Clinical trial standard protocols, approaches for more regulatory efficiency?

Wissenschaftliche Prüfungsarbeit
zur Erlangung des Titels
"Master of Drug Regulatory Affairs"

der Mathematisch – Naturwissenschaftlichen Fakultät der
Rheinischen Friedrich – Wilhelms – Universität zu Bonn

vorgelegt von

Dr. Ulrich Härtel aus Darmstadt

Bonn 2012

14. Februar 2012

Betreuer und erster Referent: Dr. Josef Hofer
Zweiter Referent: Herbert A. Jopp

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1 Abbreviations

ADaM	Analysis Data Model
CDASH	Clinical Data Acquisition Standards Harmonization
CDER	Center for Drug Evaluation and Research [within FDA]
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of [US] Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organisations of Medical Sciences
CRF	Case Report Form
CTA	Clinical Trial Application
CTEP	Cancer Therapy Evaluation Program
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency [formerly EMEA]
EU	European Union
EudraCT	European Clinical Trial Database
EVIDEM	Evidence and Value: Impact on Decision Making
EWP	European Working Party
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IND	Investigational New Drug Application [US]
JPMA	Japan Pharmaceutical Manufacturers Association
MAA	Marketing Authorisation Application
MCDA	Multiple Criteria Decision Analysis
NIH	National [US] Institute of Health
PAT	Preventive Allergy Treatment study
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
RCT	Randomised controlled trial
SCIT	Subcutaneous specific immunotherapy
SDTM	Standard Data Tabulation Model
SIT	Specific immunotherapy
SLIT	Sublingual specific immunotherapy
SMS	Symptom medication score
SPC	Supplemental Patent Certificate
TAV	Therapieallergene-Verordnung ([German] Decree on therapeutic allergens)
WHO	World Health Organisation

2 Executive Summary

Clinical research is an area which is poorly standardised on an international basis. Clinical trials are most often unique projects developed from scratch for a specific purpose using company-specific procedures and definitions. Protocol standards determining clinical design characteristics for trials intended for a specific purpose can contribute to higher quality and efficiency of research. The regulatory bodies as well as sponsors may benefit from increased regulatory acceptance and faster study approval.

Only little experience for standard protocols is available. Examples include two templates issued by CTEP providing a high level of details and guidance for two Phase I study designs in oncology. In the EU, standard paediatric investigational plans (PIPs) were recently released for pandemic influenza vaccines and allergen products for specific immunotherapy (SIT), the latter ones being the focus of this thesis.

The circumstances under which the standard PIPs for allergen SIT products were issued are unique; paediatric clinical trial obligations were defined for a large number of products, most of them being established in medical practice since a long time. Being previously on the German market with a 'named patient' basis, this product group was recently subjected to the EU medicinal product legislation. Applying the EU paediatric legislation and making a standardised 5-year paediatric trial design for many of these products obligatory led to a difficult situation for manufacturers of these products. Factors such as the non-standardisation of product tests, high itemisation of the products, and the non-harmonisation of legal status in the EU contribute to the fact that the hurdles imposed to the industry of this product group are disproportionally high.

The obligatory use of placebo control raises ethical concerns. Although the products are not identical and allergen types are different, the high number of trials conducted in accordance to the standards (according to currently approved PIPs, about 70 long-term trials) is considered a duplication of studies. The fact that obligations of the paediatric regulations were imposed for established products without patent protection or market exclusivity is considered to be not in line with the spirit and purpose of the paediatric regulation. The rationale to request long-term trials rather than short-term trials can be challenged.

As standard protocols narrow down the options for clinical development, they potentially impact the timelines of development, impact the claims that can be achieved and economic aspects of drug development. For this reason, standard protocols that are made obligatory require careful evaluation of ethical aspects, compliance with current legislation and alignment with all involved stakeholders. A four-step formal decision process is proposed to validate the scientific and regulatory rationale for the request the conduct of a trial, to decide on the standardisation versus non-standardised regulatory approaches, to decide on the clinical trial design and individual elements thereof and, finally, to evaluate risks associated with the approach.

Despite the controversial aspects as discussed above, the concept of standard protocols may become a success in the regulatory context, which could be applicable to many situations. A key success factor of such standard protocols is alignment with all stakeholders. Where applicable, the industry is asked to discuss alternatives and to clarify any outstanding issues. The ultimate goal must be to provide medications with proven efficacy and safety to patients, in which standard protocols can help but are probably not the only route, especially in a regulatory context with many challenges.

3 Introduction

Harmonisation of requirements, standardisation of clinical trial designs and formal standardisation can potentially increase the efficiency and safety of clinical research, ensure more predictable drug development for the sponsor and ease the review of applications by authorities. More than ever, increasing the efficiency of drug development is highly desired, due to many factors, as described below.

Growing constraints for clinical development
In recent years, the environment for clinical research, in particular the development of new drugs, has changed considerably. Growing constraints like time, costs and resources play a major role. New regulatory requirements have been set up. Addressing the needs of payers poses an additional hurdle for successful market entry. The increased constraints for clinical research as listed below and the fact that a lower number of new drugs are entering the market despite higher costs both call for improvement in the efficiency of clinical research, which is considered to be the main thing driving harmonisation and standardisation efforts.

Costs, complexity, feasibility
The size of drug development programs has considerably increased in terms of patient numbers as well as the costs per patient in the trials. The increased size of clinical development programs may be attributed to increased safety awareness for doctors, patients and regulatory bodies (e.g., cardiac safety trials in diabetes). Technical advances, such as biomarkers and imaging techniques, have substantially helped to profile drugs and to predict long-term outcomes more reliably. However, the more data generated, the more complex and expensive the trials are.

Time to market
Still, the time to market is an important factor which, in the case of early entry, can make a drug a success – or, in the case of delayed entry, causes development costs to increase while revenues that can be gained within the patent or marketing exclusivity periods are lessened. Even for well-designed trials, recruitment problems have a major influence on the timely conduct of clinical trials, and in many cases, it is very difficult to recruit patients due to many ongoing trials. Getz et al.[1] found that over 90% of clinical trials experience delayed enrolment[a]. With regard to study activation, Dilts et al. found a median time of 602 days [2] to process Phase III clinical trials at the Cancer Therapy Evaluation Program (CTEP), i.e., from concept submission to CTEP to trial activation.

Acceptability of results by stakeholders; cost efficiency of new medications
Due to the increased necessity for cost control of payers, the necessity of demonstrating the cost effectiveness of a new treatment and/or being clinically superior compared to existing treatments is becoming more and more important. Gaining adequate reimbursement prices is considered a fourth hurdle for market entry alongside quality, safety and efficacy (see also Chapter 4.8). Without adequate reimbursement, it is unlikely that expenses of drug development will be recovered.

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[a] Ref.[1] *As currently conducted, RCTs are inefficient and have become more complex, time consuming, and expensive. More than 90% of industry-sponsored clinical trials experience delayed enrolment. In a study comparing 28 industry-sponsored trials started between 1999 and 2002 with 29 trials started between 2003 and 2006, the time from protocol approval to database lock increased by a median of 70%.*

Regulatory aspects
International harmonisation of regulatory requirements continues to progress (see Chapter 4), but on a high level. New requirements, e.g., regulations for paediatric research [3] or to address potential safety concerns such as the requirement for cardiac safety studies for antidiabetics [4] have been set up. There are an increasing number of post-marketing study obligations, mainly to detect rare safety signals.

4 Regulatory framework in the context of clinical research

For the purpose of this thesis, only a rough outline is given containing requirements related to the conduct of clinical trials.

4.1 International guidelines

For most of the new drugs that are developed, marketing in all major markets across the world is targeted to increase the chance of obtaining a return on investments given the high costs of development. Creating a development program that fits the needs of major regulatory authorities throughout the world is a fundamental goal when designing a clinical development program. The desire to avoid redundant testing is the main driver behind the harmonisation of requirements and has led to the founding of ICH, which has established and continually updated a set of guidelines accepted by EU, US and Japan. Redundant testing must be avoided not only for efficiency of research but also for ethical reasons.
Although its guidelines do not have the status of being legally binding, following the ICH guidelines is highly recommendable. Not only do authorities in the EU, US and Japan regard them as a primary reference, but in many other countries they enjoy similar acceptance.
For all aspects of Good Clinical Practice (GCP), ICH E6 [5] is the primary reference. ICH E8, "General considerations for clinical trials"[6], contains general considerations in terms of clinical trial design and clinical development. Further ICH guidelines pertaining to clinical development address ethnic factors, dose-response studies, clinical safety, statistical considerations, the evaluation of cardiac repolarisation and paediatric development. However, specific requirements for clinical trial applications and the format and content of study protocols are not harmonised on an international basis.

The WHO and other international organisations have also contributed to the harmonisation of regulations by issuing guidelines, e.g., the CIOMS [7] guidelines on ethics, nomenclature, and the safety of medicinal products.

4.2 EU legislation and guidelines

In the EU, the "GCP" 2001/20/EC directive and related guidance has led to significant harmonisation of requirements for the authorisation of clinical trials, in particular ethics and competent authority approval. The main areas in which requirements have been harmonised in the context of clinical research are the timeframes for CTA review and approval, notification and reporting requirements, general GCP and GMP provisions, and the concept of amendments (to distinguish between substantial/non-substantial amendments).
The mandatory directives are supplemented by many EU guidelines, covering a broad range of aspects for drug development, e.g., numerous disease-specific guidelines for the clinical development of new drugs. In particular, provisions and recommendations are made regarding the design of confirmatory clinical studies. The level of detail for these provisions on clinical trial design is relatively low and requires adaptation for each respective circumstance. As with every guideline, deviation from these guidelines is allowed if properly justified.

4.3 US legislation and guidelines

In the US, clinical research under an Investigational New Drug application (IND) is regulated in the code of federal regulations (CFR)[8], where regulatory requirements are laid down, such as the requirements for IND documentation, reporting, new protocol submission and IND (supplements) updates (CFR 21 Part 312). While applications in the EU for clinical trial authorisations are submitted for each study in each concerned country with a full set of required documentation, the IND documentation is updated subsequently as soon as new study results become available, i.e., independent of individual new protocol submissions. Individual authorisations are not issued for each study, but FDA can issue clinical holds at any time.

As in the EU, guidelines are issued by this authorising body in addition to the regulations, and there are also disease-specific guidelines regarding clinical development of drugs in specific instances.

4.4 Scientific advice procedures

The FDA traditionally focuses on giving advice to manufacturers regarding drug development and aims at continuous dialogue with the sponsor during the IND phase. In meetings with the FDA, typically in a pre-IND or end-of-phase II meeting, specific comments are made to the proposed or current development program, as are requests for further development. In the Special Protocol Assessment procedure [9], the applicant can receive input on a (draft) protocol and even obtain (binding) advice with regard to potential labelling, which can be obtained with the study in planning.

The EMA and many national EU agencies have formal scientific advice procedures, providing the applicant with input on questions with regard to clinical development and also with specific protocol assistance. Scientific advice is non-binding for both parties, although following it is highly recommended.

