Master protocols in clinical trials: a universal Swiss Army knife?

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Master protocols combine several sub-trials, each with their own research objectives, which is usually presented as one single clinical trial application. Master protocols have become increasingly popular in oncology and haematology, as either basket, umbrella, or platform trials. Although master protocols are intended to accelerate drug development and to reduce futility, their use poses challenges to ethics committees, patients, study investigators, and competent authorities during the review and authorisation process of a clinical trial application. In this Personal View, we review the experiences of clinical trial applications from two European medical regulators—the Danish Medicines Agency and the German Federal Institute for Drugs and Medical Devices. We view master protocols as a good opportunity to identify new treatment options more quickly, particularly for patients with cancer. However, the complexity of trial documentation, the amount of information resulting from sub-trials, and the volume of changes and amendments made to clinical trial applications can cause issues during trial supervision, and during the analysis and review of a corresponding application for marketing authorisation. We draw attention to the potential issues arising from these trial concepts and propose possible solutions to avoid problems during clinical trial authorisation and trial conduct.

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Introduction

Master protocols are characterised by the combination of several sub-trials, each with their own research objectives, submitted as a single overarching trial protocol. A master protocol can include one or more diseases with one or more biomarker-controlled interventions (eg, targeted therapies). Master protocols are mostly found in oncology and haematology, where they have the potential to answer more questions efficiently and in less time. This approach can help accelerate drug development and minimise futility by dismissing less promising compounds to focus on those with a greater chance of success. In the EU, most master protocols are submitted as single clinical trial applications. Such protocols pose challenges to ethics committees, patients, study investigators, and competent authorities during the review and authorisation process due to their complexity. This is particularly relevant for ethics committees and authorities, since it is their task to ensure that patients are not exposed to studies with unfeasible objectives and to guarantee patient protection. In this Personal View, we present experiences with the handling of such clinical trial applications from the Danish Medicines Agency and the German Federal Institute for Drugs and Medical Devices (BfArM), discussing potential issues that arise from the handling of complex master protocols and proposing possible solutions to prevent these issues. We also draw attention to the recommendations on complex clinical trials issued by the Clinical Trial Facilitation and Coordination Group, which is a working group of the Heads of Medicines Agencies, the network of the heads of the European national competent authorities.[1]

Master protocols

Master protocols are not new to clinical drug development. For more than a decade, regulatory agencies have been aware of integrated trial protocols, especially in the early drug development phase.[2] Biomarker-targeted therapy concepts and adaptive trial designs have become part of modern drug development. Master protocols could be considered a logical consequence of such efforts and could help speed up drug development. In 2017, the US Food and Drug Administration (FDA) reviewed these master protocol concepts in detail[3] and published a draft guidance document for public consultation in 2018.[4] The three trial concepts of most interest at present are basket, umbrella, and platform trials. Basket trials include a set of parallel sub-studies in which a specific molecular compound is usually investigated in multiple diseases (figure 1). The sub-trials share the same overall concept and trial design, although diagnosis and treatment can vary substantially between different diseases. Examples of such trials are the *BRAF* V600 trial[5] investigating vemurafenib in non-melanoma cancer, or the B2225 trial[6] investigating imatinib in a series of solid tumours and haematological malignancies.

Umbrella trials are generally disease-specific and investigate different molecular targets for one disease in parallel sub-studies applying biomarker stratification (figure 2). The BATTLE-1 umbrella trial included four parallel biomarker-based phase 2 sub-studies investigating erlotinib, erlotinib plus bexarotene, vandetanib, and sorafenib in patients with relapsed advanced non-small-cell lung cancer (NSCLC).[7] Other examples for umbrella trials are the ALCHEMIST (NCT02194738, NCT02595944, NCT02193282, NCT02201992) and FOCUS4 trials.[8,9] ALCHEMIST is investigating early-stage NSCLC with two randomised sub-studies of erlotinib in patients with EGFR mutations and crizotinib in patients with ALK rearrangements.[8] The FOCUS4 umbrella trial is investigating patients with newly diagnosed locally advanced or metastatic colorectal cancer and allocates them to different sub-studies targeting several relevant mutations including those in *BRAF*, *PIK3CA*, *KRAS*, and *NRAS*.[9,10]

