world evidence for regulatory decision making will be directly dependent on the quality of such data obtained. In the authors' opinion, real-world data/real-world evidence will likely prove to be of enormous value to complement information obtained from classical randomized clinical trials. Considerations on such approaches have been recently published by European regulators⁴² as well as in a draft guidance by the FDA.⁴³ Whichever the approach,

licensing new AIT products will require the combined efforts of industry, medical practitioners, scientific societies, patient representatives, and regulators, so that patients may benefit from an increased number of licensed AIT products with proven quality, safety, and efficacy.

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