4.5 Ethical principles

Conflicts between scientific goals and the need to protect the rights, and welfare of subjects enrolled in a trial, result in the central ethical tension of clinical research. Decisions must always favour the rights and welfare of human subjects rather than scientific objectives[10]. Such general ethical principles are the acknowledged all over the world. The Declaration of Helsinki [11] is a cornerstone, and complying with it is obligatory in many countries. Similarly, the Belmont Report [12] is the basis for ethical principles in many countries, in particular in the USA. A detailed guideline of ethical principles in biomedical research has been issued by CIOMS [13]. Specific documents for paediatric research have been issued by the European Academy of Paediatrics [14]. In reference [15], further sources related to UN are cited[a]. Despite much general advice, detailed guidance regarding ethical assessment procedures is lacking, as are guidelines for handling of specific cases.

4.6 Medical treatment guidelines

Clinical research is closely interrelated with current medical practice and therefore must consider existing medical treatment guidelines on a local and, in many cases, an international

[a] Ref.[15]: *United Nations' Convention on the Rights of the Child, the Charter of Fundamental Rights of the European Union (2000), the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997), the International Declaration on Human Genetic Data (UNESCO, 2003), the Universal Declaration of Human Rights of 1948.*

level. These guidelines do not cover novel (non-approved) therapies. They are not legally binding.

4.7 Pharmacopoeia

National or Regional Pharmacopoeias are important reference documents for the testing and quality of established medicinal products. Also, they contain standard test procedures or provisions for specific dosage forms.

4.8 Health technology assessment (HTA)

Setting the price of a medication and deciding about reimbursement by national payers is a national responsibility and is not addressed within the framework of pharmaceutical legislation. Although not being a regulatory topic such as quality, safety and efficacy, it poses in fact a hurdle for successful market entry and may have similar influence on clinical studies as regulations have. Nowadays, decisions on pricing and reimbursement involve cost-efficiency analyses (health technology assessment) before a price is granted. In most cases, comparative trials in which the drug is tested versus the gold standard in the therapeutic area are needed. Specific endpoints for the economic assessment of an intervention need to be included. However, it is to be considered that the trial conditions may not reflect normal medical practice as, for instance, the patient population is restricted or the number of medical treatment options has been limited [16].

4.9 Publication requirements for protocol information and trial results

In line with the requirements of the declaration of Helsinki, the industry organisations IFPMA, EFPIA, JPMA and PhRMA have committed themselves to disclose clinical trial information via trial registries, and in addition to publish phase III clinical trial results in scientific journals [17,18]. Registries commonly used are www.clinicaltrials.gov, www.clinicaltrials.ifpma.org and the WHO clinical trials platform http://www.who.int/ictrp/en/. In the US, for certain submissions, certificate of compliance with the requirements for publication of trial information (section 402(j) of the Public Health Service Act) is mandatory [19].
As required by the Commission communication [20], sponsors of trials in the EU are obliged to send in a summary of trial results to the authority within one year after the end of a trial. For paediatric trials, this time frame is six month only. Without further input from sponsors, EMA publishes information from European clinical trial applications, i.e. a part of the EudraCT database, via the EudraPharm[a] server. Besides structured clinical trial information on all trials, it has been announced that clinical trial results will be published in a similar way.

4.10 Overall impact of regulations on design of clinical studies

The regulations above build a framework of individual requirements and recommendations for clinical drug development. So far, the regulations with the largest relevance for clinical trial design are disease-specific guidelines such as those issued by EMA or FDA. In general, such guidelines do not stipulate specific trial designs but instead propose basic clinical trial design characteristics like randomised controlled trials (RCT), minimum study duration, the type of endpoints to be used or the need for stratification. Furthermore, a guideline is not binding if deviations can be justified.
The publication of trial information is considered to be of high importance for designing new trials, in particular if results are published in detail. Publishing of trial results is poorly

[a] See http://eudrapharm.eu/eudrapharm/; see also EudraCT homepage https://eudract.ema.europa.eu/

standardised hitherto, is often not adequate, and reveals discrepancies to study protocol information [21][a] [22][b].

5 Clinical standard protocols

As defined in the Merriam Webster dictionary, a standard is *something established by authority, custom or general consent as a model or example* [23]. For the purpose of the current thesis, a protocol standard is defined as a clinical trial protocol established or acknowledged by the regulatory authority or further issuing body, defining the main characteristics but not necessarily all clinical design characteristics for the purpose of providing guidance or making the use of such standard protocol mandatory. A protocol standard must properly definition its scope, which may be an indication, the purpose of the trial, the type of drug, the type of intervention, etc.

5.1 CTEP protocol templates

The Cancer Therapy Evaluation Program (CTEP) is a publicly funded organisation within the National Cancer Institute / US National Institute of Health (NIH) involved in the coordination of oncology clinical trials. CTEP has developed two protocol templates for Phase I studies to test agents in patients with Advance Malignancies and varying degrees of Renal or Hepatic dysfunctions [24]. Notably, there are two FDA guidelines addressing the pharmacokinetic aspects of such studies [25,26].

The templates contain many predefined elements and can hence be considered standard protocols. With around 70 pages, the level of detail is rather high and the extent of text is close to the final protocol. Examples are definite criteria specifying hepatic and marrow function as inclusion criteria, the exclusion criteria, stratification requirements and a precise definition of dose-limiting toxicities. Protocol writing is further facilitated by alternative standard texts which can be selected or de-selected. In the templates, proposed informed consent text is also included.
Notably, CTEP is not a regulatory authority, and even within CTEP, the use of templates is suggested but not binding. The template is supplemented by many guidance documents.
On the webpage, there is no information as to which trials have already used this template.

Obviously, CTEP wishes to accelerate the process of protocol generation for types of studies which frequently are conducted. A well-established study design is chosen and best guidance practices are applied in order to support sponsors in setting up their studies, and to support investigators in the best possible way.

5.2 EU Standard Paediatric Investigation Plan (PIP) for non-adjuvanted or adjuvanted pandemic influenza vaccines during a pandemic

The EMA published the document “Standard paediatric investigation plan for non-adjuvanted or adjuvanted pandemic influenza vaccines during a pandemic”[27] in June 2009 and updated it in March 2010. This document defines a standard set of data to be included in PIPs when submitting an application during an emergency situation (WHO phase 5 and 6).

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[a] Ref.[21]:*We showed that the eligibility criteria published in trial reports do not adequately reflect those prespecified in the study protocols.*

[b] Ref. [22]: *Full protocols remain the most comprehensive source of methodologic information and should be made publicly available.*

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Specific requirements for non-adjuvanted vaccines or vaccines containing a known adjuvant and vaccines containing a new adjuvant are contained. Specific measures to be proposed for long term follow-up of potential safety issues are provided as well.

Although it is relatively short (2 pages), the PIP defines design characteristics, such as

- Prospective open-label, single-arm study, without controls
- Population: (healthy) Children from 6 months to less than 18 years, at least 240 total participants (details regarding subsets are given).
- Vaccination provisions (two initial injections 21 days apart; booster injection 6 or 12 months later)
- Sampling provisions
- Primary endpoint (immune responses after second injection) with details as to when it should be evaluated
- Safety follow-up measures

The standard PIP is not a complete protocol, but lists "key binding elements" which are the criteria used by PDCO to evaluate paediatric protocols in that area[a]. As with guidelines, justified modifications in specific cases are always possible. However, it is stated that this may have consequences for the assessment timelines.
The PIP makes reference to a CHMP guideline [28].

There are some PIPs which underwent modification since the release of the PIP standard, implementing elements of the PIP

- Pandemic influenza vaccine (H5N1 Vietnam) (split virion, inactivated, adjuvanted)), (EMEA-000160-PIP01-07-M01)[b]
- Pandemic influenza vaccine (H1N1 Vietnam) Arepanrix (EMEA-000687-PIP01-09-M02)[c]
- Pandemic influenza vaccine (H1N1 Vietnam) Pandemrix ((EMEA-000725-PIP01-09-M02) [d]

The standard PIP was obviously introduced to harmonise the requirements, such as the requirement to conduct studies below 6 months of age, which can be waived and below 2 months of age should be waived[e]. It was issued after experience with the swine flu vaccination pandemrix, where there was insufficient data to evaluate the risk-benefit for children.
New vaccines that may be produced in an emergency situations will benefit from plannable development and quick agreement on the plans. The use of a standard PIP rather than a guideline has advantages as in pandemic situation, the data requirement necessary needs to be defined very specifically; requirements that are too extensive would prolong the time needed to

[a] Ref. [29]: *the standard PIP is not a guideline, nor a complete protocol; it contains only the so-called "key binding elements", which are the measures and timelines on which compliance check will be performed prior to validation of the MAA or the variation application. Consequently, elements that are not cited in the study tables (e.g., the exclusion criteria), may remain at the discretion of the applicant.*
[b] http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500005874.pdf
[c] http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500017418.pdf
[d] http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500017419.pdf
[e] Ref. [27] page 2 and 5: *A waiver for newborns and infants from birth to less than 2 months should be requested. A waiver in children 2 to 6 months of age may be requested.*

make the data available, and it would be fair to impose the same requirements to all available vaccines.

5.3 EU: Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy (SIT)

In March 2010, the EMA Standard PIP [29] concerning the testing of allergen products for specific immunotherapy was established. The document contains specifications for three PIP trials, two long-term trials for allergic rhinitis / rhino-conjunctivitis (one for subcutaneous (SCIT) products and one for sublingual products (SLIT)), and one six-month trial for insect venom allergy. The focus of this evaluation is the PIPs for allergic rhinitis / rhino-conjunctivitis.

5.3.1 Legal basis for allergen products for SIT

Kaul et al. give an overview of the regulatory context of allergen products [30]. The therapeutic concept is used since about 100 years; many products on the market have a named-patient basis[a], with little data available supporting the efficacy of these medications, also supported by an article from Gödicke and Hund [31][b].
Allergens are defined as immunological medicinal products by Directive 2001/83/EC[32][c]. According to Article 5, for products on a named patient basis, exemptions from the obligation to comply with the provision of the directive can be legalised by national authorities[d]. Such products are normally not manufactured using industrial processes, which is the main argument for the exemption. Products involving industrial processes, according to Article 2 (1) of this directive, would require a marketing authorisation.

In Germany, such an exemption exists for allergen therapy products in the Arzneimittelgesetz (Medicines Product Act), Article 21 1g[33][e]. However, the "Therapieallergeneverordnung" (TAV)[34] which came into force 14th November 2008, lifted this exemption for a subset of immunotherapy products with a high prevalence (grass species of the Poaceae family, early flowering trees, house dust mites). Consequently, manufacturers had to submit a marketing authorisation application for such products by 1st December 2010. Another obligation imposed by the TAV is the obligation for batch testing by the German competent authority. Klinkowski elaborated on the consequences of this law for the German allergen manufacturing industry [35].