Some of these umbrella trials include additional adaptive elements which are not, or only vaguely,

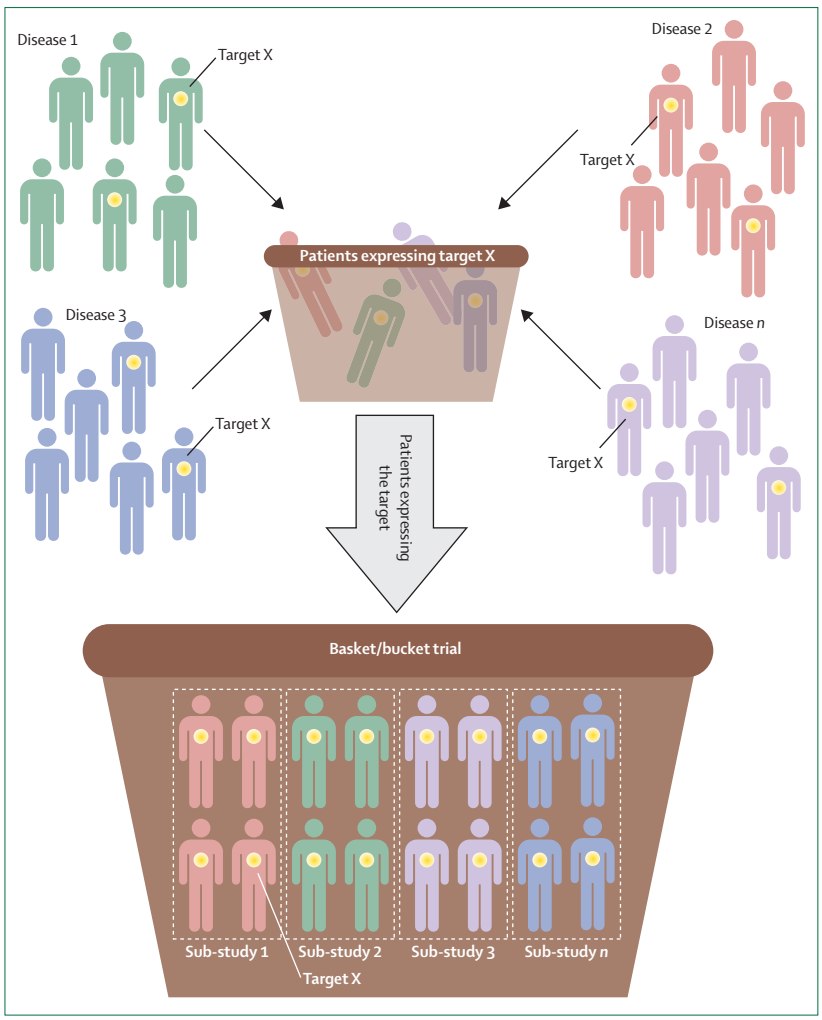

Figure 1: **Basket trial design**
Basket or bucket trials investigate multiple diseases based on a common molecular target in a single trial usually with one investigational drug. All screened patients expressing the same molecular target are enrolled in the trial and are treated with the same investigational targeted drug therapy.

prespecified at trial initiation. Such platform trials represent an extension of the concept of umbrella trials that provide for a near-continuous addition of new study arms or sub-studies and termination of unsuccessful ones. Prominent examples of large-scale platform trials are STAMPEDE (NCT00268476), I-SPY 2 (NCT01042379), and Lung-MAP (NCT02154490). The STAMPEDE trial is the largest randomised trial in prostate cancer and was started in 2005 with six initial treatment arms.[11] Since 2005, several other treatment arms have been added; however, now most of the early interventional arms have been closed and only two experimental arms are currently recruiting. STAMPEDE is expected to end in 2024 with an estimated enrolment of over 12 000 patients. Other large platform trials include I-SPY 2 for the investigation of neoadjuvant chemotherapy in patients with breast cancer,[12] and the Lung-MAP trial, which is investigating therapies for squamous cell lung cancer.[13]

Many master protocols contain adaptive elements, but these elements are often not prespecified as they are in classic adaptive designs, and are only described vaguely in the trial protocol. Most of the master protocols submitted to the Danish Medicines Agency and the German Federal Institute for Drugs and Medical Devices are therefore submitted as exploratory trials. However, master protocols—especially those that include adaptive elements—are not restricted to early-phase clinical trials but can also include phase 3 elements in the concept of multiarm multistage trials, thereby becoming relevant as confirmatory trials for marketing authorisation applications.