The reason for introducing the TAV was to apply the same criteria for safety, quality and efficacy as for products already approved and tested in this field [36]. A patient's health status during therapy may deteriorate, and the possibility is mentioned that individually manufactured

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a Ref. [30] *Until the late 1980s, some products for SIT obtained national marketing authorizations (MAs) but the majority of products were used as Named Patient Products (NPPs)*

[b] Ref. [31] *Compared to areas like cardiology, specific immunotherapy was conducted based on considerably weaker scientific evidence*

[c] Ref.[32]Article 1 (4): *Immunological medicinal product: ….b) allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.*

[d] Ref. [32] Article 5(1): *A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.*

[e] Ref. [33] Article 21: (2) *A marketing authorisation (Zulassung) shall not be required for medicinal products which: "… "1g: are therapeutic allergens manufactured to order for individual patients*

therapy allergens may have more frequent adverse events, in particular serious adverse events, as compared to approved therapies. Anaphylactic reactions occurring after SIT administration pose a serious threat in allergen medications [31][a]. In line with this, in the background section of the PIP [29] it is stated that lifting the exemption from having regular market authorisations was necessary in order "*to avoid a serious risk to public health"*.

Notably, the status of such therapy allergens is not harmonised in the EU. Still, there are many products on the market on a named-patient basis, such as those in France [30,37][b]. Obviously, in France, such products do not need to obtain marketing authorisation, and need to demonstrate quality only.

Recombinant allergen products have been developed which, in comparison to natural products, can be better defined and thus promise more predictable results. As these are manufactured by biotechnological processes, they fall under the mandatory scope of Regulation 726/2004 Article 3 (Annex I)[38] and must be authorised by the EU centralised procedure. So far, no recombinant allergen product has been approved.

5.3.2 Content of standard PIP for allergen SIT in allergic rhinitis / rhino-conjunctivitis

The content of the PIPs are closely related to an EMA guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases released in 2008 [39] ('SIT guideline'). Gödicke and Hundt appreciated this guideline in general to support predictable drug development [31][c]. However, the authors also made some critical comments, such as remarks on the fact that its clinical relevant improvement has not been defined. They expressed their concerns that using the symptom medication score (SMS) as primary endpoint, as recommended, will lead to much larger trials than for (previous) trials with provocation tests, and the assessment of primary endpoint will not be possible if there is insufficient allergen exposure in the test time window. Also, the high amount of effort to document exposure to the relevant allergens has been criticised.

In Chapter 4.4 of the SIT guideline, the requirement to test the product in children as well is mentioned, but only little guidance with regard to designing the studies of children is given, such as the statement that "*recommendations reported above remain valid for studies in paediatric populations"* and a reference to the validated quality-of-life questionnaires available for allergic rhinitis or asthma. Notably, an EMA guideline on production and quality issues of therapy allergens is also available [40].

The standard PIP, like the PIP for pandemic influenza vaccines (see Chapter 5.2) uses the concept of "key binding elements".

Similarly to the SIT guidance, the standard PIPs for Allergic Rhinitis / Rhino-Conjunctivitis do not request a specific primary endpoint to be used, but requests to use a *well defined primary endpoint (taking in account both symptom and medication).* In the standard PIP, there are

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[a] Ref.[31] page 1503: *The therapeutic concept almost disappeared from clinical practice in the United Kingdom when in 1986 the British Committee for Safety of Medicines (CSM) reported a series of deaths caused by subcutaneous SIT. This report contained 26 deaths because of anaphylactic reaction*

[b] Ref.[30]: [In France,] *The exemptions of Art. 5 of the Directive 2001/83/EC were implemented by a special decree. Clinically relevant allergen sources were defined by a working group by means of published evidence for efficacy in SIT. Only products containing extracts of these allergen sources are permitted for marketing. These preparations have to demonstrate an adequate pharmaceutical quality.*

[c] Ref. [31] A *breakthrough with regard to guidance, harmonization and transparency in the conduct of clinical trials in SIT*

several areas where the level of detail is higher than that in the SIT guideline. Main additions compared to the guideline text for allergic rhinitis / rhino-conjunctivitis are:

- The required study duration is 3 years of treatment and 2 years of follow-up, while the SIT guidance contains several options.
- The obligation to establish an external data safety monitoring board
- The use of interim data for submission data is strongly discouraged
- Age of study population more detailed; in particular, at least 45% of patients must be between 5 and less than 12 years of age
- A list of main exclusion criteria
- Superiority versus placebo must be demonstrated (the guideline leaves it open as to whether placebo or another comparator is chosen)
- The minimum level of symptoms prior to randomisation is now defined as at least moderate level in 2 symptom categories
- Participating sites must be experienced in performing skin-prick testing in children, and the same methodology is applied in all participating sites
- Sample-size calculations are to be made, with at least 80% power and a (multiple) type I error rate of 0.05 (two-sided)
- Guidance on the statistical analysis is given (in line with ICH E9)
- The rescue medication section is more detailed than in the SIT guideline

To reduce the number of studies necessary, the applicant is asked to select a reference product, i.e., one member of a "homologous group", which is tested in adults and children. If comparable results can be shown in both studies, extrapolation is considered feasible. In that case, short-term trials in children are sufficient for other allergens which demonstrated long-term efficacy in adults. Nevertheless, as stated in section 2 (Homologous group), it is necessary to submit a PIP for each product within a homologous group, cross-referring to the data / studies in the PIP of the representative allergen.

5.3.3 Use of the PIP standard for allergen therapy in allergic rhinitis / rhino-conjunctivitis

A large number of PIP applications were to be processed upon change to the regulations in Germany (see above). To date, 75 PIP decisions for allergens have been made under these standard PIPs, all with (long-term) study obligations [53]. All of these were for the indication Allergic Rhinitis / Rhino-Conjunctivitis, with no PIP for insect venom allergy so far. All these are pertinent to allergen extracts from natural sources.

In February 2010, a study in conformance with the standard PIP testing a grass tablet (Grazax) versus placebo was initiated[41]. Allergy and asthma symptoms are being evaluated. 1000 patients are planned to be recruited. The entry in clinicaltrials.gov was made in February 2010, but as of August 2011, recruitment still has not been started, and no new information had been provided up to January 2012. Notably, a study with Grazax in adult patients [42] had also three years treatment and two year follow-up period. However, the 5-year follow-up revealed no longer significant results in medication score, probably because the trial was originally planned as 1-year trial and a lower number of patients (354) entered in the extension phase[a].

[a] Ref. [42], Section 5.1: *The trial was initially planned as a 1-year trial. 546 of the original 634 subjects completed the first year. The trial was extended with 2 more years of treatment and 2 years of follow-up. At inclusion into the extension, 351 subjects chose to enrol (74 were not offered enrolment due to closure of sites), and these were a representative subgroup of the original 634 subjects.*

Other than that, no further initiated trials conformant to the standard PIP are known to the author.

5.3.4 Legal status of PIP standards and PIP decisions

With regulation 1901/2006/EC[3], the paediatric committee has been enacted for the scientific assessment and agreement on paediatric plans and for the system of waiver and deferrals. This regulation is directly valid in all EU member states. According to Article 7, unless a waiver or deferral for paediatric studies is issued, applications for new drug submissions are only valid if they contain the results of studies conducted in accordance to the agreed PIP[a].

Once the criteria as mentioned above are fulfilled and a decision has been made by EMA, a paediatric investigational plan is legally binding, and non-compliance will lead to an invalid marketing authorisation. The standard PIP as issued by EMA/PDCO, however, is not legally binding, as PDCO has no authorisation to make legally binding decisions. It is to be considered as a guideline.

As stated in the standard PIP text, PDCO will perform a compliance check on the elements of the standard PIP versus the applicant's PIP, which indicates that PDCO leaves only little room for negotiation at this point. Once the PDCO decision is transferred to EMA, EMA will issue a draft decision and there is, within 30 days after receipt, the possibility to file a request to re-examine the decision, together with written detailed grounds [43,44]. However, significant changes to the previous plan cannot be part of the re-examination request. PDCO will adopt a final opinion by day 30. EMA performs a check whether the decision is legally acceptable, once this is given, the decision will be made legally binding.

With a standard protocol, detailed requirements can be set up which become quasi-obligatory for a range of products, much more detailed than a guideline.

Obviously, applicants did not object to the PIP. There were tight timelines to file the market authorisation applications, and it is not certain whether objecting to a PDCO PIP request would have been successful in the end. Certainly, the amendment of PIP proposals will still be possible in the future, e.g., the addition of further endpoints.

The question remains in which EU countries the PIP decision, such as the obligation to conduct studies in children, is valid. Certainly, the PIP is valid for potential market authorisations of such drugs in Germany or any other country in the EU in which an application would be filed for market authorisation. However, in a country like France, because of its different legal status, there is no obligation to file marketing authorisations. Hence, a manufacturer may continue to market the product only under a named-patient-basis in such countries.

The study conducted according to the PIP will certainly be considered to be a pivotal study, i.e., a study which – if the outcome is positive - will be the basis for a claim like "long-term efficacy", or even "curing allergy". It is unclear whether or not a successful trial will

[a] Ref. [3], Article 7: *An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes,… one of the following: the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan; a decision of the Agency granting a product-specific waiver; a decision of the Agency granting a class waiver pursuant to Article 11; a decision of the Agency granting a deferral.*

automatically lead to such a claim, as in general, two pivotal trials are necessary to get a claim. The SIT guideline [39] also does not specify this; a scientific advice should clarify this in order to avoid wrong expectations with regard to the label. Assuming that the results of the long-term study in adults and the study in children are similar, i.e., the possibility for extrapolation has been proven, one can argue that these studies are two pivotal studies and fulfil the criterion above, although conducted in different patient populations.

Consequences of a negative outcome or indifferent results are unclear. Basically, the paediatric regulation enforces the conduct of studies and presentation of results thereof, but a positive outcome of the study is not necessary in order to fulfil the obligations of the paediatric regulation. As the long-term efficacy of allergen SIT products in children is considered crucial for this group of patients, a negative outcome will probably lead to a restriction of the marketing authorisation to adults. Although a negative results can be considered beneficial as it avoids exposure to a non-effective medication. An indifferent result – e.g. due to a high drop-out rate, or too high variability in endpoints - would have detrimental effects for the marketing authorisation holder; Once such results are published (which is obligatory, see Chapter 4.9), a negative or indifferent outcome will be a hurdle for successful market penetration, and also payers are expected to grant not an attractive price in this case.

5.3.5 Rationale for applying the paediatric regulation to established SIT products

All PIPs for SIT products have been issued for established products, most of them being on the market for many years.

According to Article 9 of legislation 1901/2001/EC [3], Article 7 is not applicable to well-established products and thus, similarly to generic products, these products does not have to comply with the paediatric regulation requirements. As outlined by Klinkowski [35], even if allergen SIT products could be regarded as well-established products, it is unlikely that such an application according to 2001/83/EC Art. 10a[a] for well-established use products, would be successful. High hurdles, such as the lack of standardisation of products and non-availability of published results of studies, have been identified as reasons. As there are no generic products possible due to different strengths and variants in manufacture, it seemed that a full ("new") application is the only alternative.

However, one could challenge whether legislation 1901/2001/EC [3] is applicable to those SIT products which had the named-patient status at the time when this legislation came into force; obviously, the paediatric regulation has not considered cases where a change in legal status leads to the submission of a "new" marketing authorisation for established products. There are different argumentation lines one with the intended scope (1.), and one with the wording "authorised".