The Danish Medicines Agency and the German Federal Institute for Drugs and Medical Devices consider master protocol concepts to be a good opportunity, particularly for patients with cancer, to identify new treatment options. Nevertheless, master protocols could challenge the regulatory system during trial authorisation and trial surveillance, during the assessment for potential marketing authorisation, and can cause ethical issues.

Clinical trial definition

The European legal framework defines a clinical trial as "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy".[14] This definition, published in 2001, is broad and neither promotes nor rules out master protocols. Even the new European Regulation on Clinical Trials, which was published in 2014,[15] maintains this conservative approach but at least acknowledges that there might be a need for more flexibility in the regulatory clinical trial authorisation framework. Although the use of integrated protocols containing several sub-protocols is increasing, the drug development process still consists of a series of consecutive trials that are planned and carried out based on previously gained preclinical and clinical knowledge. An all-in-one protocol containing the complete drug development process for a new compound in a single trial protocol would weaken the regulatory and ethical review system, which is intended as a third-party institutional patient protection system by the European legislation.[14,15] Only if quality-assured data are available to competent authorities and ethics committees at the time of review can they fulfil their mandate to carry out an appropriate review of trial protocols as a legal and regulatory basis for trial authorisation and positive opinion. However, many master protocols are not aimed at the development of a single new agent, but at new treatment concepts including the early detection of

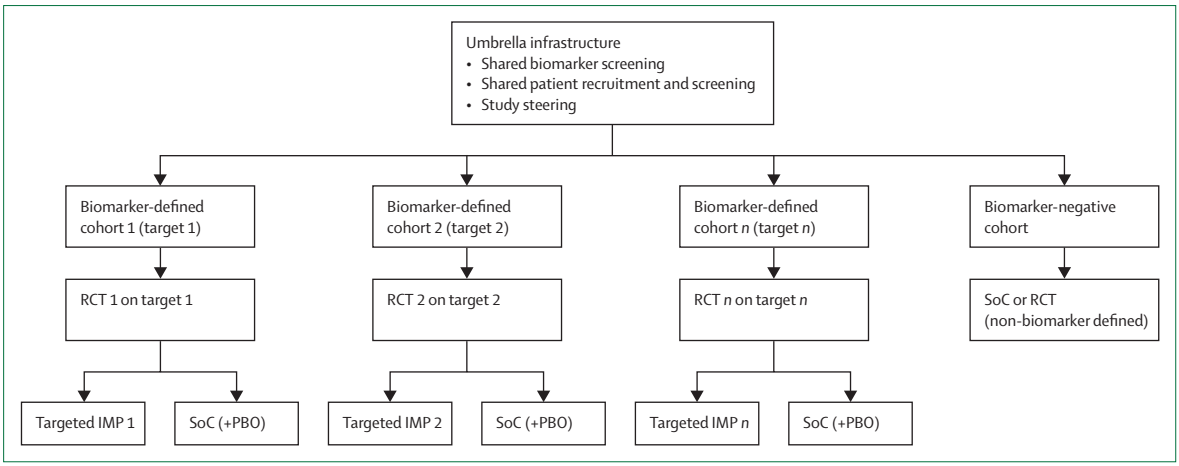

Figure 2: **Umbrella trial design**
Umbrella trials are generally disease specific and investigate different molecular targets for one (conventional) disease in parallel sub-studies applying biomarker stratification. Sub-studies are usually randomised and compare each targeted therapy against standard of care or placebo. Patients expressing none of the screened targets may be stratified to a biomarker-negative control cohort. IMP=investigational medicinal product. PBO=placebo. RCT=randomised controlled trial. SoC=standard of care.