1. In conformance with the introduction of legislation 1901/2001/EC, the intent of the paediatric legislation is to apply obligations to "new" products and those covered by a

[a] Ref. [32] Article 10a: *By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I. In that event, the test and trial results shall be replaced by appropriate scientific literature.*

patent or supplementary protection certificate[a]. It is not further defined what "new" means. However, one would consider that a criterion for being "new" is the duration and extend of their medical use, similarly to the criteria which are to be applied for well-established use. Hence, most of the allergen SIT products would not be considered as "new", and, if not covered by a patent or SPC, would not fall under the (intended) scope of the paediatric legislation.

2. In Article 7, the obligation to provide paediatric studies is linked to the authorisation status at the time the paediatric regulation entered into force. Only products *not authorised in the Community at the time of entry into force of this Regulation* fall under the paediatric regulation. It is assumed that most of the products on the market, for which PIPs have thus far been issued, have the status of a named-patient basis at the time when the paediatric legislation came into force. The question is whether "authorised" as stated in Article 7 includes the named-patient status or not.

   There are cases such as homeopathic products which are on the market without a "market authorisation", but these are nevertheless "authorised" by other means.

   Also, the wording in Article 126a of Directive 2001/83/EC suggests that medicinal products without a marketing authorisation in a specific country that are placed on the market for public health reasons are still to be considered "authorised"[b]. The (temporary) allowance for distribution of a hitherto non-authorised product by a member state is also named "authorisation" according to Article 5 of Directive 2001/83[c]. In analogy to that, allergen SIT products on the market which have been exempted from the need to have a marketing authorisation can still be considered as "authorised", and if this was the status at time of entry into force of the paediatric regulation, this regulation would not apply to them.

   It seems that the terms "authorisation" and "marketing authorisation" are not harmonised in the EU. In the Irish medicinal product legislation [45] 'marketing authorisation' means an "authorisation granted by the Board in accordance with these Regulations in respect of a medicinal product and includes an authorisation granted in accordance with Article 126a of the 2001 Directive, a product authorisation, a parallel import licence and an authorisation granted in accordance with Regulation 11". Given the evidence from various examples above, it can be assumed that the meaning of "authorised" includes various types of autorisations, and is not restricted to authorisations in full compliance to EU Directive 2001/83/EC.

In summary, both the intention behind the paediatric regulation of only applying to new products (in a common sense of being "new"), as well as the interpretation that the allowance for such products on the market with 'named patient basis' can be considered to be a type of

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a Ref. [3] Introduction (11) *It is necessary to introduce a requirement for new medicinal products and for authorised medicinal products covered by a patent or a supplementary protection certificate to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having obtained a waiver or deferral,...*

b Ref. [32] Article 126a: *In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.*

c Ref. [32] Article 5a: *Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.*

'authorisation', indicates that the paediatric legislation is unlikely to be applicable for long established allergen products.

Besides the question as to whether the paediatric regulation is to be applied or not, one would expect that manufacturers want to include children in the marketing authorisation application of allergen SIT products, and that they adequately test safety and efficacy in this population. These products are frequently used in children, as there are hints that efficacy is better in children than in adults.

5.3.6 Discussion on the request to conduct long-term studies

Fostering evidence-based medicine is in the interest of patients and payers. In light of new treatments such as the SLIT and recombinant therapies, there was a need to introduce more stringent regulation in this therapeutic area in order to not expose patients to ineffective treatments or treatments with an unduly high level of side effects. The scientific rationale for conducting a long-term paediatric study for SIT products in allergic rhinitis / rhino-conjunctivitis is the unknown magnitude of the effect of SIT products and possibly the differing safety profile between children and adults.
In particular, children are expected to have greater benefits from such therapies for the development of allergic asthma [29][a].

Safety
The safety profile of established products is well known from post-marketing experience. The occurrence of rare but severe side effects such as anaphylactic reactions is the main threat of SIT (in particular SCIT) therapy. Still, for SCIT products, there is a relatively low risk for severe adverse events[b] [46].
Due the rarity of these severe adverse events, it is unlikely that there are sufficiently high numbers in clinical trials to make a statistical analysis for these events, if they even occur at all. Even if there would be enough events to prove a significantly higher risk in the verum group as compared to the placebo group, this would confirm what is already known from SCIT products. The plan to conduct two trials per product (in adults and children) is unlikely to allow any conclusion to be drawn as to whether there is a different safety profile with regard to these severe events in adults and children.
Also, it is unlikely that information from different trials with different products can lead to the conclusion that products have a different safety profile unless products are compared against each other within the same trial.

Severe anaphylactic reactions are expected to occur right after administration. Hence, a long-term trial is not expected to provide additional information compared to a short-term trial with regard to anaphylactic reactions.

The use of post-marketing data for answering safety-related question was recently demonstrated when a request regarding the safety of aluminium-containing allergen

[a] Ref.[29] introduction, page 2: *The basic pathophysiologic mechanism of type I allergies, be it seasonal or perennial, is not fully understood but is assumed to be identical in the adult and paediatric populations. However, while SIT is expected to act in the same way in children and adults, the magnitude of the effect and the safety profile could differ. In addition, children are believed to derive potentially greater benefit from immunotherapy to inhalant allergens, due to the preventive effects of subcutaneous specific immunotherapy (SCIT) on the development of allergic asthma*.

[b] Ref. [46] *Injection immunotherapy has a known and relatively low risk of severe adverse events. We found no long-term consequences from adverse events*

preparations was answered by the Safety Working Party [47]. An analysis was undertaken of post-marketing data from a total of 2755 cases over the course of 21 years (from 1988 to 2008) where allergen preparations had been administered. Based on that, the conclusion was drawn that there were no concerns regarding allergen preparations that contain aluminium. It was recommended that PK studies address outstanding questions about the exposure.

In summary, a long-term trial with placebo control is not expected to provide further information on the drug's safety as compared to short-term trials and/or evaluation of post-marketing data. Comparative analyses across long-term trials, e.g., adults versus children or one product versus another are unlikely to be robust enough to draw conclusions.

The paediatric regulation mentions the necessity for long-term follow up on possible adverse effects, and the applicant should indicate how this is addressed[a]. However, the regulation foresees post-marketing studies or the obligation to implement a risk management system in case where there is a specific concern, i.e. after the approval.

Efficacy

Also, it is not questionable that the therapeutic concept of allergen therapy works. Radulovic et al.[48] reviewed trials conducted in SLIT and, although not shown in each of the 60 trials, a meta-analysis confirmed the overall efficacy and favourable safety profile. A similar survey for SCIT was issued by Calderon in 2009 [46]. However, these were mainly short-term trials, and only a few were conducted in children. Some therapeutic approaches such as the solutions had insufficient evidence of efficacy at all.
Thus, the lack of evidence for efficacy in long-term setting at least for some product groups is the main driver to request randomised placebo-controlled clinical studies for allergen SIT products.

The Preventive Allergy Treatment study (PAT) [49,50] evaluated the effect of SIT on the development of asthma and the level of its symptoms and found that after three years' treatment time and two years' observational time, beneficial effects on symptoms and the occurrence of asthma were to be observed. Also, these differences were maintained after five additional years. Obviously, this study made a major contribution to the design of the current standard PIP, serving as a proof that such long-term studies as requested by PDCO are generally feasible.

However, even if superiority versus placebo can be demonstrated in a RCT, it is not expected that the results of different studies can be directly compared, due to the variability of allergen exposure and the subjective character of endpoint assessment. Hence, the major question as to whether a drug has better or worse efficacy than another one cannot be answered even when conducting many similar trials. If long-term studies in adults are available and show good efficacy, it is assumed that efficacy in children would be even higher than in adults[b]. Hence, the rationale for requesting long-term studies in children in this situation is rather weak, considering that it is unlikely that results will be worse than in adults.

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[a] Ref.[3], Introduction (24): *where there is a particular cause for concern, the applicant should submit and implement a risk management system and/or perform specific post-marketing studies as a condition for the granting of the marketing authorisation.* (see also Article 34 (2.))

[b] Ref. [29] introduction, page 2: *...children are expected to have greater benefit of such therapies on the development of allergic asthma*

The rationale to conduct such trials in children will differ, depending on the amount of clinical data available for a specific product and whether there is sufficient similarity to other products who have shown long-term efficacy. For the majority of established products, it is expected that there is insufficient reason to make a long-term study obligatory. Conducting short term trials and using post-marketing data and follow up of patients, e.g., of asthma development over a long time will, in many cases be similarly useful, as a long-term placebo-controlled RCTs. Long-term studies comparing different treatments within one trial are expected to be of higher value for physicians compared to separate placebo-controlled studies.

5.3.7 Discussion on the reasons to use a standard PIP

A high number of PIP applications were expected after new regulations came into force.

In 2010, in order to cope with the expected huge number of PIP applications, a standard PIP for these products was established. Whereas 178 market authorisation applications were expected, the number of PIPs was reduced to approximately 80 due to the possibility of testing only representative products of a homologous group [51].

As issued on the PDCO website, in the Nov. 2010 meeting [52], 70 PIPs were approved for allergen products; the PIP decisions (now 75) are published on the EMA webpage [53]. A detailed overview is also provided by Klinkowski [35].

As it can be seen from the processed PIP applications, the standard PIP has been proven to be an efficient way to process many PIP applications in a short time.

5.3.8 Discussion on specific details of the standard PIP

Although acknowledging the benefit of the standard PIP in supporting evidence-based medicine, it is worth highlighting several aspects of the protocol, which may have impact on the scientific value and ethical acceptance of studies conducted with such study design.

Risks of trial failure and feasibility issues
A standard PIP study is associated with a relatively high risk of trial failure. If there is insufficient pollen exposure due to weather influence in a given year, it will be impossible to demonstrate the effects of the medication. Also, false negative or false positive results will be obtained when abnormal pollen exposure is seen in the baseline period. Children are expected to have a lower discipline for regular study visits and compliance with the procedures. Especially in puberty, when parents transfer obligations or decisions regarding the study to children, a high drop-out rate or protocol violation rate is anticipated which may cause bias in the study results.

In RCTs, the statistical significance is still the decisive criterion in drawing conclusions on efficacy. Not reaching statistical significance in the primary endpoint has to be judged as a failed study. The consequence for a company would be that product approval is endangered. Furthermore, according to the concept of the standard PIP, products of the allergen group will have to undergo long-term clinical studies. Failed PIP studies, once published, may contribute to a loss in reputation of the product.

Blinding
It may not be possible to blind the study medication, either for the patient or for the investigator; it is known that s.c. administration of allergens causes local side effects. The absence of these effects is an indicator that a placebo has been given, which may cause a bias in the assessment of symptoms. The SIT guideline [39] proposes using histamine in order to keep the blinding. Besides ethical concerns, histamine has been shown to display non-reproducible results [54].
Also, from a technical point of view, it can be challenging to produce a placebo which matches the verum fully with regard to colour, viscosity, opacity and other visual and physical characteristics. Otherwise, it is likely that the investigator gets unblinded.

Primary endpoint selection, validation
For the primary endpoint, the standard PIP requires addressing symptom severity as well as a medication score, and the exact definition of the primary endpoint is left to the sponsor. For symptoms, no validated score exists. It is questionable whether a chosen endpoint can be validated in advance of the study; it is probable that further study results must be available to validate this endpoint. Using a non-validated endpoint poses a risk to the acceptance of results later on.

Primary endpoint assessment procedure
The evaluation of symptoms is left to the "parent or the patient, depending on the age groups". The PIP states that it must be ensured that the symptoms are always rated in the same way throughout the study, but no information is given how this can be achieved[a]. When evaluating the symptoms, many subjective factors like adaptation to burdens of the disease, increase in knowledge about the disease, better handling of medications, etc., will play a role and pose a risk of introducing bias, particularly since the study duration is long. Applying GCP conditions at patients' home (e.g. verifying when an AE occurred, or a medication was taken, a diary entry was made) is challenging.

Relevance of primary endpoint for such therapies
The main threat posed by allergies and consequently the main reason to cure allergies is the development of asthma, which can take place many years after the development of allergic diseases. Jacobsen was successful in demonstrating a benefit after five and after ten years following treatment initiation on the basis of a combined endpoint (treatment, baseline bronchial hyper-responsiveness and asthma status). After ten years, a difference in asthma status was shown between active treatment and placebo [49]. Bronchial hyper-responsiveness to methacholine, which is frequently used in the diagnosis of asthma but considered to have limited specificity [55], was not statistically significant after 10 years. The primary endpoint as requested in the standard PIP for SIT, a score to address symptoms as well the rescue medication, primarily reflects the symptoms and medication of allergic rhinitis/rhino-conjunctivitis. Typical endpoints to assess asthma status and its severity like lung function parameters, asthma-typical symptoms such as cough, wheeze and shortness of breath, and asthma-typical rescue medication such as ß-agonists have not been included. Asthma exacerbations are considered adverse events of special interest and are to be reported, leading to some gains in information on the drug's efficacy. But without a proper definition of such exacerbations, a regular assessment during the study and prospective definition as an efficacy

[a] PIP guideline[29] Page 8: *No validated symptom score exists, but the measurement of symptoms on a 4-point rating scale is generally accepted in adults. This symptom score is valid for children as well if it is ensured that the symptoms are always rated in the same way throughout the study by the parent or the patient depending on the age groups.*

endpoint, it is unlikely that a difference would be considered relevant and accepted as a label claim. Hence, the main benefit of such therapies, prevention of asthma development, is unlikely to be demonstrated with such a study.

Placebo use

There are ethical concerns in conducting such a long-term study; patients receiving a placebo are kept from effective therapy for at least five years in addition to a baseline period of probably one additional year. As the benefits in preventing asthma by SIT therapy is considered to be higher in children than in adults[a], this would argue for using SCIT in the early years of life, i.e., avoiding the use of placebo in children. A similar concern was mentioned by the expert group on Immunotherapy [51][b], but obviously, concerns have been disregarded in the final decision. As stated in Article 5 of the paediatric regulation, if no consensus can be reached, decisions are taken by majority[c].

Based on the trial sizes of individual trials (Ref. [50]: 200 patients; Ref. [41]; 1000 patients), it can be anticipated that the overall number of patients in these trials is similarly high. In the worst case, i.e., about 70 paediatric studies with 1000 patients, 1:1 randomised to receive active treatment or placebo, 35.000 patients would be treated with placebo.

Replication of trials

The high number of trials initiated at the same time raises concerns and may be unethical [15][d]. The allergens tested are different and also, the formulation and manufacturing process may lead to a different safety and efficacy profile. However, even a small number of trials with similar products raise concerns.

Recruitment procedures

The age range for paediatric studies is limited to 5-18 years. Although not specified in the standard PIP, it is assumed that the treatment duration of three years should lie in this timeframe in order to have a valid paediatric study. The age range at time of recruitment (start of baseline) would be 4-14 years; otherwise, patients will be over 18 during treatment.

A separate assessment in the 5-12 age group is needed, and 45% of patients need to have this range, as required by the standard PIP. Consequently, for this subgroup, only children who are between 4 and 8 years of age at study start would be allowed to be included.

It is uncertain whether recruitment can be extended to ex-European countries, a practice frequently done for other drugs in other indications. The type and amount of allergen exposure and therefore immunisation status of patients may be considerable different in foreign countries, which may lead to significant country related differences, even within Europe.

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[a] Ref. [29] Standard PIP, page 2: *Children are believed to derive potentially greater benefit from immunotherapy to inhalant allergens, due to the preventive effects of subcutaneous specific immunotherapy (SCIT) on the development of allergic asthma.*

[b] Ref.[51] *3 years placebo-controlled studies will be very challenging, particularly for SCIT (will they be accepted by ethics committee? Feasibility to recruit enough patients?*

[c] Ref.[3], Article 5: *When preparing its opinions, the Paediatric Committee shall use its best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the Paediatric Committee shall adopt an opinion consisting of the position of the majority of the members*.

[d] Ref. [15] Chapter 19: *It is considered unethical to replicate unnecessarily trials in children.*

Klinkowski [35],[a] mentioned several arguments that recruitment poses challenges: young patients (or parents deciding on behalf of their children) may not want to take the risk of receiving a placebo rather than true medicine. Also, it can be assumed that there will be high competition with regard to eligible patients, as many trials of the same type will be conducted in parallel [35]. Companies may be forced to provide incentives to study participants. According to ICH E11 [56] recruitment procedures such as using additional incentives like payments may be of additional ethical concern[b].

Dosage-finding studies

- Klinkowski [35] also discussed the requirement to conduct dose-range finding studies in advance of the paediatric study, in particular the problem that dose finding studies may identify another dose than that currently marketed, with the consequence that a new product (strength) needs to be developed and a new market authorisation is needed (p.25).
- Another aspect of correct dose range-finding studies is that these can be reasonably conducted in a short-term setting only, by using biomarkers or other endpoints for which no evidence exists that they predict the long-term outcome. This questions the relevance of a dose identified in a short-term setting for risk/benefit in the long-term outcome. Another level of complexity is introduced if results from dose-range finding studies in adults are extrapolated to children, as stipulated by the PIP[c]. In the discussions at the EMA/PDCO expert meeting [51], this aspect was controversial, and it was decided, after dose range-finding data in adults is available, that decisions are to be made on a case-by case basis[d].

Commercial aspects

- In order to get a higher price reimbursed from payers as compared to other medications, studies as against established therapies would be necessary to demonstrate superiority in efficacy or a better safety profile. Including a comparator in the current PIP trial would increase the trial size even more. Demonstrating superiority is a tough goal in this setting, one which may not even be feasible to achieve due to the variability in endpoint measurements. Demonstrating a health economic advantage in comparison to other treatments will also be very difficult, as symptomatic treatments for allergic rhinitis like antihistamines and corticoids are relatively cheap and are expected to have low impact on overall health care resource usage. Therefore, it is unlikely that companies will be able to convince payers that higher prices are justified, despite high costs in clinical trials.

Unlike sponsors developing new chemical entities, the incentives for paediatric development as foreseen in the paediatric regulation [3], such as additional market exclusivity, do not play a role for most of the drugs undergoing this PIP (see also Section 5.3.9).

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[a] Ref. [35] Klinkowski D 2011: *Recruitment is difficult because parents are usually not willing to expose their children to clinical studies unless other medical options are unavailable, or medical care is insufficient and participation in clinical studies will improve their situation.*

[b] Ref.[56]: Section 2.6.2 "*Recruitment of study participants should occur in a manner free from inappropriate inducements either to the parent(s)/legal guardian or the study participant.*

[c] Ref. [29] Standard PIP, page 4: *Extrapolation from dose-finding studies in adults should be considered.*

[d] Ref. [51] Section 1.5*: Final consensus: First to obtain data from dose-finding studies in adults; then to evaluate and to decide in children on a case by case basis."*

Timeline aspects
In order to cope with the high number of applications, a bridging strategy was chosen, thereby potentially limiting the number of long-term studies needed. The sequential approach as stipulated by the standard PIP is as follows:

1. Dose-range finding studies in adults,
2. Potentially a dose-range finding in children,
3. Conducting parallel long-term studies in adults/children in a representative allergen product for each product group (chosen by the applicant). Based on the results, a decision on the ability to extrapolate adult and children data
4. Short-term studies for remaining groups or long-term studies in remaining products

The timeline for conducting long-term studies has been set to last until 2031, or, if studies fail, even longer. This means that possibly ineffective treatments may still be on the market until 2031, which is of ethical concern.

Alternatives approaches for paediatric studies
The question is whether alternative approaches might be employed to acquire the missing data. One could imagine a concerted approach of the industry and further stakeholders involving standardisation of extracts. Standardisation could be achieved with specific tests addressing key allergens [57][a].
Large "reference" studies with such standardized extracts could be conducted. They could answer the question as to whether orally administered extracts have similarly high efficacy as s.c. administered drugs. Also, once available, products from recombinant sources could be compared to natural products. If a non-inferiority trial design is chosen, this will be possible only in large trials, due to the low assay sensitivity[b].

The lead in initiating such a study could be The European Paediatric Research Network (Enpr-EMA). This organisation was established to "coordinate studies relating to paediatric medicinal products, to build up the necessary scientific and administrative competences at European level, in order to avoid duplication of studies in children"[58]. If sufficient safety data and short-term efficacy data are available, results could be bridged, based on the long-term reference study above, in order to compensate the lack of long-term efficacy data.

Pending applications may be authorised with the use of short-term studies. Incentives for conducting long-term studies could be given by payers, i.e., premium prices.

EMA has issued a priority list of off-patent drugs that need to be developed for use in the paediatric population [59]. Such research is funded by the European "Seventh Framework program". Thus far, the list does not contain allergen SIT products. If a specific demand can be proven so that SIT products can enter this list, one could strive to fund studies as proposed above under this program.

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[a] Ref. [57] *It is expected that assays to determine the majority of all clinically relevant major allergens from aeroallergen sources will be available in the near future. Standardized and validated mediator release assays may be a complementary tool for evaluating the biological potency of reference allergens and for correlating allergen concentrations to biological potency*

[b] Ref. [39] *Due to the variability in individual clinical responses, unpredictability and variability of allergen exposure, and the subjective nature of symptom assessment non-inferiority trials are not possible due to lack of assay sensitivity.*

Also in the US, there is a list of prioritised paediatric studies with products that do not have patent protection or market exclusivity [60]. Allergen products are not contained in this list. For drugs lacking exclusivity, as set out in the "Best Pharmaceuticals for Children Act"[61], a „written request" to conduct studies in children is issued to marketing authorisation holders. If the marketing authorisation holders do not respond within 30 days, a "request for contract proposals" is issued in order to have the studies conducted by independent organisations, such as qualified universities, hospitals, laboratories, contract research organizations. Funding of these studies is foreseen by grants[a].

Neubauer discussed the use of placebo in paediatric populations [62]. As long-term randomised placebo-controlled studies raise ethical concerns, alternatives such as meta-analyses, cohort studies or case-control studies could be envisaged. Standardised analysis from various sources would support such approaches[b]. There could be the obligation to have patient registries for each drug, so that outcomes of therapy and safety issues could be followed up, even without randomisation. Such measures are expected to be much cheaper compared to the conduct of randomised controlled trials.