promising candidates, or at the early proof of futility. Therefore, we generally acknowledge the usefulness of these concepts but do not see their strengths in the developmental programme of unapproved new drugs. A clinical trial should be driven by a major hypothesis linked to predefined endpoints and should be analysed in a prespecified manner as described in the trial protocol.[16] This ethical and methodological requirement does not exclude the use of master protocols to investigate several research questions under the same global hypothesis, but it does necessitate appropriate prespecification, especially when used for a marketing authorisation application.

Trial protocol

Although many master protocol trials—particularly basket trials—could be submitted as separate clinical trial applications under an overarching master protocol concept, many master protocols are submitted as single protocols including several sub-protocols. Such clinical trial applications contain protocols with several hundred printed pages, sometimes with several approved and non-approved investigational medicinal products. Most of these protocols can hardly be read linearly, but are structured into various appendices and attachments that are then cross-referenced. This reduces readability for regulators and members of ethics committees who evaluate these documents to short deadlines. Moreover, investigators with the responsibility of informing participating patients according to guiding ethical principles face the same readability issues and might have difficulty understanding all the details of the study within the given review time, let alone be able to explain the benefit and risks to their patients. This increases the risk of protocol violations and serious good clinical practice breaches. Furthermore, each investigator should fully understand the complex trial design including the underlying sophisticated statistical concept to explain the potential benefits and risks to the patient. Conducting a study based on a master protocol ethically could require specialised departments with a dedicated trial management and analytical organisation. These additional requirements could result in smaller local centres lacking the capacity to participate and patients having to travel long distances to be enrolled. Trial results and safety reports could be negatively affected by such complexity as they typically result in extensive documents that are hardly readable for investigators, scientific assessors, or lay people. The concentration of such studies to highly specialised centres might also reduce the possibility of extrapolating results to general hospital settings.

Amendments and trial governance

Integrated trial protocols usually result in a larger number of substantial amendments compared with conventional protocols.[2] This is particularly true for master protocols. While the Lung-MAP trial, which started in 2014, already has 25 amendments to the original protocol, 59 amendments have so far been reported for the I-SPY 2 study. As amendments have a markedly shorter deadline for scientific evaluation by competent authorities and ethics committees in the EU, such a high volume of amendments might jeopardise the quality of the review of the new sub-trials, especially in complex platform trials. The large number and complexity of amendments result in investigators, monitors, and study centres dealing with many protocol changes and versions. Protocol versioning, simultaneous distribution, and appropriate amendment training in all centres should be ensured. As many of these trials are done as multicentre, multinational trials, different amendments might be active in different EU member

states or countries. These problems raise questions about whether these complex trials are still manageable when so many amendments are made and whether the sponsors of those trials have appropriate trial oversight. Another issue with requesting a high number of clinical trial amendments is that investigators might be able to anticipate which treatment could have better outcomes, and which will not. Although this generally applies to all studies with subsequent amendments, the risk increases with the number and extent of additional amendments. This might influence the investigator's behaviour and their recruitment strategy, which in turn might jeopardise the informative value of the trial.[17]

Immortal studies

Particularly platform trials bear the risk of becoming functionally immortal by adding new sub-studies without clear stopping rules for the master trial itself. Especially in a rapidly developing field like oncology, there is a high likelihood of fundamental changes in the basic treatment concepts. It is, therefore, unlikely that an overarching trial hypothesis will remain unchanged when trials are being planned for the duration of a decade or more. The Lung-MAP trial, in which 11 treatment combinations have been tested since 2004, broadened the overall concept in 2018 to extend the study population to all patients with NSCLC, which raises the question of whether such an expansion of one trial could prevent access to other, perhaps better, trials. Could it be harder to develop new drugs outside of such mega trials? Long-term trials might seriously challenge reporting obligations and regulatory oversight. Neither the current European legal framework nor the upcoming European Clinical Trial Regulation require reporting of terminated sub-studies, but only the submission of a final report 12 months after termination of the overarching trial according to the overarching master protocol.[14,15] Although results of terminated sub-studies (positive and negative) could seriously impact the regulatory and ethical opinion of the ongoing trial, there are no legal means to force sponsors to submit sub-trial reports in a timely fashion when a master protocol has been submitted as a single clinical trial application.

Ethical considerations

Regulators and ethics committees tend to give their approval or favourable opinion at an early stage of the study, and their decision is usually based on scarce clinical data. The same applies to patients who tend to give their informed consent at an early stage of the knowledge gaining process, unlikely to know in which stage of the master protocol the relevant sub-protocol is at the time of enrolment. Increasing complexity and length of the trial result in more complicated informed consent documents. Therefore, it could become impossible for patients to understand these documents and the trial concept itself to the extent necessary to give a truly informed consent. In trials where the final dose concept has not yet been fully established, an adaptive design might change the benefit–risk ratio during the dose optimisation process as sub-optimal dose regimens are abandoned as the trial progresses. The Declaration of Helsinki considers it crucial and ethically obligatory that each informed consent document guarantee that, if new information having an impact on benefits or risks becomes available, this information is shared with the patients and patients are asked to re-consent.[18] A shift in the benefit–risk ratio can occur where patients who will be enrolled in the study at a later stage could have a greater benefit as ineffective sub-studies or ineffective dose arms have been stopped earlier. Patients should be informed about recruitment status at the time of the informed consent process to make it transparent how well the dose is established at the given time of their recruitment. The patient can then choose to participate in another trial with an already established dose and frequency, or in a trial where recruitment is further advanced, with a more clearly established benefit to risk balance. Such an approach would involve the patient more in the decision-making process, however, usually at moments of particular vulnerability and with difficult decision options. This will inherently be a challenge for both patients and investigators.

Finally, sample size calculations depend on established clinical effects and their variability. Valid point estimators are hard to collect in small phase 2 studies. Therefore, it remains questionable whether master protocols should be applied before the optimal dosage and frequency of drug administration are established.

Statistical considerations

Master protocols always involve advanced statistics. This is true for power calculations, the result analysis, and the control of the false positive (type I) error. A feedback loop is typically established with sub-studies feeding results into the master protocol algorithm that can then react to the information gained from the sub-study and adjust recruitment accordingly. This is often an automated process without any human interaction. Both regulators and ethics committees find it difficult to evaluate studies without an approximate sample size from both ethical and statistical points of view, as both assessments are dependent on sample size. At least a few different scenarios should be presented if the sample size is not fixed, and lower and upper limits should be provided in the clinical trial application. However, statistical power might be lost when master algorithms react to results from sub-studies, thereby accepting or rejecting the underlying hypotheses and resulting in the closing or opening of study arms when no adjustments were prespecified in the protocol. The interaction between the master protocol and the sub-protocol is often so complex that one might doubt whether it is possible for a non-specialised statistician to fully understand the study design. In addition, a physician or an investigator without thorough statistical training would

Panel: **Key aspects and recommendations for complex clinical trials of the Clinical Trial Facilitation and Coordination Group, a working group of the European Heads of Medicines Agencies**

Description and justification of trial design

- Description of the overall design including the relationships and interactions between the overarching trial and sub-protocols and their respective inter-relation
- Presentation of an overarching trial hypothesis in case of a single clinical trial application
- Scientific rationale for the chosen design including rationale for using a complex trial approach
- Description of all sub-protocols and study arms (closed, currently active, and intended in the future) including description of criteria for opening and closing sub-protocols
- Description of trial participant allocation and potential reallocation to specific sub-protocols and study arms
- Assessment of the benefit–risk balance for overarching trial and each sub-protocol
- Specification of the expected end of trial date

Maintenance of scientific integrity

- Sound scientific hypothesis and unchanged primary objectives during trial conduct
- Appropriate justification and description of extensive changes during conduct including new sub-protocols with new investigational compounds, or new trial populations in line with initial trial hypothesis (substantial amendments not in line with the initial trial hypothesis are considered as new trials)