Applicant's development alternatives

Assuming that despite many concerns, the PIP decisions of this product group will remain as they are, the applicant may develop their products for asthma (only). It will be easier to claim a patient's benefit for asthma, a disease which may become life-threatening, as compared to allergic rhinitis, which is not life-threatening. Endpoints in asthma are better suited to objective measurements like lung function tests. According to the EU guideline on asthma, trials with a duration of six months are expected to be sufficient in this indication [63]. However, experience from a judgement of the EU court [64] shows that an applicant may be forced to develop an indication in children which he did not apply for [65][c].

Once there is an approved therapy with proven efficacy of a product with the respective allergen, one can also apply for a waiver of PIP studies, according to Article 11 of the paediatric regulation [3], based on the fact that "*the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients*. Certainly, the indication of this product will not cover children. Prescription data from Germany indicate that the majority of allergen products is used in adult patients [66], only 18% is used in children up to 12 years, and 17% is used in adolescents (13-18 years of age).

An applicant can seek to develop a biosimilar. According to the biosimilar guideline [67], allergens have to be considered on a case-by-case basis. Applicants should take appropriate advice from the EU Regulatory Authorities. It is assumed that a detailed characterisation of both the originator and biosimilar is necessary. The authority will probably not request long-term studies to compare both products. However, new authorisations will have 8-years data

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[a] Ref. [61] SEC. 409I. c) 5. *CONTRACTS, GRANTS, OR OTHER FUNDING MECHANISMS.— A contract, grant, or other funding may be awarded under this section only if a proposal is submitted to the Secretary in such form and manner, and containing such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section.*

[b] Ref.[62] p. 44: *Standardised analysis of information from various sources and on the basis of objective criteria would be of potential interest in the absence of other methods of evaluation.*

[c] Ref.[65] *The General Court of the European Union has upheld the European Medicines Agency's decision to deny Nycomed a waiver for a paediatric investigation plan (PIP) for its imaging agent perflubutane. The ruling appears to mean that the agency can oblige firms seeking new marketing authorisations for medicines, preventative products and diagnostics to perform paediatric research into indications that they had not intended to develop*.

protection and 10 years of market exclusivity, and any successor must wait until this time is elapsed.

5.3.9 Discussion of the regulatory impact and context

The standard PIP for allergen products is outstanding in the regulatory framework, and consequences for the industry are very substantial for several reasons:

- The obligation to submit (new) marketing authorisations and the obligation to conduct long-term studies in children was coincidental.
- As mentioned by Klinkowski [35], the PIPs affect not only paediatric development, but – indirectly – make obligatory a long-term study in adults which is to be used for comparison reasons. Dose-range finding studies in adults and pivotal studies in adults as well as in children are necessary.
- The products are used frequently in children. Hence, the paediatric studies will be pivotal studies to prove efficacy, and thus determine whether a product can stay on the market or not.
- The product portfolios are mainly held by specialised small and medium-sized companies which have these products as their only products.
- The products are assumed to have local relevance only, as allergenisation is expected to be different in different climate zones.
- The legal status of such products is not harmonised within the EU, i.e., they may be marketed under the named patient in other countries than Germany, leading to barriers in free trade or commercial disadvantages (no advertisement possible) of products with a marketing authorisation.

It seems that basic concepts as in directive 2001/83/EC are inadequate for the products group of allergens for SIT, in particular those who are derived from natural sources and are on the market for long time:

- The concept of data protection is not relevant due to high itemisation, low standardisation and high impact on sourcing of materials and manufacturing for the final end product, making it very difficult, if not impossible, to place a successful “biosimilar” on the market.
- The concept of incentives for paediatric development is not applicable, because neither market exclusivity nor patents are of value to this industry.
- Although products affected being well-established in a general sense, the concept (legal status) of “well-established use” is not suitable due to lack of state-of-the art testing and rare publication of results. Similarly to traditional herbal products, a status for traditional allergen products would be helpful.
- The concept of granularity by active ingredient, strength and pharmaceutical form is inadequate. This concept means that each allergen-strength combination that is issued has its own marketing authorisation with its own clinical development program, leading to immense costs for these studies, filing and maintenance of applications. A grouping of allergens into one authorisation would make sense.

The use of a standard protocol in this context was probably needed due to the time pressure under which regulatory authorities stood. A thorough individual assessment of requirements and possibilities for a waiver would have been unlikely to be performed within the time frame given. Also, there is no hint that a public consultation of the PIP as required by the PDCO rules

of procedure [68][a] was performed. As stated by Eichler [69], alignment should be achieved with a concerted approach of academia, drug regulators and industry as well as parent/patient organizations in order to support evidence-based authorisation of allergen products for immunotherapy[b].

As outlined in Chapter 0, the development of new drugs is challenging. Innovators face increasingly high development costs while payers raise the pressure to lower reimbursement prices. If established and effective treatments without a formal proof of efficacy have to compete with innovative new drugs, this leads to disadvantages for the innovator; besides the huge development costs, the innovator must take the risk that they can't demonstrate that the new drug is better than established ones. The current regulations for the allergen SIT products enforce a large development program for established products and thereby eliminate disadvantages for innovators. One may argue that this is desirable; however, the outcome may be that many products disappear from market, and others may have insufficient proof of efficacy due to poor trial feasibility. Also, ethical concerns such as the duplication of studies remain.

The high hurdles introduced by this standard protocol aggravated the existing hurdles for this product group. Nevertheless, it is not the fact that a standard protocol was used that caused the problem; if properly aligned with stakeholders and checked for feasibility and imposed only on products relevant as discussed in chapter 5.3.5, a standard protocol can be very helpful to make drug development more predictable, results better comparable across studies, and generally ease the alignment and approval process for such studies.

In summary, it seems that the specific regulatory framework, or at least the current interpretation of it, is inadequate for this product group. The hurdles imposed to the industry of this product group are disproportionally high. The renewed EU "Lisbon strategy" takes into consideration the fact that regulations must support the competitiveness, growth and employment performance of business and must be proportionate to their aim [70][c]. Tools are in place to support this goal.

6 Decision analysis: Clinical trial protocol standards

Decisions on clinical studies have a high impact on the fate of drugs that are tested. For instance, a compound of high medical utility may fail in Phase III due to a wrong decision about study design (e.g., dosage, the population tested, the design, the endpoint), thereby preventing that a new treatment option from becoming available to patients. Wrong decisions may be taken based on the study outcome if the study shows misleading results due to high bias in the study which could have been avoided with preventive measures. In addition, there is an ethical dimension in light of the fact that the study subjects undergo a certain risk, which must

[a] Ref.[68] Article 19: *Concept papers, draft guidelines and general regulatory developments will be subject to public consultation of all interested parties (industry, health care professionals, patients/consumers or other).*

[b] Ref.[69]*These regulatory requirements provide a unique opportunity to fill the gap in knowledge concerning the benefits of SIT for children and to obtain the data needed to support evidence-based authorization of allergen products for immunotherapy. This goal can only be achieved through close cooperation between academia, drug regulators and industry as well as parent/ patient organizations.*

[c] Ref.[70] *The regulatory framework in which businesses operate is a key factor in their competitiveness, growth and employment performance. Therefore, a key objective of the European Union's Enterprise policy is to ensure that the regulatory environment is simple and of high quality. [...] To make sure that regulations are used only when necessary and that the burdens they impose are proportionate to their aim, the Commission has a number of processes and tools in place....*

be balanced out by a benefit to the community in terms of having a robust result in favour of or against the drug's efficacy and safety. In any case, decisions regarding clinical trials are associated with high costs, resource usage and time undertaken by the sponsor of the study.

Decisions must be based on the best possible evidence available from previous studies, from similar studies in the population, and from simulations of study outcome. To compensate for uncertainties, "best guess" is often applied without proper documentation as to which factors contributed to the decision. Formalised decisions promise to provide the highest possible degree of transparency for all stakeholders. Such decisions can be easily updated if new arguments and new data such as new study results become available. A systematic and consistent approach to exploring different options can lead to more thorough and faster decision-making than the normal way of discussing controversial opinions.

A decision analysis, such as the Multiple Criteria Decision Analysis (MCDA), allows for the rating of different options based on predefined objectives that have been weighed and categorised in a formal manner. Following such a rating, an assessment of adverse consequences/risks is added for each option. Recent literature contains some examples where decision analysis is applied to healthcare decisions. Goethghebheur et al. explored the steps currently used to make decisions and developed the "Evidence and Value: Impact on Decision Making" (EVIDEM) framework [71]. In addition to the MCDA approach, criteria for the quality of evidence are evaluated as well using these questions, e.g., for completeness of reporting, consistency with cited sources and relevance and validity.

Tony et al. have applied decision analysis using EVIDEM in the context of HTA assessments [72]. An evaluation of literature and its quality assessment was undertaken by investigators, and an evaluation using the MDCA model was undertaken by HTA committee members. A "contextual tool" was also implemented in order to evaluate the possible positive or negative effects of a particular decision, similar to the risk assessment as mentioned above. Thus far, there is no validated tool for decision making available[a].

So far, there are no known decision matrices for protocols. A process for decisions on standardisation of clinical study protocols is proposed below, in alignment to the approaches as discussed above. Any content, i.e., objective, rating, weighing is to be considered as example only.

6.1.1 Scope of the decision

The decision process must have a clear scope, defining what is the decision to be made.

Here, as an example, it is assumed that an authority, an organisation, a payer, an investigator or any other stakeholder wishes to establish a clinical trial standard protocol for a certain type of drugs, for a defined indication, in order to test a hypothesis. Such hypothesis may be the long-term efficacy of a drug in patients with a specific indication. Thus, the decision analysis should answer the question whether, based on predefined criteria, a standardisation of such a trial is the preferred option compared to other options. The decision analysis will depend largely on the protocol proposed. Therefore, also a protocol evaluation is included in the decision analysis process.

[a] Ref. [72]: "*there is no accepted and validated way to identify successful evaluation and decision making and still less consensus concerning the best framework to support decision making or even the most reliable process for weight elicitation.*"

Different options can be defined already on this level. Alternatively, options can be added later in the process.

6.1.2 Decision analysis steps - overview

A 4-step formal decision making process is herewith proposed which includes the following aspects:

1. **Define/check the objectives and scope of the clinical study**
   The justification for the conduct of the clinical study should be properly defined, in particular the scientific question which is to be answered by the study. Weaknesses in the justification should be identified and may lead to a revision of objectives.
   If not already contained in the scope the decision (6.1.1), the range of products for which the study design is to be applied for, must be defined. Caution must be applied in cases where the justification to perform a study may be different for different types of products within the scope.
2. **Decide on standardisation of trial design versus other options**
   A decision on standard protocols versus other options such as individual assessment or stringent guidelines is being made using the MCDA approach. Objectives must be set up and weighed based on the question: How important is this objective in influencing the decision on standardising a protocol? Each option is scored by weight and a rating scale. If there is uncertainty with regard to clinical trial design which may influence the decision to standardise the trial, step 3 must be processed first.
3. **Decide on/confirm study design or design elements**
   The study proposed must reveal a true, relevant and statistically significant result, which allows definite conclusions on the scientific question of the trial (see 1.)
   Assuming that at least one protocol is already available, e.g., of a preceding study, an assessment can be made on the level of this protocol as a whole or for individual protocol elements. The quality of evidence to support this assumption can be weighed and rated for each of specific design characteristic.
4. **Contextual evaluation / Risk evaluation.**
   This will allow also put anticipated outcomes into context in the overall regulatory, ethical, scientific and health economic environment. Scenarios such as positive / indifferent / negative trial results are to be considered. Effects on availability of medications may have to be discussed.