Quality assurance of trial conduct and optimisation of clinical feasibility

- Risk-adapted approach with appropriate risk identification and mitigation strategies
- Risk-based quality management including risked-based monitoring plans for each sub-protocol appropriate to the trial complexity
- Assurance of appropriate trial oversight by sponsor and investigators
- Focus on clinical and practical feasibility when selecting investigators and trial sites with relevant experience and additional training
- Assurance of appropriate two-way trial communication between sites and sponsor to ensure early detection of site issues and to guarantee that investigators are up to date with all relevant trial aspects

Assurance of the safety of the trial participants

- Provision of an extensive risk identification and mitigation strategy focusing on patient safety and addressing issues deriving from trial complexity
- Use of a data monitoring committee that is not dependent on the sponsor
- Assurance of early safety signal detection
- Provision of a communication plan for safety issues to ensure appropriate and timely information of all relevant stakeholders
- Provisions for reporting of serious good clinical practice breaches or protocol violations according to EU member state requirements

Maintenance of data integrity

- Assessment of potential multiplicity issues deriving from complex trial design with each planned and new adaption
- Provision of mitigation strategies in the protocol (and amendments) to avoid multiplicity issues
- Description of type I error control in trial protocol
- Analyses of potential issues derived from a shared control arm (if applicable)
- Impact assessment of disclosure of interim analyses and closed sub-protocols on patients' attitude and investigators' behaviour

Reassessment of benefit–risk balance at critical steps throughout the clinical trial

- Provision for a continuous re-assessment of the benefit–risk balance at critical steps including safety signals and extensive adaptions, such as closure or addition of sub-protocols, new compounds, or populations
- Appropriate update policy for the informed consent form(s) in the re-assessment process
- Appropriate clarity of informed consent forms, use of separate screening and treatment informed consent forms if appropriate

Validation of companion diagnostics

- Compliance with legal requirements for biomarkers and assays
- Description of biomarker assays used for treatment eligibility and allocation including validation, clinical relevance, cutoff values, acquisition, and handling of biological samples
- Biomarker hierarchy and patient allocation in case of more than one positive biomarker in a patient

Data transparency

- Assurance of data transparency and publication policy in accordance with the European clinical trial legislation
- Provision of a publication policy for interim results of closed sub-protocols or arms and final results in case of a single clinical trial application submission

probably not be able to explain the benefit and risk for the individual patient adequately, particularly in a trial where the chance of success might be changing as the trial progresses.[19] In the FDA's draft guideline, the regulators proposed to centralise the institutional review board review process to secure an adequately qualified evaluation. The current European legislation does not require a centralised ethical review, but this might improve with the upcoming Regulation, in which a joint review by several EU member states is foreseen.

Impact on marketing authorisation

Although most master protocols today are submitted as exploratory trials, some trial results are later submitted in marketing authorisation applications. When the switch from an exploratory phase 2 to a confirmatory phase 3 is prespecified and statistically anticipated, this concept could be helpful to speed up clinical development. A switch from an exploratory to a confirmatory approach that was initially not intended might be justified for simple practical or even ethical reasons. Often sponsors make the claim that patient recruitment would fail once the exploratory trial results become available to the scientific community and patients might not then take part in a randomised controlled clinical trial to test the new compound against the older standard treatment, which is already assumed to be proven as inferior. Therefore, some clinical trials originally intended and designed as exploratory might undergo several iterations of amendments and become pivotal. However, it is always essential from a regulatory perspective that the prespecified hypothesis before trial initiation remains intact. Switches from exploratory to confirmatory designed objectives during trial conduct without prespecification cannot be considered as good science, and authorities as well as Health Technology Assessment bodies should take this into account when considering trial results for an approval and when giving scientific advice before trial initiation. Discussion is warranted, particularly which minimal evidentiary standards are needed for approval and what the consequences will be for product labelling. This could be particularly true in the context of accelerated approvals and for marketing authorisations under exceptional circumstances, which are often debated controversially regarding the impact of the lower level of knowledge at the time of authorisation.[20–22]