6.1.3 Step 1: Define and check the objectives and scope of the clinical study

In order to be amenable for an assessment, the rationale for conducting a study should be split into entities which can be analysed further. For instance, the rationale for proposing a standard PIP may be worded as follows:

1. Regulations […] require that
2. all applicants submitting new marketing authorisation applications for product […]
3. conduct studies in children
4. as there is insufficient evidence for long-term efficacy
5. and long-term safety for these products
6. which will be sufficiently addressed by conducting the proposed study
7. while having no adequate alternatives

Ad 1-3. A legal check should be performed, testing that the request for the study is valid for at least a majority of products. It should be identified under which circumstances the regulations do not apply. Discussions such as in Chapter 5.3.5 will have to be made.

Ad.3: As children are vulnerable, the benefit for patients must be considered [62]. The justification to select the patient population should be provided.

Ad 4: "Insufficient evidence" can be further divided into
- An analysis of this evidence, assessing the amount of evidence available, relevance of evidence and quality of evidence (see below).
- "Insufficient" could be answered by the scientific community, and in most cases, data are insufficient in the sense of being sub-optimal. One would like to have more data for further hypothesis testing, developing better drugs, selecting the best drugs etc. However, if a study is requested by authorities, then regulatory considerations such as "Is the risk-benefit ratio for using the drug still positive without this study?" should prevail. Only studies should be requested which are decisive, i.e., if their outcome would be (clearly) negative, their risk-benefit would be negative and vice versa.

Ad.6: This question will be tested in more detail in Step 3 below. The default value is yes; if the outcome of the evaluation is "no", then either the study or the concept needs to be revised.

Ad.7: All alternatives, e.g., post-marketing study requirements or specific safety measures, should be considered and evaluated as different options in the following (Step 2).

As a result of step 1, the rationale is confirmed, or needs additions. For instance, it can lead to the exclusion of certain products from the scope of the standard protocol.

6.1.4 Step 2: General decision on protocol standardisation

6.1.4.1 Setting the criteria for rating a standard protocol

In the following, criteria (objectives) which potentially influence a decision in favour or against a standard protocol are listed. These criteria may have relevance for sponsors or for the authority, or both. The listing is considered being not exhaustive. Selecting objectives can cause bias in that the number of aspects in favour and against an option is substantially different. Weighing each objective can compensate for this.

Reduced time and workload for protocol preparation and -review
For a sponsor, producing a study outline and generating a detailed protocol can be very time-consuming. Different opinions and interests within one sponsor have to be aligned and scientific value, ethical acceptance, quality and the feasibility of conducting the trial need to be optimised; but costs, resources, and time also have to be controlled. External contract research organisations are often to be involved, and external advisors, although helpful, can cause long discussions about the best way to proceed. Regulatory approval takes time, as do numerous questions and requests to amend the protocol. A standard protocol can speed up such processes, making the question merely whether the standard needs to be adapted in some aspects or not. Also for the authority, a standard protocol is easier to process.
In some cases, the development of a standard including its alignment with stakeholders may take long and eat up the time savings.

Smooth regulatory approval and acceptance of results for MAA submission
It is relatively unlikely that the authority that has developed a standard protocol objects to its use, as long as it is used for the intended purpose. Other authorities, however, may have questions or objections. Nonetheless, compared to a scenario in which the protocol is established "from scratch", regulatory review and approval is assumed to be faster and bear fewer risks of rejection.

Enforcing a study with high scientific value - The standard protocol as a "better" alternative
Creating a clinical trial protocol is very demanding. Many skills, careful consideration of many factors and a great deal of experience are necessary to avoid pitfalls like recruitment delays or bias within a study. Full protocols are published only in exceptional cases. Most often, results of studies are not published in detail or with delay, which makes it difficult to gain knowledge from previously conducted studies. Corrections during the trial will cause costly amendments and may also not be feasible at all. The protocol assistance offered by regulatory authorities is time-consuming and may not cover all aspects needed to write a successful trial protocol. Hence, one reason to use a standard protocol may be that they are better in comparison to what the applicant is able to provide within the given timeframe. A relevant factor of standard protocols in order to consider them as a better alternative is the level of detail and amount of guidance provided, thereby helping applicants to generate a thorough protocol.
Setting a large and/or long trial as a standard can avoid that sponsors come up with too short/ too small studies which may deliver results with borderline scientific evidence.

Enhanced comparability across similar studies
When comparing several clinical studies, many factors, such as demographic characteristics, distribution of sites across different countries in a multi-centre study, not using exactly the same assessment or analysis methods, recruitment differences or the differing assessments of investigators can cause the non-comparability of study results, even if a similar design was used. Still, studies with the same protocol are more likely to be comparable than studies with different protocol characteristics, particularly if an internal comparator is tested in both studies. Although direct comparison within a study is the best method, there are cases where direct comparison is not possible, e.g., when there are too many alternative medications or treatments to compare.

Allow sponsors to profile their drugs in the best possible way
A standard will restrict the development of an alternative – and possibly better - design of demonstrating a drug's effect. A design will depend by large on the mechanism of action of a drug. There is no need to test endpoints in a study which have low relevance for the drug in question and thus, in such cases a standard protocol should be adapted.

Allow sponsors to choose the fastest and least burdensome way of drug development
A drug which is known to have very good effects in a surrogate parameter which can be measured in a short-term setting is not expected to prove benefit in a long-term outcome, although there may be scientific interest in comparing this to a drug with another mechanism of action which may have long-term effects only. Imposing obligations for long-term studies makes drug development much more expensive. Instead, a company may prefer to conduct post marketing studies in order to explore long-term effects of the drug.

Easy adaptation to scientific progress
The usual non-standard approach allows quick adaptation to scientific progress. New results from similar studies will most often trigger changes in study design, which cannot be easily implemented in standard protocols. A standard protocol which changes frequently looses the main advantage of allowing predictable development and to be comparable to other trials with the same standard.

6.1.4.2 Rating and weighing

Criteria are to be inserted into the MCDA grid. Criteria are weighed and the options (example here: Mandatory Standard / Guidance with low details / Non-Standard) are rated.

The example in (Table 1) is based on the assumption that an authority or further organisation decides on issuing a protocol standard. The option with the highest score (here: mandatory standard, 32 points) will be chosen.

Table 1 Step 2: General decision on protocol standardisation - MCDA matrix

General objectives of standardisation	*Classification Must/want*	*Weight*	*Rating of options*					
			Mandatory Standard (full details)		***Guidance with low details***		***Non-Standard (also: observational study)***	
		W	***R***	***WR***	***R***	***WR***	***R***	***WR***
Reduce time and workload needed for review and alignment with sponsor	***Want***	***3***	***5***	***15***	***3***	***9***	***1***	***3***
Study results with high scientific value	***Want***	***2***	***5***	***1***	***1***	***2***	***1***	***2***
Enhanced comparability across similar studies	***Want***	***1***	***4***	***8***	***2***	***4***	***1***	***1***
Allow sponsors to profile their drugs in the best possible way	***Want***	***2***	***1***	***2***	***3***	***6***	***5***	***1***
Allow sponsors to choose the fastest and least burdensome way of drug development	***Want***	***1***	***1***	***2***	***3***	***6***	***5***	***5***
Allow easy adaptation to scientific progress	***Want***	***1***	***2***	***2***	***5***	***5***	***5***	***5***
Score				***30***		***32***		***17***

W= Weighing of objectives (relative values; 1 = low importance to 3 = high importance)
R=Rating (values between 1=not supported by option; 5= full support by the option)
WR=Combined score (Weight x Rating)

6.1.5 Step 3: Protocol evaluation

The protocol design evaluation aims at identifying the design which best supports the objectives of the study (as identified in Step 1). If there are already several specific protocol options elaborated, e.g., from existing trials in the field, these can be directly taken as options and compared against each other in this grid. Otherwise, one would start with the high-level design elements, e.g., arms, type of control and duration, and then proceed with details of the design.

As in Step 2, different objectives have to be set up, which will normally include ethical aspects and feasibility aspects, or further aspects. These criteria will have to be set up anew for each decision. Also, they are weighed.

Table 2 gives an example as to how protocol design characteristics (here, study durations) can be evaluated. As the objective of the study is – according to Step 1 – to provide long-term results, a short-term study can only be an option if there are long-term studies to which they can be bridged. Choosing the option of a short-term study would mean that a case-by-case evaluation has to be made, i.e., step 1, the objective of the trial, has to be changed and re-evaluated.

Based on the scoring in this example, the options are relatively similar but favour long-term studies (score: 40). It must be kept in mind that differences found here (40 versus 34) may be not significant enough to base a decision on that. If other results such as the contextual evaluation (step 4) show high risks, then a decision on a trial result may have to be revised.

The decision analysis could then proceed with evaluating the best comparator, the best age range of patients to include, the endpoints to be chosen, etc. For each design element, a new decision table has to be used. Of course, some decisions will limit the options for further decisions. For instance, if a decision on a short-term study has been made, this will limit the options for endpoints which can be measured.

It seems logical to include only design characteristics with a high level of evidence (in supporting the objective) in the standard protocol and leave the definition of other design elements to the sponsor. However, this will then result in a shift of responsibility to the sponsor, not making the option itself better. Evaluating study design questions should include all aspects of the trial, even if not determined in the standard protocol.

Table 2 Step 3: Protocol design evaluation: Suitability of a specific protocol versus study objectives

General objectives of trial design	***Evidence***	*Must/want*	*Weight*	*Rating of options*					
				short-term study + bridging		***long-term study 5 years***		***long-term study 3 years***	
			W	***R***	***WR***	***R***	***WR***	***R***	***WR***
Study (design element) will fulfil scientific objectives[a]	Amount of evidence[b]	*Want*		*2*		*3*		*3*	
	Relevance of evidence[c]	*Want*		*3*		*5*		*5*	
	Quality of evidence[d]	*Want*		*2*		*3*		*2*	
	Combined evidence score:[e]	***Want***	***4***	***12 (1x)***	***4***	***45 (4x)***	***16***	***30 (3x)***	***12***
Ethical acceptance[f]		***Want***	***3***	***5***	***15***	***3***	***9***	***4***	***12***
Early availability of results		***Want***	***1***	***5***	***5***	***5***	***5***	***3***	***3***
Feasability of study		***Want***	***2***	***5***	***10***	***2***	***10***	***2***	***4***
Score[g]					***34***		***40***		***31***

[a] Rated 1-5
[b] Evidence rated as amount (e.g., reflecting patient numbers, numbers of trials)
[c] Is the evidence (e.g., from other studies) fully transferable or of low relevance for the question?
[d] Is the evidence generated credible; are the studies adequately controlled, do they at risk to have bias?
[e] Calculated by multiplication of Amount, Relevance and Quality score. The rating (1-125) is then transferred to a 1-5 scale (see brackets)
[f] Of course, ethical acceptance - and feasibility of study - must not go below a certain level.
[g] Sum of individual WR values

6.1.6 Step 4: Contextual evaluation

Once a decision has been made to use a standard protocol of a specific design, the contextual evaluation is to identify any untoward consequences of that decision to all stakeholders. The trial-specific aspects, such as feasibility, have already been included in step 3.
The acceptance risks must be judged on a subjective basis. If risks are considered unacceptably high, the process has to be restarted, for instance, with altered study objectives (step 1).

Table 3 Step 4: Context evaluation for decision to apply standard protocol with 5-year duration

Contextual evaluation / Risks	***Probability of occurrence***	***Severity***	***Mitigation***	***Contingency***
Economic aspects (resource usage/costs) exceeding feasibility for small companies	*high*	*medium-high*	*extend timelines; keep studies short and small*	*ensure funding*
Amount of trials anticipated lead to duplication of studies (ethical concerns)	*high*	*medium-high*	*Apply concept of representative groups*	*consider waiver for studies based on "no benefit compared to existing treatments"*
Lack of international harmonisation of requirements and alignment	*medium-high*	*medium*	*Get alignment with authorities, industry and other stakeholders for harmonisation*	*Accept isolated solutions*
No information relevant for payers	*high*	*medium*	*Get alignment with payers to include relevant endpoints*	*-None-*

6.2 Discussion and outlook

Standard protocols for clinical trials are relatively new types of documents issued by regulatory bodies or associations, being neither a guideline nor a full protocol. Little experience with them is available so far.

Goals of clinical standard protocols
The trial-specific protocol templates as issued by CTEP aim to facilitate the generation of protocols and will harmonise the conduct of a specific type of study by providing standard design elements and standard terminology. Investigators, sponsors and regulatory bodies as well as patients are expected to benefit from well-written and well-planned templates, in particular when many studies of the same type are conducted. Although many elements are binding, the templates leave flexibility to choose various options.

Compared to these templates, a standard protocol such as the standard PIPs issued by EMEA/PDCO is different in terms of the main objectives. Here, the main focus is to impose detailed obligations for a group of products to ensure that clinical research addresses definite scientific objectives. Compared to regulatory guidelines, clinical standard protocols are much more specific in determining the requirements for a study. Although not legally binding, they are considered to be a potent instrument in enforcing the use of a specific study design. Both the regulatory body as well as the sponsors are expected to benefit from an increased regulatory acceptance and faster study approval. Also, using a standard protocol will give the certainty that the requirements are fulfilled exactly without the presence of superfluous elements.

Alignment of standard protocols
The more specific and demanding the requirements imposed by a standard protocol are, the more effort is needed to ensure that they are in conformance to scientific and ethical principles and that the objectives of the studies fit into the regulatory framework, economic environment, and context of medical practice in which they are meant to be used. Study designs with borderline feasibility and borderline ethical acceptance should not be subjected to a standard protocol. A key factor for the success of standard protocols is alignment with all stakeholders such as authorities, the industry, payers, patient organisations, and academia. Preferably, a consensus should also be reached on an international basis. Only a broad consensus will ensure that advantages such as a smooth approval can be realised. Of benefit is the existence of a regulatory guideline where basic aspects to be considered for the design of clinical studies in this indication are laid down.

Over the course of the alignment process for a new standard protocol, there will be diverging opinions. Consolidation will not always provide the best possible solution. The standard may become the lowest common denominator and thus unacceptable from scientific and/or ethical point of view – or the standard may be a ‘high-end solution’ that makes trial conduct more costly and may have borderline feasibility. In the case of the standard PIP for allergen products for SIT, a five-year study has been made obligatory for specific products, thereby defining the standard as a long-term trial to prove a long-term efficacy. Here, additional alignment with stakeholders may have helped to avoid the conduct of many studies with similar products in parallel, which, at least for some products, is poorly justified and raises ethical concerns.

Knowledge as a key factor
Proposing a standard protocol only makes sense if there is sufficient information from other trials in same the indication, or from modelling/simulation approaches in order to allow recommendation of a specific study design. Every new protocol bears the risk that the studies will have poor feasibility or that the test has low discriminative power, so a signal may be detected, but without reaching statistical significance. If new data become available, standards need to be adapted to the scientific progress. Starting many studies in parallel hinders that knowledge gained from one can be used for the design of upcoming studies.

Feasibility
Any study which undergoes a standard PIP should be critically reviewed in terms of whether the conduct of the study, according to a standard PIP, is feasible and suitable to support the objectives for the specific product in question. The more heterogeneous the product group is, the more exemptions from the standard are expected to occur. Different routes of administration, different safety profiles, different market/medical experience with drugs and different excipients could be reasons to deviate from the standard or to seek a waiver for a study. Formalised decisions such as proposed in chapter 6 may help in finding the best solution in an efficient way.

Ethical concerns in duplicating studies
An obligation to test many compounds in the same (extensive) manner may raise ethical concerns; the more trials are conducted with similar substances in the same trial setting, the less information is gained per trial. The benefit of conducting new studies with such design is lower, but the risks for patients will most likely be the same.

The question is whether the products different enough to justify separate trials. This would call for an individual assessment of study requirements in cases where a high number of similar studies is requested.

Sponsor's responsibility in adapting the standard / avoiding wrong expectations
A standard may reduce the sponsor's responsibility for the trial design – objectively or only in a perceived way – and transfer responsibility to a mixed group of stakeholders who can't be made responsible at the end. Any standard protocol should be reviewed carefully to see whether it fits to the requirements in a specific situation. Deviations are allowed if justified.

Standardisation will not fully prevent trial results from sometimes being ambiguous or trial results not being accepted due to bias or error in study conduct. Risk-benefit is different for each compound and is also subject to changes, which are to be expected when new therapeutic or diagnostic options become available. This does not differ from other protocols, but using a standard protocol may lead to wrong expectations in terms of such shortcomings.

It must also be considered that the protocol must fit the conditions at the site chosen, e.g., a technically demanding assessment may be feasible only in hospitals. The correct integration of the protocol in the overall set of documents like standard operating procedures, contracts - often from different sources - is challenging and may bear a similar level of complication to writing a protocol from scratch. As stated in the standard protocol documents, adaptation is necessary in certain cases.

Formal standardisation

The use of electronic systems for capturing, storing and analysing data from clinical trials is increasing and is expected to contribute to more efficiency in clinical trials. Formal standardisation is a prerequisite for efficient data management. Formal standardisation has many facets:

- Firstly, standardisation of terminology is important, e.g., names of diseases, naming of findings, drugs, etc. There are still many ongoing activities with regard to standard terminology, particularly disease-specific terminology. In many cases, definitions are needed to specify what is meant by which term.
- Secondly, data entities that can be processed by electronic systems need to be defined. The establishment of electronic data submission standards (SDTM) by CDISC was a milestone in such technical standardisation. Data acquisition standards were further harmonised with the introduction of ADaM. There is now a very specific description and unique naming of the data field available for almost every data element in clinical trials. The CDASH standard allows for harmonised development of electronic case report forms.
- Thirdly, the interrelation of data entities is to be standardised. Data standards for clinical trial designs and clinical trial protocols serving as a backbone for electronic protocols have been set up [73]. Data can always be traced back to the original data entry of an investigator during study conduct, analysis of the data and compilation of study results for the report and the regulatory submission. Characteristics are defined once and consistently used in the same predefined way throughout the life cycle of the protocol. Data quality is implemented from the beginning, even when planning a clinical trial. Data can be analysed across different clinical studies, even if they were conducted with different electronic systems.
- Fourthly, the protocol structure, i.e., the content and display of information can be standardised in order to ease the reading, finding of information and for making comparisons [74].

Such formal standardisation can become even more important than standardisation of clinical trial designs. Comparability of trials depends not only on standardisation of major design parameters but also using similar terminology and criteria for selection of study population. Publication of detailed trial data – on the basis of individual patients – can allow powerful meta-analyses across many studies. An example is the database containing 4000 patients with Alzheimer's disease developed by the Critical Path Institute [75]. Existing data from trials has been remapped to fit CDISC standards.

Decision analysis

Decision processes related to clinical studies and thus also to standard protocols have a high level of complexity, considering that by proposing a study design one must predict whether a test achieves a relevant outcome which may lay certain years ahead. Predictions will have to be made in view of many known and unknown biases and sources of variability in terms of the endpoints. The outcome will not only guide investigators to use a drug in one way or another, it will also, as in the case of allergen standard PIP, affect the granting of a marketing authorisation of new and existing products.

Hence, applying majority voting or "best guess" in deciding about trial design is considered not adequate. Formalised decisions can shed light on the various levels of objectives (regulatory, scientific, trial-specific) and can make the levels of evidence on which decisions are based transparent.

The four steps as proposed in section 6 foresee to validate the scientific objective of trial, to decide on the level of standardisation, of a trial, to decide on the trial design elements, and finally to evaluate contextual risks.

Outlook
Given their benefits, standard protocols are expected to be more frequently used by regulators, as the number of drugs in specific indications and thus the amount of experience with study designs is increasing. If properly aligned, the use of a standard protocol offers valuable benefits for sponsors, such as smooth approval and well-accepted results. Also, within the scientific community, a harmonised design and duration of endpoints and terminology as enforced by a standard is desired, as it allows for more reliable meta-analyses.

In case of the allergen standard PIP, many questions have arisen which should be clarified in a constructive dialogue between industry, payers, academia, legislative bodies and regulatory authorities. In particular, areas to be discussed may include the following:

- Harmonisation of the legal basis of allergen products within the EU
- The applicability of the paediatric regulation to established products not having the regulatory status of “well-established use”.
- Clarification by which mechanisms manufacturers can gain incentives for paediatric research, in particular for demonstrating a disease-modifying effect. Possibilities for funding long-term studies with EU
- Possibilities to bridge clinical trial data on the basis of tests versus a reference allergen
- Possibilities for waiving the requirement to submit individual marketing authorisations for each individual allergen / allergen mixture. A core dossier could contain all formulation specific details. An allergen-specific sub-dossier could contain many types of allergens
- Defining product types for which long-term efficacy has already been sufficiently proven or can be extrapolated so that further long-term studies can be waived
- Clarification on the label claims that can be achieved with a single long-term paediatric study, considering that two studies are normally necessary to achieve a claim.

It is expected that in the future, electronic protocols will be available where a standard structure, standard terminology and standard data sets are implemented. Study simulation, CRF generation, study calendar generation, data analysis and further functions for clinical trial conduct will be much more efficient with these protocols. Detailed electronic standard protocols with the possibility for adaptation, where elements of guidance, standard terminology and data sets in compliance with formal standards are implemented, are considered to be helpful for sponsors in order to speed up protocol development and to efficiently use valuable resources.

7 Concluding remarks

The clinical or ethical aspects mentioned go sometimes beyond a regulatory evaluation and should be regarded as a basis for discussion only; each product is different and will require a case-specific in-depth analysis with various experts involved, before any definite conclusion can be drawn. It is also obvious that different stakeholders may come to different conclusions, therefore, alignment is necessary in a constructive dialogue.

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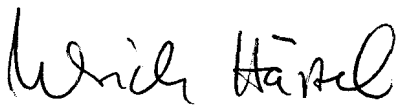
DGRA Master Thesis
Clinical trial standard protocols, approaches for more regulatory efficiency?

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.



Ravensburg, 14. Februar 2012 Dr. Ulrich Härtel