Proposals for complex clinical trial applications

Many of the above-mentioned issues arise from the integration of the master protocol with all sub-protocols into one single clinical trial application, resulting in long and complex documents. Sponsors should split up protocols in an overarching master protocol describing master hypothesis, patient population, screening platform, and patient allocation, while treatment sub-protocols should be submitted as distinct individual clinical trial applications. This approach has been applied in many umbrella and even platform trials, such as in the ALCHEMIST and the Lung-MAP trials. As sub-protocols might refer to the overarching master protocol, they can be designed as lean and smart protocols only specifying the sub-protocol relevant procedures and requirements and referring to the overarching master protocol for common procedures and requirements, as the European legislation allows references to already approved clinical trial application protocols. This approach also addresses most of the transparency issues arising from the long-term approach of some platform trials, because it ensures that for each sub-protocol a study report has to be submitted 1 year after termination of the respective sub-protocol. Unfortunately, European legislation does not allow the submission of applications without any investigational medicinal product added. An adaptation of the future legislation to enable overarching platform protocols describing the overall concept including screening and allocation procedures without the investigational medicinal product but referring to further sub-protocols specifying all test and comparator products could facilitate this. Many European medicines agencies are increasingly facing issues when reviewing and authorising master protocols. Therefore, the Clinical Trial Facilitation and Coordination Group published recommendations for complex clinical trials. Eight key aspects and their respective recommendations are summarised in the panel. The main points focus on design description and design justification, scientific integrity and data integrity, as well as on patient safety and data transparency. The recommendations generally ask for prespecification of all relevant study parts and sub-protocols, which does not prohibit the use of dummy sub-protocols to be extended later on in the application process, but would require a multiple clinical trial application approach rather than a combined single application.

Conclusion

Many of the problems and risks of master protocols are neither new nor a fundamental problem in themselves. However, due to their complexity, master protocols increase the risk of such problems becoming apparent. Therefore, master protocols should only be used when they are unavoidable for scientifically sound methodological reasons. To keep trial documentation and trial governance manageable, we strongly encourage sponsors to submit separate clinical trial applications under a master protocol concept rather than to integrate a huge number of sub-studies into one application submission for the EU. The use of master protocols as a simplified authorisation vehicle or to reduce regulatory contacts or shorten review timelines for regulators and ethics committees must be considered unethical and inappropriate. We encourage sponsors planning to submit complex trial protocols to discuss these key aspects in their trial protocols and cover letters. Sponsors can deviate from the recommendations but should justify

major deviations scientifically and should do a risk analysis on the impact these deviations may have. Particularly for complex platform trials, scientific advice before the first clinical trial application submission with all EU member states concerned could be helpful to the authorisation process and to clarify design questions and issues at an early stage. The upcoming European Clinical Trial Regulation will also facilitate this process through the combined review of a clinical trial application by all agencies and ethics committees concerned.[15] Both the current and the forthcoming European legal frameworks on clinical trials provide short deadlines for scientific review of the trial documentation by ethics committees and competent authorities. As pointed out in the Clinical Trial Facilitation and Coordination Group recommendations, "increased operational efficiency and speed of development cannot be the only justification for choosing a specific trial design that may compromise scientific integrity, trial participant safety, or quality of trial conduct at the investigator and/or sponsor site".[1] We believe that overloading clinical trial applications with over-complex trials could weaken the independent review system and result in an unethical conduct of studies. Master protocols should be carefully designed and restricted to what is necessary to protect patients from harm and ensure data integrity.

Contributors

TSe and KB had the idea for the concept of this Personal View. TSu and NCB designed the paper, developed the first drafts of the manuscript, and contributed equally to the paper. CR and AR added important input on clinical and statistical issues. All authors contributed to the review and amendments of the manuscript for important intellectual content and approved the final version for submission.

Declaration of interests

KB is the president of the Federal Institute for Drugs and Medical Devices, a national competent authority responsible for the authorisation of clinical trial applications in Germany. TSe is director general of the Danish Medicines Agency, a national competent authority responsible for the authorisation of clinical trial applications in Denmark. The other authors declare no competing interests.

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